Combining Complements: Theory and Evidence from Cancer Treatment Innovation

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Abstract

Innovations often combine several components to achieve outcomes greater than the "sum of the parts." We argue that such combination innovations can introduce an understudied inefficiency—a positive market expansion externality that benefits the owners of the components. We demonstrate the importance of this externality in the market for pharmaceutical cancer treatments, where drug combination therapies have proven highly effective. Using data on clinical trial investments, we document several facts consistent with inefficiently low private innovation: firms are less likely than publicly funded researchers to trial combinations, firms are less likely to trial combinations including other firms' drugs than those including their own drugs, and firms often wait to trial combinations including other firms' drugs until those drugs experience generic entry. Using microdata on drug prices and utilization, we quantify the externalities that arise from new combinations and find that the market expansion externality often dominates the standard negative business stealing externality, suggesting too little innovation in combination therapies. As a result, firms may have incentives to free ride off others' innovation, which we analyze with a dynamic structural model of innovation decisions. We use the model to design cost-effective policies that advance combination innovation. Redirecting publicly funded innovation toward combinations with high predicted market expansion or consumer surplus spillovers minimizes crowd out of private investments, increasing the rate of combination innovation and total welfare while remaining budget neutral.

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1 Introduction

Many of the technologies that shape our world are inherently combinatorial, employing multiple innovative components together to achieve outcomes superior to what each component could accomplish individually. For example, smartphones enable wireless communication and information processing by integrating a radio transceiver, a microprocessor, and a lithium-ion battery, technologies that were individually recognized with Nobel prizes: Marconi and Braun (1909), Alferov et al. (2000), and Goodenough et al. (2019), respectively. Electric vehicles similarly combine many innovations used in gas-powered vehicles, such as suspension systems, aerodynamic designs, and safety features, with more recent breakthroughs in battery technology and electric motors. And leading treatments for medical conditions ranging from ADHD to HIV/AIDS to COVID-19 consist of multiple drugs that are more effective when used together.[1] While combination innovations like these are thought to play a critical role in long-run technological progress (Schumpeter, 1934; Romer, 1992; Weitzman, 1998), firms' incentives to invent new combinations remain less well examined.

In this paper, we study incentives to innovate combinations. Innovation, in general, results in numerous externalities that can distort the efficiency of equilibrium investment (Arrow, 1962). Innovating firms may steal business from existing substitutes, generate positive spillovers for consumers through better products or lower prices, or benefit other firms through information spillovers that improve their innovation productivities.[2] We argue that combination innovation introduces a new externality on other firms, a *market expansion effect* that arises when it increases profits for underlying component products not owned by the innovator.[3] This positive externality reduces the private value of innovation below its social value, potentially leading to underinvestment in combinations. Moreover, component owners may have an incentive to free ride off others' combination innovation, leading to delayed innovation.

To what extent does the market expansion externality drive a wedge between equilibrium and socially optimal innovation of new combinations, and how should policy respond? We develop an empirical framework to answer this question in a healthcare context: the market for cancer drug combination therapies, where combination innovation occurs through running clinical trials for new combinations of cancer drugs.

[1] Adderall, approved in 1996, treats ADHD using amphetamine and dextroamphetamine, discovered in the 1920s and 1930s. Pfizer's COVID-19 drug, Paxlovid, combines nirmatrelvir and ritonavir.

[2] Early literature on innovation focused on a single innovation at a time, while the more recent "Schumpeterian" literature (Aghion and Howitt, 1992) emphasizes dynamic models of repeated innovation. Quality ladder models feature business stealing, where each innovation replaces demand for previous generations and enables the development of the next.

[3] Similar effects can arise when an innovation increases profits for complementary products.

Cancer combination therapies offer a policy-relevant setting in which to study combination innovation. Cancer is the second leading cause of death in the United States (CDC, 2024), and innovations in chemotherapy have been important contributors to reductions in cancer mortality (Cutler, 2008; Lichtenberg, 2010; Siegel et al., 2023), with combination therapies emerging as some of the most potent weapons in the war on cancer (Mokhtari et al., 2017).[4] Innovating a new combination therapy by demonstrating safety and efficacy in clinical trials is costly, and pharmaceutical companies face substantial legal, logistical, and strategic barriers that prevent them from internalizing externalities through Coasian bargaining (Humphrey et al., 2011; Institute of Medicine et al., 2012; Deng, 2015; Boshuizen and Peeper, 2020; Podkonjak et al., 2021; Sanofi, 2022).[5] Government intervention is common in this market through publicly-funded combination trials (Holbeck et al., 2017; Meric-Bernstam et al., 2023), opening questions about designing cost-effective policies to support combination innovation that balance private and public funding (Schilsky, 2013).

We use data from publicly recorded investments in clinical trials to observe combination innovation decisions for both successful and failed innovations, and data on drug demand and prices to estimate the value of successful combinations to innovators and the spillovers on patients and firms. An advantage in studying drug combination innovation is that we can readily identify the risk set of potential innovations (i.e. all possible combinations of existing drugs), something that is typically more challenging to do in empirical studies of innovation.[6] This greatly enhances our ability to characterize the direction of innovation and the nature of "missing innovations."

We formalize externalities arising from combination innovation using a stylized model of cancer drug combination innovation. Firms own one or more individual drugs and can run a clinical trial to, if successful, introduce a treatment regimen that combines multiple drugs. The introduction of a new combination regimen may impose pecuniary externalities on consumers and other firms, leading an innovator investing in combination innovation to not fully internalize the change in industry profits and consumer surplus.

An important case of such externalities is when there are *missing property rights* from combination innovation. This issue is especially stark in our setting of cancer treatment. Unlike

[4]Recently, the promise of more effective treatments and the sense that new combination therapies have been slow to arrive have prompted extensive discussion in the medical research community about the causes of delay (Boshuizen and Peeper, 2020).

[5]For example, uncertainty over the success and potential qualities of combination therapies may contribute to imperfect or private information across different parties. Dynamically, drug owners may have an incentive to free ride off of the combination innovation of others. We discuss these forces in detail in Section 2.1 and Appendix F.

[6]A recent exception is Kim (2023), which studies innovation in structural biology and uses a database of all known proteins to study the direction of innovation.

many oral medications (e.g., Adderall and Paxlovid[7]), cancer combination therapies are typically not packaged together since component drugs may be taken over the course of many days or weeks in a clinical outpatient setting and in dosages that depend on patient characteristics. Because of this, an innovating firm cannot prevent patients (or doctors) from adopting the new regimen using its underlying drugs. Thus, the innovator of a combination can profit from the innovation only by selling more of the component drugs it owns at their non-discriminatory prices.[8] Similar missing property rights arise in other settings, such as the innovation of software and hardware.[9]

In our setting, the externalities that result from introducing a new drug combination include a market expansion externality distinctive to combination innovation, as well as two externalities that are common to many kinds of innovation, consumer surplus spillovers and business stealing from existing regimens. This market expansion externality arises whenever a firm introduces a regimen that uses drugs patented by another firm, raising demand for those complementary drugs and hence their owners' profits. Consumer surplus spillovers are also exacerbated by missing property rights, because a firm cannot price discriminate based on the value of a drug used in a particular regimen. These new features tend to reduce the private value of innovation below its social value.

We use our stylized model to formulate three predictions about private and public innovation decisions that we test using comprehensive data on clinical trials for cancer drugs between 1990 and 2022. First, all else equal (particularly, regimen prices and qualities), market expansion externalities imply that a firm's research portfolio will consist of a smaller share of combination trials than will a social planner's. The data support this prediction: while 58% of cancer drug clinical trials are for combinations rather than single-drug therapies, this percentage is significantly lower for trials sponsored solely by firms (49%) compared to trials sponsored by publicly-funded (i.e., likely more social-welfare minded than firms) innovators (63%).

Second, the missing property right problem implies that firms will trial combinations of their own drugs more often than combinations involving drugs they do not own, therefore directing innovation towards own-drug combinations. Focusing on two-drug combinations,

[7]These drugs are examples of Fixed Dose Combinations, combinations of two or more drugs in a single dosage form. We discuss the differences from our setting in more detail in Section 2.1.

[8]The fact that the combination cannot be sold as a physically combined drug also precludes selling at a bundled discount since the component drugs could be resold.

[9]New computer software or smartphone applications increase the demand for manufacturers of the associated hardware (e.g., processors, memory, screens, ...). However, developers may struggle to appropriate all of the surplus because of the competition that they face in their product markets. Conversely, improvements in hardware quality increases the demand for software but the associated positive externality on developers may not be fully internalized.

firm trials are biased towards combinations consisting of their own on-patent drugs—11 times more likely than if combinations were drawn uniformly at random from the set of possible combinations—instead of combinations with other firms' on-patent drugs or generic drugs. One might propose an alternative explanation for this result, arguing that firms prefer trialing their own drugs due to greater familiarity or technological compatibility. We present two pieces of evidence against these alternative explanations. First, we show that the probability of a firm trialing its own on-patent drug and a generic drug is largely unaffected by whether the generic drug was initially patent by the firm. Second, we examine data from laboratory tests (Holbeck et al., 2017) of pre-clinical measures of efficacy from all possible two-drug combinations from a set of marketed cancer drugs. These "bench test" measures show that combinations that consist of drugs owned by the same firm or two different firms have similar measures of efficacy across a wide range of cancer cells. Together, these results suggest that financial incentives created by property rights for drugs drive trialing decisions.

Third, the missing property right problem implies that the owner of a drug will run fewer combination trials including that drug after it faces generic competition, while other innovators will run more. Price declines after generic entry may increase demand and thus the value of the combination to other innovators. To examine this prediction, we compare innovation before and after generic entry. We find that a drug is used in more combination trials on average after generic entry (11.0% increase), with the original owner running fewer (-59.4% decrease) and publicly-funded innovators and other firms running more (7.9% and 41.7% increase, respectively). The increase in total trialing is driven by an increase in the probability of a newly generic drug being trialed with an on-patent drug.

Motivated by these empirical results, which are consistent with inefficient underinvestment in combination therapies because of the market expansion externality and missing property right problem, we develop an empirical framework to quantify the externalities from combination innovation and design innovation funding policies to correct these externalities. This framework consists of two steps. First, we model cancer drug demand and price setting, which allows us to estimate the welfare change from combination innovation and decompose this change into externalities on patients and firms. Second, we develop a dynamic combination innovation model that captures the incentive to free ride off others' combination innovation and the possibility of public crowd-out. We use this model to recover primitives of the combination innovation decision and evaluate counterfactual innovation funding policies.

In this first step, we estimate a model of patient demand for cancer drugs and drug price setting. Each patient makes a joint decision with her doctor over what treatment regimen to take, either a single drug or combination therapy. The demand model captures complementari-

ties between drugs by modeling demand over bundles (regimens) of drugs following Gentzkow (2007), using insights from the medical literature to define the set of recommended regimens (Chu and DeVita, 2019). Substitution patterns depend flexibly on patient demographics and type of insurance (public or private), which is important for accurately measuring the value of new combinations. We estimate the model using claims data for Medicare and privately insured patients, from the Marketscan database, between 1998 and 2019. These microdata allow us to develop a novel method to measure market shares and prices of combination regimens, which cannot be recovered from aggregate drug sales alone. We model price setting as simultaneous Nash bargaining between drug owners and private insurers, which captures the role of insurers as intermediaries in determining drug prices for their relatively price inelastic beneficiaries. We recover marginal costs of drug production and parameters of the bargaining problem. These estimates are important inputs into firm profit functions, including predicting how prices respond to innovation.

We use these models to quantify the externalities from combination therapies that have been successfully trialed and introduced to the US market between 1999 and 2019. This analysis is selected on combination therapies that, despite the market expansion externality, were likely privately profitable to develop. We find that new combination therapies with at least two branded drugs owned by different firms have large positive spillovers on other firms that own component drugs in the regimen but did not sponsor the trial, so that the sum of business stealing and market expansion is large and positive on average: one year after introduction it averages approximately $27 million, and extrapolated over the average patent length of the component drugs implies positive profit externalities upwards of $200 million over the life-cycle of each new combination therapy. New combination therapies also have positive spillovers on patients ($31 million per year per new combination therapy on average), but there are also large negative externalities from combination innovation on insurers that increase their costs ($24 million per year per new combination therapy on average). These results suggest that firms are often under-incentivized to conduct trials for combination therapies because of large, positive spillovers to other firms and patients.

Finally, in the second step of the empirical framework, we study how these externalities affect the path of combination innovation by developing and estimating a dynamic model of combination therapy innovation decisions. For each combination regimen that is trialed in the data, we model the timing of when that regimen is trialed, and which innovator trials the regimen, as a dynamic discrete-choice game. The game is finite horizon, capturing the fundamental non-stationarity of the setting that occurs through new drug introduction and intellectual property protections. The agents in the game are innovators that have interests

in trialing the regimen (i.e., firms that have at least one on-patent drug in the regimen and a publicly-funded innovator). Each innovator maximizes the discounted sum of variable surplus from successfully trialed regimens net of trialing costs. Market expansion externalities create an incentive for firms to free ride off others' combination innovation. And innovation by the public innovators similarly may crowd out private combination innovation.

We estimate the model using a full-solution likelihood-based approach, recovering the fixed cost of innovation and parameters of the public innovator's objective function. To make this estimation procedure computationally tractable, and facilitate the computation of counterfactuals, we develop a variant of oblivious equilibrium (Weintraub et al., 2008) that creates separability across the games for different regimens. We also apply sieve value function approximation (Arcidiacono et al., 2013), which allows us to approximate each game's solution.

We then use the estimated model to design cost-effective policy solutions to support combination innovation. We focus on combination regimens that were trialed in the data and three types of policies that could affect the speed with which these new regimens were trialed. Specifically, we study the effects of (i) research subsidies, (ii) varying the amount of public innovation, and (iii) varying the direction of public innovation. These three policies are motivated by existing interventions in this market which take the form of research grants and publicly-funded trials, and our counterfactuals are informative about the design of these interventions. They are also simple to implement compared to the relatively information intensive Pigouvian subsidy.

Increasing public innovation is a cost-effective policy for increasing the rate of combination innovation, even though the model predicts private firms will to some extent free ride off public innovation. Focusing on colorectal cancer, increasing the public trialing budget by approximately $416 million can increase consumer surplus and profits by as much as $840 million, with a total welfare increase of $616 per patient-year. Despite being an untargeted policy, research subsidies can also be a cost-effective way to advance combination innovation as they increase private trialing probabilities while reducing public-crowd out, increasing consumer surplus and profits by $750 million at a cost of $307 million, with a total welfare increase of $642 per patient-year. Finally, redirecting public innovation towards combinations that firms are particularly under-incentivized to trial, that is, combinations with many generic drugs or combinations with high market expansion potential, minimizes public crowd out of private investments and can increase the rate of combination innovation and total welfare while remaining budget neutral. These policies increase total welfare for colorectal cancer regimens by as much as $367 million ($533 per patient-year), giving similar gains to uniformly increasing public innovation or research subsidies but at much lower implementation cost.

Related Literature: Our work contributes first to a vast empirical literature on the efficiency of private innovation decisions (including Griliches, 1979, 1991; Jaffe, 1986; Klette, 1996; C. Jones and Williams, 1998, 2000; Hall et al., 2010; Bloom et al., 2013; Lucking et al., 2019; Zacchia, 2020; B. Jones and Summers, 2021). Papers in this literature use a variety of methods to measure innovation externalities, and typically estimate that social returns to R&D are higher than private returns. Our study of combination innovation externalities highlights a new force leading to underinvestment. Recent work including Bloom et al. (2013) focuses in particular on quantifying the knowledge spillovers and business stealing externalities emphasized in the Schumpeterian growth literature (Aghion and Howitt, 1992). We emphasize the distinctive pecuniary externalities that arise under combination innovation, including market expansion and severe consumer surplus spillovers from missing property rights, and we develop a structural model to estimate them in the cancer drug market. To our knowledge, this paper is the first to provide an empirical analysis of combination innovation in a market setting, complementing a primarily theoretical literature on its role in economic growth (Schumpeter, 1934; Weitzman, 1998; Arthur, 2009; Clancy, 2018; C. Jones, 2023). Relative to these papers, our paper also highlights how market expansion externalities can arise in models with imperfect competition. Since combination innovations necessarily build on existing technologies, our work is also related to the literature on follow-on innovation (e.g., Kitch, 1977; Green and Scotchmer, 1995; Heller and Eisenberg, 1998; Lerner and Tirole, 2004; Scotchmer, 2004; Williams, 2013; Sampat and Williams, 2019), which typically has not focused on quantifying the externalities that result from follow-on innovation.[10] Our discussion of the missing property rights problem for combination therapies is particularly related to the missing property rights problem for "new uses" for generic drugs discussed in Roin (2013) and Conti et al. (2020), but we emphasize that it also shapes incentives to innovate combination therapies when the underlying drugs are still on-patent.

We also contribute to a literature on the economics of the pharmaceutical industry, including work on pharmaceutical demand and pricing (papers with closely related models include Dubois and Lasio, 2018; Dubois et al., 2022; Maini and Pammolli, 2020; Cuddy, 2021; Dafny et al., 2023; see Scott Morton and Kyle, 2011 for a broader review) and innovation (Budish et al., 2015; Dubois et al., 2015; Gilchrist, 2016; Rao, 2020; Krieger et al., 2022; Agha et al., 2022; Aryal et al., 2022; Frankel et al., 2023). Most related are several papers that study demand for combination therapies and the pricing of the underlying drugs: Song et al. (2017) estimates a model of demand and pricing for combination therapies for colon cancer, and uses it to explore the potential price-reducing effects of mergers between firms with complementary

[10] A follow-on innovator may have positive externalities on a previous innovator who has IP protection.

drugs. Cao and Chatterjee (2023) similarly studies the pricing of *fixed-dose* combinations, in which the constituent drugs are bundled in a single dosage form. We instead focus on combination therapies that use separately marketed drugs, which are much more common in cancer treatment and limit firms' ability to price discriminate. We focus on the incentives to innovate combination therapies rather than pricing, and we develop a structural model of combination innovation. Our characterization of the pecuniary externalities from combination innovation is similar to that of Brekke et al. (2023), that develops a model of duopoly pricing in the presence of a combinatorial good. We use our empirical model to quantify these externalities and explore the implications for innovation, and we stress the role of intellectual property protections for individual drugs in shaping innovation incentives. Finally, Wang (2022, 2023) studies the effects of the Medicines Patent Pool on drug diffusion and innovation, focusing on generic firms' production of HIV drug cocktails. Such patent pools have not been widely used for cancer drugs, and we focus on quantifying the incentives to innovate these cocktails that contain combinations of patented and generic drugs and the resulting externalities.

Finally, our combination innovation model draws on existing work in the structural modeling of dynamic games, especially related to entry and innovation decisions (e.g., Pakes, 1986; Bajari et al., 2007; Pakes et al., 2007; Goettler and Gordon, 2011; Sweeting, 2013; Igami, 2017; Igami and Uetake, 2019; Bodéré, 2023; Hodgson, 2024). We develop a computationally tractable model of combinatorial product innovation by applying approximation methods (Arcidiacono et al., 2013) and a variant of oblivious equilibrium (Weintraub et al., 2008).

Outline: The remainder of the paper is organized as follows. Section 2 describes the empirical setting and data. Section 3 presents a stylized model of combination innovation and facts consistent with predictions of this stylized model using data on investments in clinical trials, suggestive of inefficiencies in the innovation of cancer combination therapies. Section 4 develops our model of cancer drug demand and price setting, and Section 5 uses this model to quantify the externalities from combination therapy introduction. Section 6 develops a dynamic model of combination innovation to examine how externalities shape combination innovation decisions, and Section 7 designs cost-effective policies to support combination innovation. Section 8 concludes.

Table 1: Example Cancer Drug Combination Regimens

Cancer	Drugs	Firm	Dosage	Cycle	Trial Sponsor (Paper)	Trial Year
Colorectal	5-Fluorouracil Leucovorin Oxaliplatin	(Generic) (Generic) Sanofi	3,000 mg/m^2 IV day 1, 2 200 mg/m^2 IV day 1 100 mg/m^2 IV day 1	2 weeks	Public (de Gramont et al., 2000)	1999
CLL	Chlorambucil Obinutuzumab	(Generic) Roche	.5 mg/kg PO on day 1, 15 100 mg IV day 1; 900 mg IV day 2; 1000 mg IV day 8, 15	4 weeks	Roche (Goede et al., 2014)	2013
Breast	Gemcitabine Trastuzumab	Eli Lilly Genentech	1,200 mg/m^2 IV day 1, 8 2 mg/kg IV day 1	3 weeks	Eli Lilly (O'Shaughnessy et al., 2004)	2002
Non-Small Cell Lung	Carboplatin Paclitaxel Bevacizumab	Bristol-Myers Squibb Bristol-Myers Squibb Genentech	AUC of 6, IV day 1 200 mg/m^2 IV day 1 15 mg/kg IV day 1	3 weeks	Public (Sandler et al., 2006)	2001

Notes: Table shows four example cancer combination regimens from Chu and DeVita (2019), for colorectal, chronic lymphocytic leukemia (CLL), breast, and non-small cell lung cancer, respectively. For each regimen, the second column gives the component drugs, the third column gives the drug owner (original patent holder) at the year of trial submission, the fourth column gives the dosage of each drug, the fifth column gives the cycle length, the sixth shows who ran the pivotal clinical trial, and the final column is the submission year of that trial to ClinicalTrials.gov. IV means intravenous, and these drugs are administered into a vein using a needle or tube. PO means taken orally. AUC stands for area under the curve, and measures the exposure of a drug.

2 Cancer Combination Therapies: Setting and Data

2.1 Setting

Combination therapies, treatment regimens consisting of two or more drugs, are widely used in the treatment of most cancers.[11] Biological justifications for using combination therapies include reduced drug resistance,[12] reduced toxicity or side effects, and chemical synergies (Chu and DeVita, 2019). Most combination therapies consist of injectable (IV) drugs delivered in an outpatient clinical setting, while some regimens also contain prescription drugs taken orally. Example combination regimens are shown in Table 1, which displays the component drugs, dosage information, and firms with patented drugs in the regimen at the time of the first trial. These example regimens highlight that combinations are often taken over the course of many days or weeks, and the exact dosage can depend on patient characteristics (e.g., size of the tumor). Combinations contain a mix of on-patent drugs, potentially owned by different firms, and generic drugs.

[11] One of the first, and most influential, cancer combination therapies was discovered in the 1960s by Emil Frei (Frei et al., 1965) and was used to treat pediatric patients with acute lymphoblastic leukemia, resulting in dramatic reductions in mortality. It is known as the "VAMP" regimen and consists of 4 drugs: vincristine, amethopterin (methotrexate), 6-mercaptopurine, and prednisone.

[12] Approximately 90% of cancer-related deaths are associated with drug resistance (Bukowski et al., 2020; Dhanyamraju, 2024).

Combination therapies are evaluated in clinical trials to prove safety and efficacy.[13] Every recommended regimen in authoritative treatment guidelines such as Chu and DeVita (2023), UpToDate (Connor, 2024), and National Comprehensive Cancer Network (2024) cites a scientific paper reporting results from pivotal clinical trials demonstrating the regimen's safety and efficacy. While off-label use in untested combinations is theoretically feasible, it is uncommon: in addition to concerns about safety, efficacy, and liability, there are potential issues with insurance coverage (NCI, 2014).[14] Combination therapies often undergo combined Phase I-II or II-III trials rather than separate Phase I, II, and III trials.[15] In our sample of combination clinical trials (defined below), we estimate a success rate of 1.5% across cancers, with a range from .1% to 5% by individual cancer.[16] These clinical trials can be extremely costly, with average per-patient-phase costs in cancer trials exceeding $\$100,000$ (Sertkaya et al., 2014, Moore et al., 2020),[17] with combination therapy trials enrolling 116.2 patients on average.[18] Various entities may conduct combination trials, including private firms, universities, government agencies (including the National Cancer Institute, NCI), and other research institutions.[19] These trials can occur at different stages of a drug's life cycle. While most drugs are initially approved for solo use, some receive their first approval as part of a combination therapy.

In the spirit of Coase (1960), firms may attempt to internalize the market expansion externality by collaborating on trials (splitting trial costs) or contracting over the resulting revenues. However, such negotiations are limited in practice by a variety of frictions, including uncertainty about commercial potential of regimens or newly generated IP, concerns about violating

[13] Combinations do not go through the same approval process as individual drugs, as the FDA does not typically explicitly approve combinations (unless the results from a combination trial are used in support of an individual drug's new drug application). Combinations are instead evaluated in clinical trials, and the results are reviewed by experts, such as oncologists, before being included in treatment guidelines.

[14] For example, CMS and the private insurer UnitedHealthcare use the NCCN Compendium (National Comprehensive Cancer Network, 2024) as their reference for oncology coverage policy. UnitedHealthcare requires prior authorization for these treatments, which necessitates the regimen be included in the NCCN Compendium.

[15] Phase I trials focus on safety and determining dose range. Phase II trials evaluate efficacy, and Phase III trials evaluate efficacy relative to the current standard of care.

[16] This success rate is calculated as the fraction of regimens trialed (in any phase) that appear in cancer treatment guidelines (Chu and DeVita, 2019) and are taken by patients in our drug usage microdata. We discuss these guidelines and drug usage microdata in more detail in Sections 2.2 and 4.3. Wong et al. (2019) estimates a success rate of 3.4% for oncology drugs, where the success rate is measured as the fraction of trialed drugs (single-agents) that receive FDA approval. The success rate we measure differs for two reasons. First, it is a success rate of combination therapies rather than individual drugs. Second, our definition of success is more restrictive in that we require the combination therapy to appear in treatment guidelines and be taken by patients.

[17] A breakdown of the cost components of clinical trials using data from industry reports is included in Appendix F.

[18] Unger et al. (2019) estimates costs for a subset Phase 3 trials run through the National Cancer Institute Clinical Trial Network, finding an average cost to the NCI of $16.6 million per trial.

[19] The NCI allocated approximately $857 million to research projects conducting clinical trials in 2022 (NCI, 2022b) out of its budget of $6.8 billion. The NCI also allocates significant funds to projects such as Cancer Centers and Clinical Cooperative Groups, which may also fund clinical trials (NCI, 2022a).

the IP of component drugs, potential liabilities associated with the combination and negative effects on component drugs, and potential antitrust enforcement (Humphrey et al., 2011; Institute of Medicine et al., 2012; Deng, 2015; Boshuizen and Peeper, 2020; Podkonjak et al., 2021).[20]

The price of a combination therapy is constrained to be the sum of the prices of component drugs, precluding price discrimination based on whether a particular drug is used in a regimen. This feature limits a firm's ability to extract surplus from innovating combination therapies, and occurs for two key reasons. First, the drugs in combination therapies are typically not packaged together, as drugs are taken over the course of many days or weeks and in dosages that depend specifically on patient characteristics (e.g., measurements of the tumor), as shown in the example regimens in Table 1. This feature distinguishes cancer combination therapies from from fixed-dose combinations (e.g., Adderall) in which multiple drugs are packaged in a single physical dosage form (see, e.g., Cao and Chatterjee, 2023), and patenting is possible. Second, doctors' right to prescribe drugs for off-label use allows them to use any treatment regimen that has successfully completed clinical trials by simply prescribing and combining the individual drugs for their patients, making "self-production" of the regimen easy. These features reduce the value of patents for combinations, and pharmaceutical firms have generally not obtained exclusivity extensions for new combinations.[22]

2.2 Data

Making progress on characterizing incentives to innovate combinations requires data on cancer drug characteristics, clinical trials, treatment guidelines, drug usage and prices, and patient characteristics. We summarize each component in this section, while a detailed description of the data and sample construction procedure is given in Appendix A.

Cancer Drugs and Characteristics: We combine data from GlobalData, Drugs@FDA, and the Surveillance, Epidemiology, and End Results (SEER) Program to construct a comprehensive list of cancer drugs and their characteristics. Our primary source is GlobalData, which

[20] 2021

[22] In general, firms may apply for New Clinical Investigation (NCI) exclusivity for demonstrating that a drug (or drug in a combination) is effective for some new indication not covered in the initial NDA. However, the exclusivity term that may be granted from successfully trialing a drug in a combination for a new indication will only apply to that new indication, rather than the original indications the drug was approved for. Enforcement of this exclusivity is difficult, especially for combinations, as the FDA may approve ANDAs for the original indications during this NCI exclusivity period. The potential to arbitrage across regimens and indications limits the usefulness of this type of exclusivity extension. We describe these regulatory details in more detail in Appendix F. We also we use data from the FDA Orange Book (Durvasula et al., 2023) to confirm that exclusivity extensions due to successful combination therapy clinical trials are relatively rare in practice, which is consistent with the small benefits from this type of NCI exclusivity.

provides information on approximately 27,000 pipeline and marketed oncology drugs.[23] This database includes details on original drug manufacturers (i.e., patent holders), patent and exclusivity information, and other drug characteristics. The earliest drugs in our sample were approved in the 1950s, and we have information on drugs through 2023, including investigational drugs. For drugs marketed in the US, we supplement this data with information on generic competition from Drugs@FDA, quantified by the number of approved Abbreviated New Drug Applications (ANDAs). Finally, we use data from the SEER CanMED Healthcare Common Procedure Coding System (HCPCS) database to compile current and historical HCPCS codes for each drug, which we use to identify patient usage of drugs delivered in an inpatient or outpatient setting.

Clinical Trials: We use a registry of privately and publicly-funded clinical trials from ClinicalTrials.gov, focusing on trials run between 1990 and 2022. Submission of trials run in the US has been mandatory since 2007,[24] though many trials were documented prior to this date due to factors such as patient recruitment needs, funding requirements, or journal publication mandates. This data includes information on the particular treatment tested (including what drugs), sponsor, collaborators, indication, start and end dates, and trial phase.[25] We classify sponsors as either private or public, where public includes the NIH, universities, and other non-profit research groups.

We subset to oncology clinical trials using the list of oncology Medical Subject Headings (MeSH) terms and free text keywords in Califf et al. (2012). We use a large language model, OpenAI's GPT-4o, to extract information on drugs used in the control and treatment arm(s) of each trial and remove oncology trials that use only non-pharmaceutical treatment methods like surgery or radiation.[26] Our sample of clinical trials includes trials that test at least one drug

[23] GlobalData acquires its information from myriad sources, including scientific publications and conferences, company annual reports, regulatory filings, and direct contact with companies. Their comprehensive coverage of pipeline drugs begins in 2000, and marketed drugs in 1983.

[24] We will use clinical trials run from 1990 to 2022 as our main sample, but we show robustness of our analysis to focusing on clinical trials run after 2007 given the beginning of mandatory reporting in that year.

[25] ClinicalTrials.gov defines a "sponsor" as the entity that "initiates the study and who has authority and control over the study", while a "collaborator" is any organization other than the sponsor that provides support (funding, design, implementation, data analysis, or reporting). The Food and Drug Administration Amendments Act of 2007 requires that clinical trial information submissions include the sponsor, but not collaborators (42 CFR 11). It is not clear how extensive reporting of collaborators is. Manual comparison of a small set of clinical trials and their associated publications (author affiliations and funding source disclosure) suggests that the collaborators field for firms involved in the trial is relatively complete, though additional work could be done to further complete the field by examining funding disclosures in research papers associated with trials.

[26] We test the performance of this approach by constructing a random sample of 100 oncology clinical trials from 2007. We manually extract the drugs used in the treatment arm(s) of each trial, if applicable. The large language model produces the correct result for 98 of the 100 trials. In one case, the model omitted a component drug of combination, and in the other failed case it incorrectly classified a surgical implement as a drug.

with at least one location in the United States,[27] leaving approximately 28,000 trials. We merge this panel of clinical trials with the drug information constructed above for each drug used in a treatment arm of the trial. This requires harmonizing sponsor names and drug names over the life-cycle (investigational, branded, generic)—details about our merging procedure are given in Appendix A. Approximately 85% of trialed drugs merge to GlobalData, and drugs that do not merge are typically pipeline drugs that are trialed in at most Phase I. We define a combination trial as a trial that tests at least two drugs together in a treatment arm.

Table 2a presents summary statistics for the clinical trials in our sample, which includes both single-agent and combination therapy trials. 58.1% of trials are for combination therapies. The median number of drugs tested in a combination trial is 2, with a median of 1 generic drug and 1 on-patent drug as a component. The table additionally shows the fraction of trials run by different lead sponsor–collaborator pairs. Firms with no collaborators run a higher fraction of single-agent trials (38.7%) than combination trials (24.2%). There are relatively few trials with multiple firms collaborating (3.9% of single-agent trials, 4.8% of combination trials), and there is a higher fraction of firm-public collaboration for combination trials (21.7%) compared to single-agent trials (13.6%). Combination therapy trials enroll more patients than single-agent trials on average, with a mean enrollment of 116.2 patients compared to 104.0 patients. Table 2b presents summary statistics for drugs that are trialed in cancer clinical trials in our sample. Trials may include drugs that are approved or that are still investigational (i.e., not yet approved), whether for single-agent therapies or combination therapies.

Cancer Treatment Guidelines: While the clinical trial data provide a comprehensive list of trialed single-agent and combination therapies, it is difficult to parse the results of those trials to determine what regimens were "successful."[28] We use treatment guidelines from the medical literature (Chu and DeVita, 2019) to define successful regimens for each cancer, and this subset of successful regimens then forms the set of products for our demand system, developed in Section 4.[29] These treatment guidelines are a reference for oncologists when determining treatment for a patient, and are updated regularly to incorporate new treatments. These guidelines contain similar regimens to compendia that are used by insurers to determine coverage of cancer drugs, such as the National Comprehensive Cancer Network (2024) compendium. Chu and DeVita (2019) contains information about approximately 700 regimens for

[27] We focus on trials with at least one location in the United States as these trials are the most likely to be included in treatment guidelines published in the US and thus taken in the US, which our demand data covers.

[28] Furthermore, many cancer clinical trials do not provide timely public reporting of results (Kao et al., 2023).

[29] While we could use the set of all trialed regimens as the products in the demand system, it is computationally convenient to focus on the (significantly) smaller set of successful regimens as defined by Chu and DeVita (2019). We show that these regimens account for most of patient drug usage, and "unsuccessful" or regimens that have not been trialed typically see little use.

Table 2: Cancer Clinical Trial and Drug Summary Statistics

(a) Cancer Drug Clinical Trials

	Single			**Combination**		
	Mean	Median	Std Dev	Mean	Median	Std Dev
Number of Drugs	1.0	1.0	0.0	3.03	2.0	1.64
Number of Generic Drugs	0.07	0.0	0.25	1.0	1.0	1.37
Number of Patented Drug Owners	1.0	1.0	0.0	1.5	1.0	0.87
Sponsor Firm Solo	0.39			0.24		
Sponsor Firm + Firm	0.04			0.05		
Sponsor Firm + Public	0.14			0.22		
Sponsor Public Solo	0.44			0.49		
Enrollment	104.01	38.0	255.15	116.16	40.0	276.59
Total Trials	11,959			16,596		

(b) Cancer Drugs in Trials

	Approved			**Not Approved**		
	Mean	Median	Std Dev	Mean	Median	Std Dev
Number of Drugs	399			3,281		
Total Trials	107.9	25.0	223.61	3.3	1.0	7.32
Fraction Combination	0.68	0.75	0.28	0.47	0.5	0.44
Biologic Indicator	0.09			0.07		

Notes: Panel 2a shows summary statistics of characteristics of clinical trials in our sample, separately for single (columns 1-3) and combination (columns 4-7) trials. Number of Drugs is the number of drugs included in treatment arms of the trial. Number of Generic drugs is the number of generic drugs (determined at the start of the trial) included in the treatment arms of the trial. Number of Patented Drug Owners is the number of unique firms that own on-patent drugs in the regimen (calculated at the time of trial). Sponsor Firm Solo is the fraction of trials run with a firm as the lead sponsor and no collaborators. Sponsor Firm + Firm is the fraction of trials run with a firm as the lead sponsor with a firm (and no other agents) as a collaborator. Sponsor Firm + Public is the fraction of trials with a Firm and Public innovator collaborating. Sponsor Public Solo is the fraction of trials run with a public innovator as the lead sponsor and no firms (but potentially other public innovators) as collaborators. Enrollment is the number of patients enrolled in the trial. Panel 2b shows summary statistics of drugs that are trialed in cancer clinical trials, separately for drugs that were eventually approved (i.e., approved at some point during our sample) (columns 1-2) versus not (or not yet) approved during our sample period (columns 3-4). Number of Drugs is the number of unique drugs in each group. Total Trials is the total number of cancer drug clinical trials a drug is involved in. Fraction combination is the fraction of a drug's trials that are for combinations. Biologic indicator is an indicator of whether a drug is a biologic drug.

40 different cancers. The average number of drugs included in a regimen is 2.05, with a range between 1 and 11. Each recommended regimen cites a scientific paper that presents results from a pivotal clinical trial showing that regimen's efficacy. When new combination therapies demonstrate efficacy in clinical trials, they may be incorporated into existing guidelines, either as additional options, modifications to current protocols, or in some cases, replacements for older treatments, depending on their comparative benefits and safety profiles for certain patients.

Cancer Drug Usage, Prices, and Patients: To determine regimen usage, prices, and patient demographics, we analyze claims and enrollment data from two sources: the Center for Medicare and Medicaid Services (CMS) for traditional Medicare beneficiaries, and Marketscan Commercial Claims and Encounters database for a sample of privately insured individuals. The Medicare data is from 1998 to 2019, and includes information about a 20% random sample of Medicare beneficiaries, of which we observe claims information for traditional Medicare beneficiaries.[30] The MarketScan data is from 1996 to 2013, and is a sample of individuals under age 65 with employer-provided health insurance and their dependents. The sample of patients included in Marketscan expands considerably throughout the sample period, covering approximately 3 million individuals in 1996 and over 50 million by 2013. We discuss this data, including how we measure regimen usage and prices, in detail in Section 4.3.

3 Stylized Model and Descriptive Evidence

This section introduces a stylized model of combination innovation in the pharmaceutical industry and presents evidence supporting its predictions regarding combination innovation decisions. We first use the model to characterize privately and socially optimal innovation decisions, highlighting the existence of market expansion externalities and missing property rights for combinations. The model also reveals the economic primitives underlying the innovation externalities that we estimate in Sections 4 and 5.

We then document three facts consistent with predictions of the stylized model with market expansion externalities: Private firms are significantly less likely than public researchers to trial combinations relative to single-drug therapies (Fact 1). When private firms do trial combinations, they are biased toward combinations consisting of their own branded drugs (Fact 2). Finally, after (and in anticipation of) generic entry, a drug is less likely to be trialed in a

[30] Physician-administered drug claims from Medicare Advantage (Part C) patients are excluded from our CMS data. These Part C plans were first introduced in 1985, and enrollment has dramatically increased since the beginning of our sample. At the end of our sample, 2019, approximately 39% of Medicare beneficiaries were enrolled in a Medicare Advantage plan, with the remaining 61% enrolled in traditional Medicare, as reported by the Kaiser Kaiser Family Foundation (Ochieng et al., 2023).

combination by its original owner, but it is more likely to be trialed by other firms, suggesting potential delays in combination innovation due to intellectual property protections (Fact 3). These facts demonstrate that private innovation decisions are driven by the ownership structure of drugs, and thus that market expansion and missing property rights decisively shape the magnitude, direction, and timing of combination innovation. They also suggest inefficient underinvestment in combination therapies by firms, which we explore in greater detail in the remainder of the paper.

3.1 A Stylized Model of Externalities Arising from Combination Innovation

The key features of combination innovation can be best understood using a static model of the market for drug regimens used to treat a given cancer.[31] A regimen is a set of drugs $r = \{d_{r1}, \ldots, d_{rn}\}$ taken in fixed proportions by a patient, and for simplicity we assume that a patient who takes regimen r consumes one unit of each drug $d \in r$. The set of all drugs that can be combined to form regimens is $\mathcal{D}$, and the set of all regimens that have been introduced and can be taken by patients is $\mathcal{R} \subseteq 2^{\mathcal{D}}$, where the power set $2^{\mathcal{D}}$ is the set of all possible regimens. Each drug d is either generic or owned by a firm, and we identify each firm with the set of drugs it owns, $f = \{d_{f1}, \ldots, d_{fn}\}$. The set of all firms is $\mathcal{F} \subseteq 2^{\mathcal{D}}$.

Drug d is produced at marginal cost $mc_d \geq 0$ and sold at price $p_d \geq mc_d$.[32] As discussed in Section 2, firms cannot price discriminate between patients taking different regimens, so the price of any regimen r is simply the sum of the underlying drug prices, $p_r = \sum_{d \in r} p_d$. The share of patients who take regimen r is $s_r(p)$, and we normalize the total mass of patients to one for convenience. The profits earned by drug d through regimen r are

$$\pi_{dr}(p) \equiv (p_d - mc_d) s_r(p) \mathbb{1}[d \in r].$$

The total profits earned by drug d are then $\pi_d(p) \equiv \sum_{r \in \mathcal{R}} \pi_{dr}(p)$, while we assume profits for generic drugs are zero. We let $\text{CS}(p)$ denote aggregate consumer surplus, and we denote total welfare (Marshallian surplus) by[33]

$$W(p) \equiv \text{CS}(p) + \sum_{d \in \mathcal{D}} \pi_d(p).$$

[31] We incorporate dynamics into our structural model in Section 6.

[32] In this stylized model, we make a simplifying assumption for exposition that each drug has a single price that all patients pay, ignoring the potential difference between list prices and out-of-pocket prices and price dispersion across patients. We model these features in our empirical framework in Section 4.

[33] In this stylized model, we exclude insurer costs from the total welfare function for simplicity. Patients are often not responsible for the full cost of drugs and the total welfare function must capture insurer welfare. We defer analysis of insurers (both public and private) to the empirical model in Section 4.

A pharmaceutical firm can pay a fixed cost $\kappa > 0$ to run a clinical trial for a new regimen r^+. With probability $\chi > 0$ the trial is successful and the regimen can be taken by patients; with complementary probability $1-\chi$ the trial fails. When successful, the addition of the "new product" r^+ leads to new market shares $\tilde{s}_r(p)$ and a new set of equilibrium drug prices $\tilde{p}$. The change in shares reflects how patients adjust their regimen choices at each price vector, while the change in equilibrium prices reflects pricing conduct in the market. We use tildes ($\sim$) to distinguish post-introduction values from pre-introduction values, and we use Δ to denote the equilibrium change in a value. For example, $\tilde{\pi}_d(p)$ denotes the post-introduction profit function for drug d, while $\Delta\pi_d \equiv \tilde{\pi}_d(\tilde{p}) - \pi_d(p)$ denotes the change in equilibrium profits.

Private versus Socially Optimal Innovation Incentives: In this static model, a private firm $f \in \mathcal{F}$ finds it profitable to trial the new regimen r^+ given existing regimens $\mathcal{R}$ if and only if the expected change in its profits exceeds the trial cost, $\chi \sum_{d \in f} \Delta\pi_d > \kappa$. We can decompose the change in profits $\Delta\pi_d$ for each drug d into three terms:

$$\Delta\pi_d = \underbrace{\sum_{r \in \mathcal{R}} (p_d - mc_d)[\tilde{s}_r(p) - s_r(p)]\mathbb{1}[d \in r]}_{\text{business stealing}} + \underbrace{(p_d - mc_d)\tilde{s}_{r^+}(p)\mathbb{1}\left[d \in r^+\right]}_{\text{market expansion}} + \underbrace{\sum_{r \in \mathcal{R} \cup \{r^+\}} [(\tilde{p}_d - mc_d)\tilde{s}_r(\tilde{p}) - (p_d - mc_d)\tilde{s}_r(p)]\mathbb{1}[d \in r]}_{\text{price adjustment}}. \tag{3.1}$$

The first term captures the change in the profits drug d derives from existing regimens $r \in \mathcal{R}$, holding initial prices p fixed. This *business stealing* effect arises as patients substitute away from existing regimens and toward to the new regimen r^+, and it is weakly negative provided that patient preferences satisfy the Weak Axiom of Revealed Preference (WARP). The second component is instead weakly positive and captures the profits earned from the new regimen r^+ at initial prices p, which we refer to as the *market expansion* effect. At fixed prices, any drug not used in the new regimen $d \notin r^+$ earns lower profits because of the business stealing effect, while a drug used in the new regimen $d \in r^+$ earns higher profits as the market expansion effect dominates the business stealing effect.[34] Without property rights over regimens, a firm can only profit from the introduction of r^+ if it owns a drug used in this regimen, and even then only if the market expansion effect dominates the business stealing effect on average across its drugs. The balance of these effects depends critically on patient substitution patterns. The final term reflects all changes to profits because of the equilibrium price adjustment from p

[34] More generally, the business stealing and market expansion effects arise whenever a firm innovates a new product that is respectively substitutable or complementary with an existing product. A distinctive feature of combination innovation is that these effects appear simultaneously.

to $\tilde{p}$. This adjustment depends on pricing conduct, drug ownership, and the change in the demand system. It affects both the observed market shares $\tilde{s}_r(\tilde{p})$ and the margins $\tilde{p}_d - mc_d$.

To derive the *net externality* of firm f's introduction of regimen r^+, we compare the change in surplus internalized by the firm to the change in total welfare. The change in total welfare includes both the change in consumer surplus and the change in profits:

$$\Delta W \;=\; \Delta \text{CS} \;+\; \sum_{d \in \mathcal{D}} \Delta \pi_d.$$

The *net externality* of firm f's introduction of regimen r^+ is then:[35]

$$\text{Net Externality}_{r^+} \;\equiv\; \Delta \text{CS} \;+\; \sum_{d \notin f} \Delta \pi_d. \tag{3.2}$$

The first term is the *consumer surplus externality* (i.e., the standard non-appropriability of consumer surplus that arises in innovation), and WARP implies that it is weakly positive when prices are fixed ($\tilde{p} = p$).[36] This externality is not specific to combination innovation and arises whenever an innovating firm cannot appropriate all consumer surplus, though it may be particularly large in this setting since firms cannot price discriminate by regimen. The second term is the *net profit externality*, which captures the pecuniary externality on other firms $f' \neq f$. As the decomposition (3.1) demonstrates, the net profit externality includes business stealing, market expansion, and price adjustment effects. Even at fixed prices, the presence of business stealing implies that the net profit externality, and thus the overall net externality, may be positive or negative.[37] But if the positive effects on consumers through increased surplus and other firms through market expansion dominate business stealing, then firms will underinvest in combination innovation relative to the social planner.

Measuring Innovation Externalities: The stylized model clarifies the economic primitives that we must measure in order to quantify the net externality from combination innovation and any corresponding inefficiency. The definition of the net externality (3.2) from firm f's introduction of regimen r^+ requires that we measure the corresponding change in consumer

[35]The externality from the firm's decision to *trial* regimen r^+ is simply the net externality multiplied by the success probability χ.

[36]When quantifying these externalities in Section 5, we additionally include a term for the fiscal externality on insurers that pay remaining drug costs after patient deductibles, co-payments, or co-insurance. The change in this net surplus (consumer surplus minus insurer costs) may be positive or negative.

[37]The endogenous growth literature identifies another externality, knowledge spillovers, which arises when one firm's innovation builds on (and thus benefits from) another firm's innovation (Romer, 1990). This externality plays a critical role in combination innovation, because new combinations often use components invented by different firms. Knowledge spillovers are pervasive but challenging to measure in the pharmaceutical industry, so we limit our focus to pecuniary externalities.

surplus and the change in profits earned by other firms' drugs, neither of which are directly observable. In Section 4, we estimate a discrete-choice random coefficients demand system for regimens that allows us to compute ΔCS given prices p and $\tilde{p}$. Similarly, to recover marginal costs of drug production and compute the profit change $\Delta\pi_d$, we estimate a model of Nash bargaining over drug prices between manufacturers and insurers. Both the demand system and the pricing model are crucial for decomposing the profit change $\Delta\pi_d$ into the business stealing, market expansion, and price adjustment terms in (3.1). To assess the extent to which the net externality yields inefficient innovation decisions by firms, we must additionally recover the innovation fixed costs κ and the success probability χ. In Section 6 we estimate a dynamic innovation model that allows us to recover these parameters, making use of the estimated demand system and pricing model as well as firms' observed clinical trial decisions.

Before recovering these primitives, we first document three facts related, respectively, to the amount, direction and timing of combination innovation. These facts are consistent with predictions of the stylized model having positive market expansion externalities and missing property rights that shape firm incentives to innovate combinations, and highlight the importance of drug ownership in determining the amount, direction, and timing of combination innovation.

3.2 Who Funds Combination Innovation? Single versus Combination Trials

Our first fact explores incentives to innovate single versus combination therapies, motivated by a prediction of the stylized model: all else equal (e.g., regimen quality, price), market expansion externalities imply that a firm will be less likely than the social planner to trial a particular combination compared to a single-agent therapy. The data support this prediction:

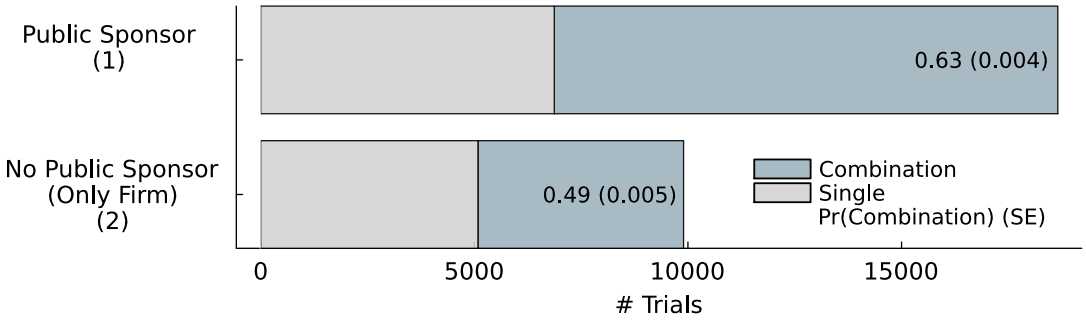
Fact 1. *A firm's research portfolio consists of a smaller share of combination trials than that of a social planner or its proxy (social-welfare minded public researchers).*

To provide evidence for this fact, we calculate how many cancer combination and single-drug trials are sponsored by publicly-funded innovators versus firms. In Figure 1, we see that trials with public funding are the most numerous and more likely to trial combination therapies (63% of trials are for combinations)[38] compared to trials with only firm sponsors (49% of trials are for combinations).[39] Standard errors of a trial-level regression of an indicator of being a combination trial on indicators for different funding types are also displayed, indicating statis-

[38] We also note that public institutions run many single drug clinical trials, often for second uses or indications that were not tested by the drug's original manufacturer. We decompose these types of trials in Appendix A.

[39] Collaborative trials between firms and public sponsors are included in the "Public Sponsor" bar (22% of total combination trials), while collaborations between 2 or more firms (and no public sponsors) are included in the "No Public Sponsor" bar (5% of total combination trials).

Figure 1: Clinical Trials by Funding Type



Notes: Figure shows the number of trials run by different sponsors broken into combination (blue) and single drug trials (gray) and the fraction of that sponsor's trials that are for combinations (black number). The "Public Sponsor" bar includes trials with at least one public sponsor. The "No Public Sponsor (Only Firm)" bar includes trials that are solely sponsored by firms. Robust standard errors are in parentheses on each bar, which come from a trial-level regression of an indicator for being a combination trial on sponsor type. The corresponding regression table is shown in Appendix B, where we also show robustness with respect to the time period of trials included, additional controls (cancer, trial submission year, and trial size), and estimating separately for collaborative trials.

tically significant differences between the combination trialing behaviors of different funding types.[40]

This fact demonstrates that firms are biased away from clinical trials for combination therapies relative to publicly-funded researchers. Firms may be dissuaded from trialing a regimen if many of the resulting profits accrue to other firms that own drugs in the same regimen, unlike publicly-funded researchers with other (potentially aggregate welfare-minded) objectives. However, this fact is also consistent with the idea that firms are "crowded out" of funding clinical trials for combination therapies by public institutions, so this fact does not provide direct evidence of *inefficient* underinvestment. We disentangle these effects in the remaining facts.

3.3 What is the Direction of Combination Innovation? Trials and Ownership

Our next fact characterizes the direction of combination innovation by calculating the probability of running a particular combination clinical trial as a function of drug ownership. In the stylized model, all else equal, a firm earns the highest expected profits from combination regimens that consist primarily of its own drugs, compared to drugs owned by other firms or generic drugs. Compared to a firm, the social planner is more likely to trial generic drugs, since it considers the positive externality on consumers. The data support this prediction:

[40] We show robustness of this fact and the remaining facts in this section to focusing on clinical trials run after 2007 in Appendix B. We also show robustness to controlling for other trial characteristics, such as cancer type and trial (submission) year.

Fact 2. *Firms are more likely to trial combinations of their own branded drugs than combinations with other firms' branded drugs or generic drugs. Compared to firms, publicly-funded researchers are more likely to trial combinations with generic drugs.*

To demonstrate this empirically, we construct a panel of trialing decisions for two-drug combinations and calculate the probability of trialing a combination as a function of drug ownership. We focus on two-drug combinations for ease of exposition, which include approximately 50% of the combination trials in our data.[41] Let $\mathcal{D}_t$ denote the set of all drugs discovered by the beginning of year t, and let $\mathcal{L}_{2t} \subset \mathcal{D}_t^2$ denote the set of all two-drug clinical trials $r = (d_1, d_2)$ that have yet to be run (but can be run) by the beginning of year t.[42] As discussed earlier, an unusual and attractive feature of this setting is that we are able to observe the risk set of potential innovations; in other words, we can observe combinations that have not been trialed since we can enumerate the set of potential combinations for any given set of drugs. We classify two-drug combinations in $\mathcal{L}_{2t}$ into groups depending on whether the components are branded or generic and owned by the same or different firms.

We then measure how clinical trial decisions deviate from the benchmark in which clinical trials are chosen uniformly from all possible clinical trials $\mathcal{L}_{2t}$. Let L_{it} denote the total number of trials run by innovator of type i in year t, where i is either private (firms) or public. If these trials were chosen uniformly at random, the probability that any given trial r is chosen (with replacement) would be

$$\beta^{\text{unif}}(L_{it}) = 1 - \left(1 - \frac{1}{|\mathcal{L}_{2t}|}\right)^{L_{it}}.$$

We then estimate the following equation for private innovators i, pooling across two-drug combination regimens r and years t:

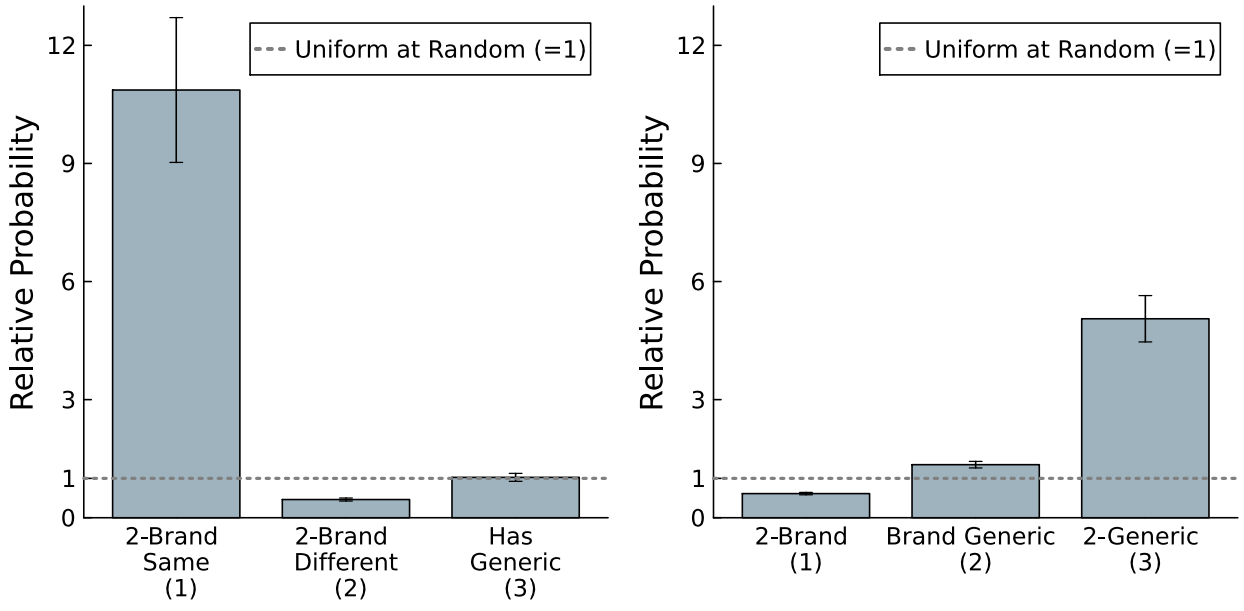
$$\frac{\text{Trial Now}_{rit}}{\beta^{\text{unif}}(L_{it})} = \gamma_1 (\text{2-Brand Same})_{rit} + \gamma_2 (\text{2-Brand Different})_{rit} + \gamma_3 (\text{Has Generic})_{rit} + \varepsilon_{rit}, \tag{3.3}$$

where Trial Now_{rit} is an indicator that regimen r is trialed by innovator type i in year t. Each coefficient γ_k measures how many times more likely an innovator of type i is to run a given trial of type k in a year relative to uniform selection from the set of available combinations. We estimate a similar equation for public innovators, where the types of combinations included

[41] An extension of this fact to 3 or more drugs amplifies the general patterns of this exercise, and is discussed in Appendix B.

[42] For computational tractability, we restrict to drugs that are trialed in at least one Phase 2 trial (or later phases). This drops drugs that are investigational and fail Phase 1 trials.

Figure 2: Relative Probability of Trialing 2 Drugs Together by Drug Ownership Status



(a) Firm

(b) Public

Notes: Figure shows estimated γ_k coefficients of Equation (3.3). Private innovators (firms) are on the left panel, and public innovators on the right. The dotted line at 1 displays what trialing behavior would look like if innovators selected combinations uniformly at random from available combinations. 95% confidence intervals for the regression coefficients calculated from robust standard errors are displayed on each bar. Regression tables and additional robustness checks are given in Appendix B.

are 2-Brand, Brand and Generic, and 2-Generic.

Figure 2 plots the estimated coefficients, where firms are shown on the left and public innovators the right. Firms have a significantly higher relative probability of trialing combinations consisting of two branded drugs owned by the same firm (approximately 11 times more likely than uniformly at random) compared to combinations that contain two branded drugs owned by different firms (relative probability of .46) or combinations with a generic drug (relative probability of 1.03). Compared to firms, public innovators are more likely to trial combinations with a branded drug and a generic drug (relative probability of 1.35) or two generic drugs (relative probability of 5.05).

While this fact is consistent with firms directing combination innovation based on financial incentives towards high-profit own-drug combinations and away from combinations with market expansion externalities on other firms, it could also stem from a number of confounding factors. First, firms might be more familiar with their own drugs and therefore more likely to trial them in combinations. Second, running trials with a firms' own drugs might be sig-

nificantly less expensive. Third, drugs produced by the same firm might be more likely to be complementary because of specialization in particular research areas.[43] Finally, public innovation in combinations with drugs owned by different firms or generic drugs could cause crowd-out. We present evidence against each of these alternative hypotheses.

To address the potential for intra-firm familiarity, we refine the types of combinations considered in Equation (3.3) to exploit variation in ownership over time. Focusing on combinations that consist of a branded drug and a generic drug, we can decompose these combinations into two groups: those where the two drugs were both initially owned (i.e., patented) by the same firm or not. Greater familiarity with own drugs suggests that firm innovation decisions would be significantly biased towards combinations where they initially had patents for both drugs versus only one. Estimating an expanded version of Equation (3.3) largely rejects this hypothesis. Figure 3a plots the key coefficients. Firms trial combinations of a branded drug and a generic drug where both drugs were initially owned by the same firm 1.76 (.56) times more than uniformly at random (left bar), compared to 1.01 (.05) times more than uniformly at random (right bar) when patented by different firms. This difference is small relative to the bias towards combinations of two branded drugs by the same firm (11 times more than uniformly at random).[44]

Reports of the different contributors to trialing costs suggest that the cost of the clinical procedure, which in the case of combination trials includes the cost of the drugs and any costs associated with administering the drugs, makes up at most 20% of total costs on average.[45] This fraction is likely too small to rationalize the large difference in observed trialing decisions.

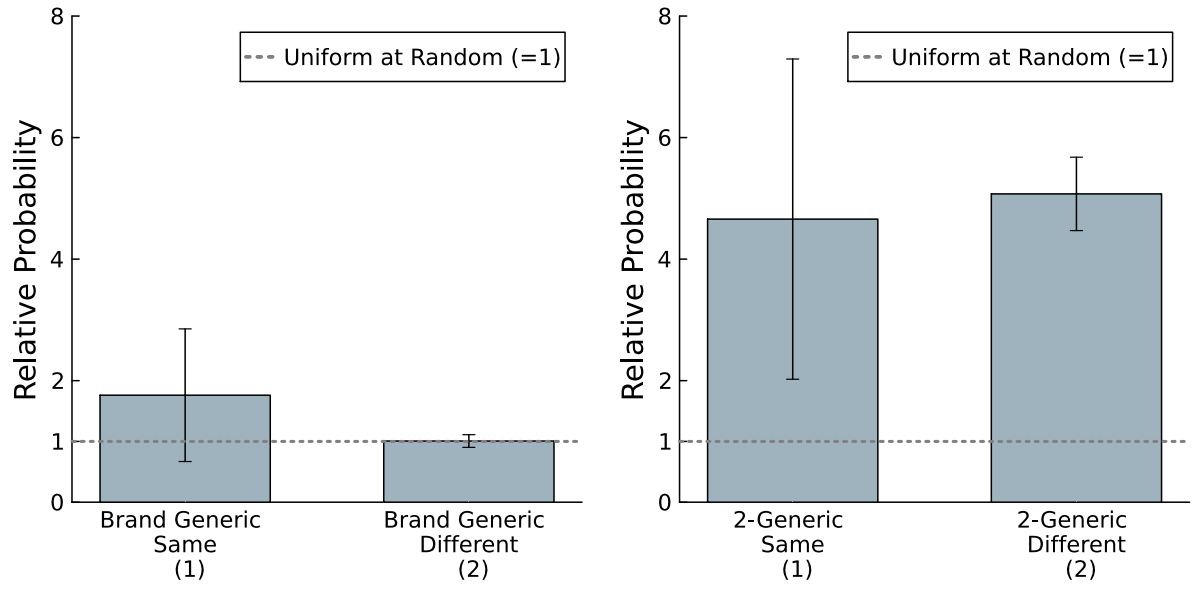
To address the potential for intra-firm complementarity of drugs, we provide two additional pieces of evidence. First, we can conduct a similar test to the intra-familiarity test but with public innovation decisions, where we decompose the 2-Generic category into two groups: combinations where both generic drugs were initially patented by the same firm or not. Estimating an expanded version of Equation (3.3) reveals that publicly-funded innovators trial these two types of generic drug combinations with similar relative probabilities, as shown in Figure 3b. They trial combinations with two generic drugs originally patented by the same firm 4.66 (1.34) times more than uniformly at random (left bar) and two generic drugs originally

[43] The other direction is also possible: as many combinations are often effective through reducing drug resistance, if a firm is more likely to produce multiple drugs with similar mechanisms of action, then its drugs may be less likely to form effective combinations.

[44] This difference in relative probabilities between can also be explained by the small but positive profits original patent holders may still earn from their drugs that have experienced generic entry. Generic entry erodes monopoly profits over a number of years as patients substitute away from the branded drug, leaving higher financial incentives combinations with their own generic drugs for a few years.

[45] We present a detailed breakdown of these trialing costs in Appendix F.

Figure 3: Relative Probability of Trialing 2 Drugs Together – Alternative Explanations



(a) Firm

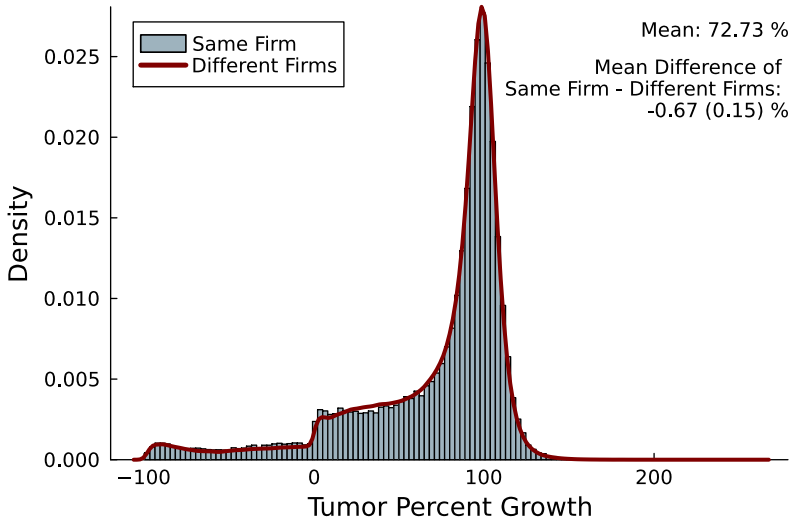
(b) Public

Notes: Figure shows estimated γ_k coefficients of Equation (3.3), expanded to include (and only showing coefficients for) the additional categories of Brand + Generic Same and Brand + Generic Different for private innovators and 2-Generic Same and 2-Generic Different for public innovators. Private innovators (firms) are on the left panel, and public innovators on the right. The dotted line at 1 displays what trialing behavior would look like if innovators selected combinations uniformly at random from available combinations. 95% confidence intervals for the regression coefficients calculated from robust standard errors are displayed on each bar. Regression table given in Appendix B.

patented by different firms 5.07 (.31) times more than uniformly at random (right bar). Thus, publicly-funded researchers trial combinations consisting of two generic drugs with similar probabilities, regardless of original ownership.

The second piece of evidence against intra-firm complementarity of drugs uses data on laboratory measures of two-drug combination efficacy. In 2017, the National Cancer Institute (NCI) released the NCI ALMANAC ("A Large Matrix of Anti-Neoplastic Agent Combinations"): a database of laboratory tests of all two-drug combinations derived from a set of approximately 100 FDA approved cancer drugs (Holbeck et al., 2017). The laboratory tests measure tumor growth rates on 60 different tumor cell lines for various dosages, resulting in approximately 3 million tests. We merge drug ownership information with this database and show that combinations consisting of drugs owned by the same firm or different firms result in similar tumor growth rates, displayed in Figure 4. While the mapping between laboratory results and clinical trials is not immediate, this fact suggests ex-ante measures of complementarity are not significantly different for combinations consisting of two drugs owned by the same firm or

Figure 4: NCI ALAMANC Distribution of Tumor Growth Rates by 2-Drug Combination



Notes: Figure shows the distribution of tumor growth rates for combinations in the NCI ALMANAC, separately for combinations consisting of drugs owned by the firm or not. Each distribution is normalized to show a density. The mean growth rate is 72.73%, and the coefficient (SE) of a combination-level regression of the tumor growth rate on an indicator for the combination having two drugs owned by the same with drug and cancer fixed effects is -.67% (.15%). Regression tables and additional results are included in Appendix B.

not.[46]

Finally, crowd-out by publicly-funded researchers is a less compelling explanation for low firm activity in 2-Brand Different trials, because public institutions also run few trials with two branded drugs (relative probability of .6) relative to other two-drug combination therapies. Public researchers, whose objective may be closer to aggregate welfare than firms, are more likely than firms to run trials consisting of generic drugs (relative probability of 5.05).

3.4 When Does Combination Innovation Occur? Trials and Generic Entry

Our final fact characterizes how the regulatory environment affects the timing of combination innovation. In the stylized model, generic entry into a drug reduces the original owner's incentive to trial it in combinations. In contrast, the decline in price due to generic entry may incentivize other firms and publicly-funded innovators to trial it in new combinations.[47] The

[46]Robustness checks of this result are described in detail in Appendix B, which test additional measures of complementarity and find similar results.

[47]This holds formally when some drugs d and d' become "more complementary" in demand after the introduction of a new regimen r^+:

$$\frac{\partial \Delta\pi_d(p)}{\partial p_{d'}} < 0 \iff \frac{\partial \tilde{s}_{r^+}(p)}{\partial p_{d'}} + \sum_{r\in\mathcal{R}:d\in r} \frac{\partial \tilde{s}_r(p)}{\partial p_{d'}} < \sum_{r\in\mathcal{R}:d\in r} \frac{\partial s_r(p)}{\partial p_{d'}}.$$

data support this prediction:

Fact 3. *A cancer drug is involved in more combination therapy clinical trials after (and in anticipation of) generic entry. The original firm runs fewer trials, but both other firms and public researchers run more.*

To provide evidence for this fact, we construct a panel of drugs that experience generic entry before 2023. For each drug d and year t, we calculate the total number of combination trials involving that drug that start in that year, and how many of those combination trials are run by (either as lead sponsor or as a collaborator) the firm that originally patented the drug, publicly-funded innovators, or other firms. These groups are not mutually exclusive since trials can potentially be run with collaborators. We then estimate

$$Y_{dt} = \beta \mathbf{1}(\text{Generic Indicator}_{dt}) + \delta_t + \delta_d + \varepsilon_{dt}, \tag{3.4}$$

where Y_{dt} is one of the counts of combination clinical trials listed above, Generic Indicator$_{dt}$ is an indicator of whether drug d is within five years of experiencing generic entry at time t, δ_t is a year fixed effect to control for different rates of trialing over time, and δ_d is a drug d fixed effect to control for unobservable drug characteristics that affect the rate of trialing. We define the generic indicator starting 5 years before generic entry as combination trials may start in anticipation of generic entry, with results from the trial coming as generic entry occurs.

Table 3 summarizes the results. A drug is used in more combination trials on average in the five years leading up to generic entry (i.e., in anticipation) and after generic entry, compared to the period more than five years before generic entry, an 11.0% increase. The original owner runs fewer (-59.4% decrease) and publicly-funded innovators and other firms run more (7.9% and 41.7% increase, respectively). The increase in total trialing is driven by an increase in the probability of a newly generic drug being trialed with an on-patent drug, as shown in Table 4.

This fact clarifies that the ownership status of a given drug is critical not only for the original owner's clinical trial decisions, but also for other firms' and public innovators' decisions. Public crowd-out does not provide an explanation for this fact since overall more private trials are run with a drug after generic entry. The timing of combination innovation is shaped by the existing intellectual property protections, and inefficient investment by firms might result in delayed arrival of life-saving combination therapies to market.

To summarize, these facts demonstrate that firms are generally biased away from combination therapy trials, and in particular those trials that involve other firms' branded drugs. This is consistent with the stylized model, which together with these facts suggests inefficient underinvestment by firms in clinical trials for combination therapies because of market expan-

Table 3: Combination Trials and Generic Entry Regression

	Original Firm	Public	Other Firms	Total Trials
	(1)	(2)	(3)	(4)
Generic Indicator	-0.136	0.307	0.610	0.530
	(0.020)	(0.181)	(0.112)	(0.227)
Year Fixed Effects	Yes	Yes	Yes	Yes
Drug Fixed Effects	Yes	Yes	Yes	Yes
N	3,881	3,881	3,881	3,881
Mean Pre	0.229	3.894	1.462	4.815

Notes: Table shows estimates of β in Equation (3.4). Each column shows a different count of combination trials involving a drug: those run by the original firm that patented the drug (Column 1), publicly-funded researchers (Column 2), other firms (Column 3) and total trials (Column 4). Robust standard errors are in parentheses. Additional robustness checks are included in Appendix B.

sion externalities on other firms and positive spillovers to patients. We next quantify these externalities using an empirical model of demand and pricing of cancer drugs.

4 Static Model of Drug Consumer Surplus and Profits

In this section, we develop and estimate an empirical model of cancer drug demand and price setting, which we use to recover patient substitution patterns, consumer surplus, and firm profits. We estimate the model using microdata on patient drug usage and prices, and in Section 5 we use the estimated model to quantify the externalities associated with observed introductions of combination therapies.

4.1 Cancer Drug Demand

The main role of the demand model is to measure patient substitution patterns and willingness to pay for different regimens, which are important inputs into measuring the externalities from combination innovation. The model has two key features. First, it allows for complementarities between drugs by modeling demand over bundles of drugs (similar to Gentzkow, 2007), which we refer to as *regimens*, using insights from the medical literature (Chu and DeVita, 2019) to define these regimens. Allowing for complementarities across drugs is crucial for estimating the value of trialing combinations. Second, it allows for heterogeneity in substitution patterns by patient demographics, including type of insurer, which is important for predicting substitution patterns and price effects of combination innovation.

Table 4: Combination Trials and Generic Entry Regression

	With All Generic Total	With at Least One Brand Total
	(1)	(2)
Generic Indicator	0.028	0.502
	(0.038)	(0.208)
Year Fixed Effects	Yes	Yes
Drug Fixed Effects	Yes	Yes
N	3,881	3,881
Mean Pre	0.490	4.325

Notes: Table shows estimates of β in Equation (3.4) where Y_{dt} is either total combination trials with all generic drugs (i.e., all *other* drugs in the combination are generic) (Column 1) or total combination trials with at least one branded drug (Column 2). Robust standard errors are in parentheses.

At each time t, each cancer patient j makes a joint decision with her doctor over what drug regimen r, either single or combination, to take from the set of available regimens $\mathcal{R}_t$.[48] The patient j has cancer $c \in \mathcal{C}$ and will consider taking only regimens recommended for that cancer, which is subset a $\mathcal{R}_{ct} \subseteq \mathcal{R}_t$ of available regimens.[49] The patient j also has an insurance type $\iota \in \mathcal{I}$, where the set of insurance types is defined as

$$\mathcal{I} = \{\text{Medicare, Medicare + Medicaid, Private}\}.$$

Regimen r characteristics at time t for insurer ι are given by $(p_{rt\iota}, x_{rt}, \xi_{r\iota})$, where $p_{rt\iota}$ is the regimen price, x_{rt} is a vector of observable characteristics, and $\xi_{r\iota}$ is unobserved (to the econometrician) regimen quality.[50] Given that our demand system is over regimens, similar to Gentzkow (2007), this regimen quality term captures complementarity of the regimen components. Patient j's characteristics are given by $(z_{jt}, \nu_{jt}, \varepsilon_{jt})$, where z_{jt} is a vector of patient demographics, ν_{jt} is a patient unobservable, and ε_{jt} is a vector of patient-regimen preference shocks, where each element is distributed Type I extreme value. We suppress conditioning on cancer type c in what follows. We take t to be a month.

[48] By modeling this choice as a joint decision between patients, doctors, and in some cases, insurers, when interpreting the model's implied welfare, we make the assumption that these other agents are trying to maximize patient utility. In reality, the utility function is some combination of patient, doctor, and insurer utility. This assumption is common in work estimating demand for pharmaceuticals (e.g., Dubois and Lasio, 2018).

[49] In cases where a patient has more than one type of cancer, she will appear in each cancer's demand system. Generally, a patient just has one type of cancer in any given year.

[50] We allow regimen quality to differ across insurers as variation in cancer incidence and patient demographics among their respective populations may influence the effectiveness of specific regimens.

The utility u_{jrt} of patient j, who has insurer ι, from taking regimen $r \in \mathcal{R}_t$ at time t is given by the sum of a regimen-insurer mean utility term $\delta_{rt\iota}$, a patient heterogeneity term μ_{jrt}, and a patient-regimen preference shock ε_{jrt},

$$u_{jrt} = \delta_{rt\iota} + \mu_{jrt} + \varepsilon_{jrt}.$$

The regimen-insurer mean utility $\delta_{rt\iota}$ is given by

$$\delta_{rt\iota} = \alpha_\iota p_{rt\iota} + \xi_{r\iota} + \xi_{y(t)\iota} + \Delta\xi_{rt\iota},$$

where $\xi_{y(t)\iota}$ is a year fixed effect that captures changes in the quality of the outside option and $\Delta\xi_{rt\iota}$ is a structural error that captures unobserved demand shocks.[51] The patient heterogeneity component of utility μ_{jrt} is given by

$$\mu_{jrt} = \theta^z_{\iota 1} a_{jt} p_{rt\iota} + \theta^z_{\iota 2} a_{jt} \mathbf{1}_{r \text{ biologic}} + \theta^z_{\iota 3} a_{jt} \mathbf{1}_{r \text{ combo}} + \theta^z_{\iota 4} \nu_{jt} p_{rt\iota},$$

where age a_{jt} is an element of z_{jt}, $\mathbf{1}_{r \text{ combo}}$ is an indicator of whether regimen r is a combination regimen (rather than single-drug), $\mathbf{1}_{r \text{ biologic}}$ is an indicator of whether r contains at least one biologic drug,[52] and ν_{jt} is a random coefficient on price. Throughout, prices are normalized to be in thousands of dollars, and age is divided by 100.

We include a random coefficient ν_{jt} on price in the patient heterogeneity term to capture unobserved supplemental insurance, heterogeneity in insurance schedules, and other heterogeneity in regimen prices. We specify ν_{jt} to be a Bernoulli random variable, which takes the value of 1 with probability $\psi^\nu_{t\iota}$.[53] This probability is set to the average fraction of patients with low (instead of high) cost-sharing. For Medicare and dual-enrolled Medicare patients, $\psi^\nu_{t\iota}$ is the probability of having supplemental insurance, derived from annual aggregate data from the Medicare Current Beneficiary Survey (MCBS). For privately insured patients, $\psi^\nu_{t\iota}$ is the average fraction of patients who have reached their out-of-pocket maximum.[54]

The coefficient α_ι and patient heterogeneity coefficients $\theta^z_{\iota 1}$ and $\theta^z_{\iota 2}$ allow price sensitivity

[51] Important examples of demand shocks we do not explicitly model include drug shortages (negative shocks), which are becoming increasingly common for certain injectable drugs (Yurukoglu et al., 2017), and marketing of cancer drugs (a positive shock) to physicians (Carey et al., 2024).

[52] We do not include the individual terms (i.e., not interacted) $\mathbf{1}_{r \text{ combo}}$ and $\mathbf{1}_{r \text{ biologic}}$ as they are absorbed in the regimen fixed effect. Similarly, the mean effect of price is already included in $\delta_{rt\iota}$. Finally, we omit the mean effect of age.

[53] This specification is similar to "discrete-type" random coefficients models (e.g., Berry and Jia, 2010).

[54] In 2022, approximately 89% of Traditional Medicare beneficiaries had some form of supplemental coverage (Ochieng et al., 2024). In the Marketscan data, approximately 80% of claims for cancer drugs list the patient as already having hit her out-of-pocket maximum at the time of the claim.

to vary by insurance type.[55] This is motivated by the different out-of-pocket costs associated with different types of insurance and potential heterogeneity in price sensitivity that occurs through the insurer (via e.g., prior authorization) or doctor. Though some Medicare patients with supplemental insurance and privately insured patients may have low out of pocket costs for much of their drug usage, price sensitivity may also occur through doctors or insurers. For example, many chemotherapy and biologic drugs require prior authorization. Nevertheless, there is evidence that many patients face high out-of-pocket costs that may affect treatment decisions.[56]

The patient heterogeneity term allows patient substitution patterns to vary by patient characteristics and regimen characteristics, reflecting clear patterns in the data. For example, in the Medicare data, older patients tend to receive less expensive drugs, are less likely to receive regimens containing biologic drugs, and have a lower likelihood of taking combination therapies, even when controlling for cancer type. We estimate the parameters in the patient heterogeneity term by matching micro moments (discussed in detail in Section 4.4).

We define the outside option to be taking a drug regimen that does not appear in treatment guidelines. We discuss the construction of the outside option in Section 4.3. With this outside option, we take the decision to treat a patient with drugs rather than other means, such as surgery or radiation, as exogenous.[57] We normalize the utility of the outside option as $u_{i0t} = \varepsilon_{i0t}$.

The share of patients taking regimen r at time t conditional on insurance type ι is

$$s_{rt\iota}(p_{rt\iota}) = \int_{\nu}\int_{z} \frac{\exp\left(\delta_{rt\iota} + \mu_{jrt}\right)}{1 + \sum_{r' \in \mathcal{R}_t}\left(\exp\left(\delta_{r't\iota} + \mu_{jr't}\right)\right)} dz_{jt}\, d\nu_{jt}.$$

[55] Note that the price sensitivity coefficient α_ι can represent $\tilde{\alpha}_\iota \times \zeta_\iota$, where ζ_ι is the fraction of drug costs (i.e., from co-insurance, co-payments, or deductibles) that the patient pays.

[56] Narang and Nicholas (2017) documents significant out-of-pocket costs for Medicare patients with cancer for a range of types of supplemental insurance using data from the Health and Retirement Study: "$2116 among those insured by Medicaid, $2367 among those insured by the Veterans Health Administration, $5976 among those insured by a Medicare health maintenance organization, $5492 among those with employer-sponsored insurance, $5670 among those with Medigap insurance coverage, and $8115 among those insured by traditional fee-for-service Medicare but without supplemental insurance coverage." Furthermore, these OOP costs were on average 23.7% of household income. More generally, the "financial toxicity" of cancer is a growing concern (Smith et al., 2022). The American Cancer Society Cancer Action Network (2024) reports 47% of patients surveyed in their 2024 Survivor Views research panel have had medical debt related to their cancer, and 25% of patients delayed or skipped care to avoid further debt.

[57] A larger fraction of patients are taking cancer drugs over time (instead of exclusively other treatment modalities like radiation or surgery), so our analysis likely underestimates this market expansion effect of new drug innovations. Appendix A presents these trends. Accounting for an increasing fraction of patients taking drugs in the analysis would require us to model innovations in other treatment modalities, which is beyond the scope of this paper.

Let $M_{ct\iota}$ be the market size cancer type c patients at time t with insurance type ι and let M_{ct} be the market size of cancer type c at time t, summing over insurance segments. We describe the calculation of market size, regimen market shares, and regimen prices in detail in Section 4.3.

4.2 Cancer Drug Price Setting

The price setting model serves two key purposes. First, we use the model to estimate marginal costs of drug production, which are important inputs into calculating firm profits and externalities from innovation. Second, we estimate price setting conduct that enables predicting counterfactual drug prices after combination innovation.

We model drug price setting as simultaneous bilateral Nash bargaining between manufacturers and a single insurer in each year.[58] This single insurer serves as a stand-in for the private insurance market. A bargaining model captures the role of the insurer as an intermediary in determining drug prices for its relatively price inelastic beneficiaries. We assume gross drug prices p_t are bargained each year and that this gross price applies to both publicly and privately insured patients. Indeed, since 2005, maximum reimbursement rates for drugs covered by Medicare Part B are set to be the Average Sales Price (ASP) of the drug plus 6%, and thus the government does not directly negotiate with manufacturers over drug prices for its beneficiaries.

Prices p_t are the gross drug prices for privately insured patients, and individual patients may pay different amounts to receive the drug because of different insurance benefits. The difference between the gross price and the patient price contributes to insurer costs. Some of these costs are paid by the government (e.g., the cost after coinsurance for Medicare patients) and some are paid by private insurers (e.g., those for privately insured non-Medicare beneficiaries).

The surplus of the private insurer, denoted by ι_{private}, in the bargaining problem is a weighted sum of consumer surplus for its beneficiaries and drug costs paid by the insurer (following, e.g.,

[58] We abstract from dynamic pricing concerns, including those created by Medicare Part B's lagged-price reimbursement contracts (Acquatella et al., 2023).

Capps et al., 2003, Gowrisankaran et al., 2015, Dafny et al., 2023):[59]

$$V_{t\iota_{\text{private}}}(\mathcal{R}_t, p_t) = \rho \sum_{c \in \mathcal{C}} CS_{t\iota_{\text{private}}}(\mathcal{R}_t, p_t, c) - \sum_{c \in \mathcal{C}} TC_{t\iota_{\text{private}}}(\mathcal{R}_t, p_t, c),$$

where ρ is the relative weight the insurer places on consumers relative to its own costs. The idea behind this objective function is that the insurer sets premiums to extract the expected difference between surplus for its consumers net of insurer costs in a first-stage problem that we do not model.

The weight ρ, similar to the welfare weight in Gowrisankaran et al. (2015), may be different than 1 for a number of reasons. For example, if consumers underestimate their drug costs (Abaluck and Gruber, 2011) or overestimate their surplus from taking drugs (e.g., overestimating the probability of requiring chemotherapy), then ρ may be greater than 1. We microfound these reasons in Appendix D.

Consumer surplus for the private insurer's patients with cancer c given regimens $\mathcal{R}_{ct}$ and prices p_t at time t is given by

$$CS_{t\iota_{\text{private}}}(\mathcal{R}_t, p_t, c) = -M_{ct\iota_{\text{private}}} \int_\nu \int_z \frac{1}{\alpha_{\iota_{\text{private}}} + \theta^z_{\iota_{\text{private}}1} a_{jt} + \theta^z_{\iota_{\text{private}}4} \nu_{jt}} \log\left(1 + \sum_{r \in \mathcal{R}_{ct}} \exp\left(\delta_{rt\iota_{\text{private}}} + \mu_{jrt}\right)\right) dz_j d\nu_j.$$

Total insurer costs for the private insurer's patients with cancer c are

$$TC_{t\iota_{\text{private}}}(\mathcal{R}_t, p_t, c) = M_{ct\iota_{\text{private}}} \sum_{r \in \mathcal{R}_{ct}} (1 - \zeta_{\iota_{\text{private}}}) p_{rt} s_{rt\iota_{\text{private}}}(p_t),$$

where $\zeta_{\iota_{\text{private}}}$ is the expected patient payment fraction (i.e., combining any co-payments, co-insurance, or deductibles) from taking a regimen.

For each firm $f \in \mathcal{F}$, let $f_t \subset \mathcal{D}$ denote the set of drugs owned by the firm at time t. Firm f's profits at time t are

$$\pi_{ft}(p_t) = \sum_\iota \sum_{c \in \mathcal{C}} M_{ct\iota} \sum_{d \in f_t} \sum_{r \in \mathcal{R}_{ct}} (p_{dt} - mc_{dt}) s_{rt\iota}(p_t) \mathbb{1}[d \in r],$$

[59] We assume the consumer surplus of privately insured patients is the sum of two components. First, the consumer surplus of patients under the age of 65, which comes from Marketscan. Second, the consumer surplus of patients enrolled in Medicare Advantage. We do not have data on the claims of these patients, so we assume the demand estimates for this group are the same as Traditional Medicare beneficiaries. Our Marketscan data end in 2013, so we assume the privately insured demand primitives remain constant after this date.

where we assume that firms have constant marginal costs of production mc_{dt} for each of their drugs. This profit function sums across profits from each insurance segment ι, which includes both privately and publicly insured patients. We assume that a firm only "owns" a drug when it is currently patented, and we do not include generic price setting in the model. Regimens including generic drugs are still in the demand system, but the price of a generic drug is fixed at the average price we observe for that drug in the data each year.[60]

The drugs in our sample can be classified into two types: small molecules and biologic drugs. Small molecules are manufactured from chemicals and generally considered to have very low marginal costs of production. Biologic drugs are generally manufactured from living cells, and the costs associated with production can be substantial. We will assume that marginal costs are zero for all small molecule drugs, but we allow for and estimate positive marginal costs for biologic drugs.[61,62]

The prices p_{ft} of drugs produced by firm f at time t satisfy

$$\max_{p_{ft}} \quad \pi_{ft}(p_t)^{\gamma}\left[\mathrm{V}_{t\iota_{\text{private}}}(\mathcal{R}_t, p_t) - \mathrm{V}_{t\iota_{\text{private}}}\left(\mathcal{R}_t \setminus \mathcal{R}_{ft}, p_t\right)\right]^{1-\gamma}.$$

The parameter γ gives the bargaining weight of a firm relative to the insurer. The insurer's outside option is the value when drugs from a given manufacturer are not available, holding all remaining drug prices fixed but allowing demand to adjust. The manufacturer's value is simply total profits, and the manufacturer's outside option is zero.[63]

4.3 Market Shares and Prices

We measure cancer regimen usage and prices by combining data from Medicare (for publicly insured patients) and Marketscan (for privately insured patients), as described in Section 2.2. We use data from both publicly and privately insured patients for three reasons. First, in order to estimate the value of combination innovation, we must estimate a demand system for cancer drugs that is representative of the target market, which we define as the US population. The Medicare data contain relatively few individuals under the age of 65, and may not capture

[60] While we do not model generic pricing, we allow generic drug prices to adjust exogenously as the number of generic competitors changes.

[61] There is some evidence (Hill et al., 2016) that even relatively expensive small molecule drugs like small molecule inhibitors have relatively low marginal costs of production.

[62] We do not consider advertising (such as detailing) to be a marginal cost. Both types of drugs may accrue significant costs from detailing, though whether these costs are marginal is unclear.

[63] Our specification of the bargaining model assumes that all the profits associated with the drug go to the manufacturer, rather than dividing profits between manufacturers and providers that deliver the drugs (e.g., hospitals). Hospitals likely charge positive markups on drugs (Robinson et al., 2021, Robinson et al., 2024), and we abstract from the split of profits between hospitals and manufacturers.

drug usage patterns for cancers that skew younger or have different recommended treatments for younger patients. Second, our model of cancer drug price setting must match important institutional features. Prices for drugs in Medicare Part B are set based on average national sales prices of the drugs, including sales to privately insured patients. Third, a concern with estimating price elasticities of demand from the Medicare data is the presence of unobserved supplemental insurance (Medigap). We allow for unobservables to affect price sensitivity, but use the privately insured patients to benchmark the price elasticities we estimate in the Medicare data.

To identify patients with a particular cancer in a year in the Medicare data, we combine claims from the inpatient, outpatient, and carrier (professional provider service) fee-for-service files. For the Marketscan data, we combine claims from the outpatient, inpatient services, and inpatient admissions files. We classify a patient has having a particular cancer in a given year if she has at least one claim (line) with a primary diagnosis code of that cancer, where we make a crosswalk between diagnosis codes (ICD9 and ICD10) and types of cancers in Chu and DeVita (2019). The vast majority of cancer drugs are delivered in a clinical outpatient setting and thus covered by Part B for Medicare beneficiaries and medical benefits for privately insured patients (there is a small subset of regimens that include prescription drugs that would be included in Part D plans for Medicare beneficiaries or pharmacy benefits for privately insured patients).[64]

Calculating regimen usage is complicated by the fact that combination regimens are typically not packaged together (and therefore do not have their own billing codes, and instead must be identified via the usage of component drugs in microdata) and drugs in the regimen are taken over the course of many days or weeks. To assign patients to regimens, we use the following algorithm. For each year and cancer, we subset to patients who we identify to have that cancer in that year. We further subset to patients taking at least one of the drugs in a recommended regimen for that cancer in that year. The cardinality of this set of patients (scaled by the corresponding sampling weights) is the size of the market. We pick a number of days N, where $N = 30$ is our baseline assumption. For each patient and each day she takes a cancer drug, we make a list of all drugs she takes N days before or N days after the current day. We assign the patient to the largest (in terms of number of component drugs) regimen she takes during that window, if any.[65] For days the patient does not take drugs but are within N days

[64] For Medicare beneficiaries, enrollment in Part D is voluntary and thus we do not observe usage of prescription drugs for patients who elect to not enroll in Part D. Furthermore, Part D was created in 2006, so we do not see usage for these drugs before 2006. The Marketscan data include prescription drug benefits in all years of our sample.

[65] For example, suppose the set of recommended regimens for a cancer is given by $\{\{A,B,C\},\{A,D\},\{A,C\}\}$. Suppose the patient takes drugs A,B,C within N days of a date τ. The algorithm would assign the patient to regimen $\{A,B,C\}$ (not regimen $\{A,C\}$) on date τ. If the patient takes drugs A,B,C,D within N days of date τ the

before or after a day she does and is assigned to a particular regimen, we "fill in" these days with the closest (in terms of days) regimen.[66]

We calculate each regimen's market share at a monthly level, where the numerator is the number of patient-days taking a given regimen in a month, and the denominator is the number of patient-days taking any drug for that cancer in a month. A regimen's price is the average (over patient-days assigned to that regimen) total spending on component drugs during the rolling window. This regimen assignment procedure performs well, and patients take relatively few "extra" drugs, less than .3 on average, not included in their regimen (but included in other recommended regimens for that cancer) during each N day window.[67] The average share of the inside option (taking one of the recommended regimens) is 0.77 for the Medicare dataset and 0.76 for the Marketscan dataset.

There is both observed and unobserved regimen price dispersion across patients. In the Medicare and Marketscan datasets, there is observed priced dispersion because of variation in quantities of component drugs taken by patients and provider markups.[68] For privately insured patients, there is observed price dispersion in the patient's financial responsibility (the sum of deductibles, co-pays, and co-insurance). For Medicare beneficiaries, there is additional price dispersion because of Medicaid dual enrollment and private supplemental insurance (Medigap) plans, the latter of which we do not observe. In our analysis, we abstract away from price dispersion due to differences in quantities of component drugs and provider markups by considering average prices across all patients, and we account for both observed and unobserved price incidence on patients in our demand model.

We obtain patient characteristics (e.g., age) from the enrollment files in each dataset. We use aggregate data from the Medicare Current Beneficiary Survey to calculate rates of supplemental insurance over time.

We define the market size of a particular insurance segment, cancer type, time to be the total number of patients in the US taking drugs for that cancer at time t. We scale the number of patients observed in the Medicare data to match the total population of traditional Medi-

algorithm would still assign the patient to regimen $\{A, B, C\}$ at date τ, denoting drug D as an "extra drug."

[66] More precisely, suppose a patient takes drugs for regimen r and is thus assigned to regimen r on dates she takes the component drugs. Suppose these dates are January 20th and 25th. The algorithm would "fill in" dates and assign the patient to take regimen r for N days before January 20th, between January 20th and 25th, and for N days after January 25th. If a patient is assigned to more than one regimen on different dates, the algorithm fills in the remaining dates using the closest (in terms of days) regimen.

[67] See Appendix A.

[68] One important source of unmodeled price dispersion is the 340B drug pricing program (see Levengood et al., 2024 for a review of its effects on drug access and providers), which provides certain healthcare organizations (those serving many uninsured or low-income patients) with discounts on outpatient drugs.

care and Medicare Advantage patients, and we scale the number of patients observed in the Marketscan data to match the remainder of the US population.

Table 5 presents summary statistics of drug usage, prices, and patients for the Medicare and Marketscan data. We include cancers with at least one thousand Traditional Medicare patients in our sample taking drugs for that cancer per year on average, leaving 19 cancers. The average total market size (summing across all cancers) is 823,839 Medicare patients and 549,694 Marketscan patients, with an average 43,360 Medicare patients per cancer and 28,931 Marketscan patients per cancer. Additional summary statistics about patient regimen usage are presented in Appendix A.

4.4 Estimation and Identification

Demand: We estimate the demand model using a generalized method of moments (GMM) estimator, combining aggregate sample and micro moments, following the method of Berry et al. (1995) and best practices in Conlon and Gortmaker (2020, 2023). We use a nested fixed point algorithm to optimize over nonlinear parameters governing patient heterogeneity, and we concentrate out the linear parameters. We estimate the demand model separately for each insurance type. We approximate the distribution of patient demographics z_i by creating age bins by insurance type.[69]

We use two types of instruments for regimen prices. The first is a baseline price-weighted average of the number of manufacturers producing drugs in the regimen interacted with indicator variables for the baseline revenue share bin of the regimen. More precisely, this instrument b_{rt}^{D1} for regimen r and time t is given by

$$b_{rt}^{D1} = \frac{\sum_{d \in r} p_{d1} n_{dy(t)}}{\sum_{d \in r} p_{d1}} \times h_1(r),$$

where p_{d1} is the (median) price of drug d in the first period it appears in our data (either the first period of our data if the drug was already being marketed, or the price the first year it is marketed), $n_{dy(t)}$ is the number of manufacturers that produce drug d in year $y(t)$, and $h_1(r)$ an indicator for the baseline bin of the revenue share of the regimen (calculated across all cancers), where we use three bins in our baseline specification. Intuitively, an increase in the

[69] We do not impose that the regimen fixed effects are the same across insurance types. It is possible that the quality of the regimen for a patient depends on patient demographics, so allowing the regimen fixed effect to vary across insurance type captures this heterogeneity. In the dynamic model in Section 6, we will make a simplifying assumption that regimen quality is drawn from a distribution that represents average quality over different insurance types. We find that the fixed effects are highly correlated, making this assumption reasonable given the patterns in the data (see Appendix C). An alternative assumption would be to estimate the demand model jointly for different insurance types and impose common regimen fixed effects.

Table 5: Cancer Drug Usage, Price, and Patient Summary Statistics

Cancer	Patients			Shares		Regimens		Price
	Total	Drug Fraction	Market Size	Inside	Combo	Total	Combo	$
Medicare								
Prostate	202,962	0.2	293,025	0.97	0.03	26	11	942
Colorectal	80,160	0.17	76,634	0.83	0.64	35	27	7,127
Head and Neck	73,280	0.05	21,252	0.59	0.19	20	12	950
Bladder	52,901	0.09	25,986	0.44	0.3	20	12	1,268
Breast	48,581	0.14	41,656	0.94	0.14	63	42	2,997
Non-Hodgkin Lymphoma	47,019	0.33	94,912	0.61	0.09	33	18	6,842
Non-Small Cell Lung	32,537	0.33	67,184	0.82	0.43	47	28	3,561
Malignant Mesothelioma	23,244	0.2	26,302	0.39	0.12	12	7	2,440
Chronic Lymphocytic Leukemia	20,030	0.13	15,360	0.97	0.19	22	10	6,179
Hepatocellular	18,235	0.24	24,370	0.61	0.17	10	3	2,968
Endometrial	17,240	0.11	9,399	0.74	0.45	15	10	720
Multiple Myeloma	16,358	0.2	15,049	0.96	0.24	27	19	9,814
Biliary Tract	16,032	0.27	26,286	0.42	0.06	8	5	1,787
Brain	14,521	0.16	12,391	0.39	0.03	9	4	3,710
Hodgkin Lymphoma	14,192	0.22	17,554	0.52	0.04	14	6	7,891
Ovarian Epithelial	13,741	0.32	26,336	0.89	0.47	24	11	2,456
Pancreatic	11,854	0.25	14,817	0.93	0.24	12	9	1,658
Gastric	7,981	0.19	9,054	0.67	0.46	18	14	806
Esophageal	4,005	0.29	6,272	0.62	0.25	9	7	349
Mean (patient weighted)	37,625	0.19	43,360	0.77	0.21	27	16	3,001
Marketscan								
Prostate	55,842	0.08	42,481	0.99	0.04	25	12	1,437
Colorectal	31,978	0.25	69,599	0.87	0.63	32	26	13,416
Head and Neck	31,160	0.06	21,292	0.6	0.23	18	12	2,751
Bladder	15,282	0.07	9,617	0.49	0.4	15	12	5,125
Breast	48,604	0.19	83,918	0.98	0.16	57	38	4,902
Non-Hodgkin Lymphoma	32,120	0.29	81,790	0.45	0.13	28	17	7,922
Non-Small Cell Lung	13,092	0.4	41,438	0.87	0.51	33	21	6,195
Malignant Mesothelioma	11,948	0.23	24,252	0.35	0.13	10	7	5,360
Chronic Lymphocytic Leukemia	5,909	0.15	8,202	0.97	0.31	19	8	3,299
Hepatocellular	9,182	0.31	25,460	0.68	0.07	8	3	6,683
Endometrial	11,095	0.1	9,778	0.82	0.34	15	10	2,077
Multiple Myeloma	5,714	0.18	9,215	0.85	0.29	21	15	7,141
Biliary Tract	8,478	0.38	27,286	0.65	0.11	9	6	6,096
Brain	12,542	0.16	16,895	0.73	0.07	10	5	7,265
Hodgkin Lymphoma	15,790	0.2	28,606	0.24	0.12	10	4	4,867
Ovarian Epithelial	12,336	0.23	25,267	0.91	0.48	22	11	5,242
Pancreatic	4,242	0.31	11,683	0.95	0.29	12	9	5,984
Gastric	3,502	0.29	8,665	0.74	0.52	18	16	4,886
Esophageal	1,568	0.37	4,250	0.64	0.41	10	9	3,251
Mean (patient weighted)	17,389	0.19	28,931	0.76	0.23	26	17	5,411

Notes: Table shows summary statistics for Medicare patients (top panel) and Marketscan patients (bottom panel) by cancer for the 19 cancers included in our sample. The table is sorted in descending order of the median (over years) number of Medicare patients we observe with that cancer. Patients Total is the median (over years) number of patients we observe in each dataset that have a diagnosis code for a particular type of cancer in a year. The Medicare data is a 20% sample of beneficiaries, and we observe claims for traditional Medicare beneficiaries. The number of individuals included in the Marketscan dataset grows considerably during the sample period, as discussed in the main text. Drug Fraction is the median (over years) fraction of those patients that receive at least one cancer drug in that year. Market Size is the median (over years) market size we consider for each cancer, defined to be the number of patients taking drugs for that cancer. We calculate this measure by subsetting to patients who take drugs for that cancer and apply sampling weights. Shares Inside is the median (over months and years) sum of market shares of recommended regimens in Chu and DeVita (2019), where the market share for a regimen is calculated for each month as the number of patient-days (within a particular month) assigned to that regimen divided by the total number of patient-days taking drugs (for a particular cancer-month). Combo is the median (over months and years) sum of market shares of recommended combination regimens in Chu and DeVita (2019). Regimens Total is the total number of recommended regimens we observe taken for that cancer, and Combo is the number of combination recommended regimens we observe taken for that cancer. Price is the median (over regimens, time windows, and years) total price, in dollars, of taking a regimen for that cancer for the N (= 30) day rolling window. The last row in each panel gives a patient weighted mean (except for total patients) of each column.

value of the instrument suggests greater generic entry at t, which we expect to reduce the price p_{rt} of the regimen r. We interact with baseline regimen share bin to allow the effect of generic entry to vary flexibly based on size (determined as baseline revenue share) of the regimen.

The second instrument is a baseline price-weighted average of the time relative to patent expiry (measured in years) of drugs in the regimen interacted with indicator variables for the baseline revenue share bin of the regimen. Time before patent expiry is coded as negative values. More precisely, this instrument b_{rt}^{D2} for regimen r and time t is given by

$$b_{rt}^{D2} = \frac{\sum_{d \in r} p_{d1} g_{dt}}{\sum_{d \in r} p_{d1}} \times h_1(r),$$

where g_{dt} is the time since generic entry time of drug d at time t.[70] The idea for this instrument is similar to the first.

To target the interactions between observable patient characteristics and regimen characteristics, we match the covariance between (i) regimen prices and patient age (ii) regimen combination status and patient age (iii) regimen biologic status and patient age. Micro moment targets and patterns are discussed in Appendix C.

Price Setting: Given estimates of patient demand for cancer treatment regimens, we then estimate the price setting model. We specify the marginal costs of biologic drug d at time t as $mc_{dt} = \overline{mc}_d + \eta_{dt}$, where $\overline{mc}_d$ is the baseline cost of drug d and η_{dt} is a structural error unobserved by the econometrician that represents changes in production costs over time (e.g., changes in input prices, shocks to manufacturing). We set $mc_{dt} = 0$ and $\eta_{dt} = 0$ for all non-biologic drugs.[71] We also assume that there is one bargaining weight γ for all drugs. Therefore, the parameters to be estimated are γ, ρ, and one baseline marginal cost per biologic drug.

This setting has the standard identification problem of bargaining models with unobserved costs. For example, observing high prices could be either because costs are high and the manufacturer bargaining weight is low, or because costs are low and the bargaining weight is high. To separately identify the bargaining weight, costs, and consumer surplus weight, we follow the outline of the identification argument in Lee et al. (2021). We construct instruments that shift demand (and are uncorrelated with demand except through the effects on prices) and

[70] We allow g_{dt} to be negative before generic entry rather than bottom coding it at 0 for all values of t before generic entry as this captures a trend in the price (often increasing) before generic entry. For example, suppose drug d had generic entry in 2005. Then g_{dt} is -1 in 2004, 0 in 2005, and 1 in 2006.

[71] An alternative assumption we could make is to assume mc_{dt} is the lowest price we see in the data once the drug has generic entry. For small molecules that never have generic entry during our sample period, we could calculate the average markup for small molecules that have generic entry and set costs to match this average markup.

use them as surplus shifters. Movement in prices in response to these shifters will be informative about the bargaining weight and costs. For example, suppose there is a positive shock to demand for a particular drug. If the insurer has all the bargaining power, the negotiated drug price will equal marginal cost, and there will not be a price change in response to the positive demand shock. If instead the manufacturer has all the bargaining power, then we expect to observe increases in price.

We construct drug demand shifts for a focal drug d by calculating how many manufacturers are marketing *other* drugs used in regimens containing the focal drug. More precisely, we construct this surplus shifter b_{dt}^{S1} for drug d at time t as

$$b_{dt}^{S1} = \sum_{r \in \mathcal{R}_{ct} : d \in r} \frac{\sum_{d' \in r \setminus \{d\}} p_{d'1} n_{d'y(t)}}{\sum_{d' \in r \setminus \{d\}} p_{d'1}},$$

using the same data on baseline prices and number of generic entrants as in the demand instrument construction. Intuitively, an increase in the instrument suggests generic entry in drugs that are complementary to d, likely lowering their prices $p_{d't}$ and hence increasing demand and raising the surplus to be split between the manufacturer of d and the insurer.

We simplify estimation by optimizing only over the bargaining weight γ and consumer surplus weight ρ. For biologics, given a guess of γ and ρ, the vector of biologic costs (mc_{dt}) can be solved in closed form via the bargaining first-order conditions. Assuming the error terms (η_{dt}) are mean independent of the baseline costs allows us to calculate the baseline costs $\overline{mc}_d$ for each drug d in closed form. Then, we can calculate moments of the form $\mathbb{E}\left[\eta_{dt} B_{dt}^S\right] = 0$ and estimate via GMM, while only optimizing over γ and ρ. Here, B_{dt}^S is a vector of instruments we use for drug d, where $B_{dt}^S = b_{dt}^{S1} \times \mathbf{1}_{d'=d}$ (i.e., interacted with an indicator for each drug).

4.5 Estimation Results

Demand: Table 6 shows estimated parameters and summary statistics of own-price elasticities of demand. Each column presents estimates for a different insurance segment: Medicare (not dual-enrolled), Medicare dual-enrolled in Medicaid, and privately insured (Marketscan). With regimen price instruments, we estimate a median own price elasticity of demand of -1.16 for Medicare, -0.17 for Medicare dual-enrolled, and -2.49 for Marketscan. Previous papers estimating Medicare patient demand for cancer drugs report own-price elasticities of demand ranging between $-.7$ and -2.7 (Jung et al., 2017, Song et al., 2017),[72] and our median elasticity for Medicare patients falls within this range.

[72] Jung et al. (2017) estimate price elasticities for cancer drugs covered under Medicare Part D. Song et al. (2017) estimate price elasticities for colorectal combination therapies.

The ranking of these elasticities across insurance types is what we would expect based on the price incidence of drugs on patients and the price sensitivity of insurers. Medicare dual-enrolled patients face little to no cost-sharing, and we estimate that they are the most price inelastic group. Medicare patients likely face the highest cost-sharing depending on supplemental insurance but do not face prior authorization for drug usage. And while privately insured patients in our sample typically hit the out-of-pocket maximum relatively quickly after diagnosis, prior authorization is often required, so that the relative elastic demand curve reflects the price sensitivity of the insurer.

Similar to Gentzkow (2007), regimen fixed effects are informative about the complementarity of component drugs. We find that combination regimens often have higher fixed effects than single-agent regimens of the components. These patterns are detailed in Appendix C.

The model's implied micro moments are shown in Rows 15-18. The model fit is reasonable, with the model implied micro moments having a similar magnitude to the targets. Appendix C presents additional estimation results.

Price Setting: We estimate a bargaining weight of 0.69 and a consumer surplus weight of 8.04. These parameter estimates are similar to those estimated in other health contexts. Dafny et al. (2023) estimates a bargaining weight of .69 in a similar bargaining problem over the prices of drugs for multiple sclerosis. Gowrisankaran et al. (2015) estimates a weight on consumer surplus of $2.79 - 6.69$, depending on the specification, in a similar bargaining problem over hospital prices.[73] For these parameters, the mean markup over marginal cost for biologic drugs is .25, with a standard deviation (across drugs and years) of .44. While there is limited information about the accounting manufacturing costs of biologic drugs, estimates of the price declines after biosimilar entry range from 1-25%, suggesting our estimated markups fall in a reasonable range.[74] We present robustness checks of the estimated bargaining weight and implied markups to different values of ρ in Appendix D.

5 Externalities from Combination Innovation

This section estimates externalities from successful drug regimen innovation, comparing the distinctive externalities that arise from combination innovation to externalities present in standard innovation settings. To calculate the externalities for regimens introduced in the data,

[73] Our estimate falls within the confidence interval of their estimate of 6.69 with standard error 5.53.

[74] Price et al. (2015) reports European manufacturers expending between $100 million to $250 million to reverse engineer biologic drugs, with prices dropping by about 25% after biosimilar entry. In the US, estimated price declines range from 5-9% percentage points (Frank et al., 2022, Stern et al., 2021). Compared to the US, competition resulting from biosimilar entry in Europe is much stronger. For comparison, after generic competitors enter, small-molecules may see a decline in price of over 95% (Conrad and Lutter, 2019).

Table 6: Demand Model Estimates

	Medicare	**Medicare Dual**	**Marketscan**
	(1)	(2)	(3)
α_ι	-0.489	-0.311	-0.628
	(0.012)	(0.006)	(0.047)
θ_1^z (age × price)	0.0867	0.2437	-0.0405
	(0.02389)	(0.01525)	(6.0e-5)
θ_2^z (age × biologic)	0.0039	0.0078	0.0101
	(0.00083)	(0.00059)	(0.00091)
θ_3^z (age × combo)	0.0014	0.0	-0.0182
	(0.00072)	(0.00028)	(0.0002)
θ_4^z (r.c. × price)	0.0122	0.0497	0.0028
	(0.00013)	(0.0002)	(0.00088)
Median Own Price Elasticity	-1.156	-0.175	-2.492
Median Own Price Elasticity (no price ins)	0.068	-0.076	0.114
Median Own Price Elasticity Logit	-1.1	-0.454	-5.402
Age Price Covariance	-0.0361	-0.0375	0.0006
Age Biologic Covariance	-0.0019	-0.0022	0.0008
Age Combo Covariance	0.0011	-0.0008	-0.0008
Regimen FE	Yes	Yes	Yes
Year FE	Yes	Yes	Yes

Notes: Table shows parameters and summary statistics of the demand system, estimated separately for each insurance type in each column. Column (1) is traditional Medicare beneficiaries, Column (2) is traditional Medicare patients who are dual-enrolled in Medicaid, and Column (3) is privately insured patients in Marketscan. The α row shows the price sensitivity coefficient. Rows θ_1^z through θ_4^z are the patient heterogeneity coefficients. Rows Median Own Price Elasticity through Median Own Price Elasticity Logit are own price elasticities of demand for the baseline, no price instruments, and Logit specifications (using the same price instruments, but without demographic heterogeneity), respectively. Rows Age Price Covariance through Age Combo Covariance show the estimated micro moments. The final two rows indicate the inclusion of regimen and year fixed effects. Standard errors are in parentheses.

Table 7: Bargaining Model Estimates

Variable	Mean	Standard Error (Deviation)
Bargaining Weight γ	0.69	0.29
Consumer Surplus Weight ρ	8.04	4.41
Markup over Marginal Cost (Biologics)	0.25	0.44

Notes: Table shows parameter estimates and summary statistics of the bargaining model. The first row is the estimated bargaining weight. The second row is the estimated weight on consumer surplus in the insurer's objective function. Standard errors for each of these parameters are given in the second column. The final row computes the mean and standard deviation markup over marginal cost for biologic drugs.

we augment the stylized model in Section 3.1 to incorporate additional details of our setting and parameterize it using the demand and price setting models estimated in Section 4.

5.1 Measuring Externalities after Regimen Introduction

We start by outlining how we measure innovation externalities after regimen introduction, extending the stylized model in Section 3.1 to incorporate fiscal externalities on the insurer. Suppose firm f introduces new regimen r^+ at time t. Since consumers do not pay the full price of treatment, we must add the change in total costs of the insurer (ΔTC) to the changes in consumer surplus and total profits to recover the change in welfare at time t:[75]

$$\Delta W = \underbrace{\text{CS}\left(\mathcal{R} \cup r^+, \tilde{p}\right) - \text{CS}\left(\mathcal{R}, p\right)}_{\Delta\text{CS}} - \underbrace{\left[\text{TC}\left(\mathcal{R} \cup r^+, \tilde{p}\right) - \text{TC}\left(\mathcal{R}, p\right)\right]}_{\Delta\text{TC}} + \sum_{d \in \mathcal{D}} \underbrace{\pi_d\left(\mathcal{R} \cup r^+, \tilde{p}\right) - \pi_d\left(\mathcal{R}, p\right)}_{\Delta\pi_d}. \tag{5.1}$$

As in the stylized model, $\tilde{p}$ is the observed price vector after introduction of the new regimen r^+, while p is the counterfactual price vector without r^+. Firm f internalizes only the change in its own profits after regimen introduction, so the net externality is now

$$\text{Net Externality}_{\mathcal{R}^+} = \Delta\text{CS} + \Delta\text{TC} + \sum_{d \notin f} \Delta\pi_d. \tag{5.2}$$

This definition differs from (3.2) only because of the new insurer cost term.

The expressions above describe the externalities at the time of introduction t, but profit externalities will persist throughout the exclusivity periods of the affected drugs, while the consumer surplus and insurer cost externalities will persist until demand for the new regimens

[75] Throughout this section, we suppress the dependence of all values on t.

falls to zero.[76] Extending the calculation of these externalities requires assumptions on the future path of innovation, which we address with the dynamic model in Section 6. Here we focus instead on calculating each externality at the time of introduction, recognizing that this likely understates the magnitude of the full dynamic externality because of gradual adoption dynamics.

We observe 131 combination therapy introductions and 92 single-agent therapy introductions between 1999 and 2019.[77] Table 8 summarizes these events. Of the combination therapy introductions, 66 contain at least two branded drugs owned by different firms (at the time of introduction). The remaining 65 either consist of at least two branded drugs owned by the same firm or at most one branded drug (e.g., a branded drug in combination with a generic drug).

A significant fraction—85%—of trials for the combinations that are introduced are sponsored by public innovators. These publicly-funded trials are likely to generate positive profit externalities on firms (as we demonstrate below), but may overstate these externalities compared to a counterfactual scenario where a firm conducts the trial itself (since the firm would own at least one drug in the regimen). To separately identify public spillovers and likely externalities arising from private innovation of combinations, we compute the effects of new combination introductions using two methods. For method 1, we calculate the externalities from new combination introductions from the perspective of each firm that would earn positive profits from the trial—that is, firms owning at least one branded drug in the combination. This approach allows us to leverage the publicly funded trials we observe to estimate externalities over a broad set of combinations. For method 2, we compare these results with estimates of externalities based on the actual innovator who conducted each trial in our data, analyzing publicly and privately funded trials separately. The former set is informative about public spillovers, while the latter set show realized externalities for the selected set of combinations that firms trial.

For each approach, we compute each term in the net externality definition (5.2) by introduction event. As in the stylized model, we decompose the net profit externality component into business stealing, market expansion, and price adjustments. We use the estimated demand and bargaining models to simulate these changes the year after entry of a particular regimen. We hold all other primitives constant.

[76] There will also be effects on generic drugs, but significantly smaller given that prices for generic drugs are substantially lower than branded drugs.

[77] There are more entry events that occur according to guidelines such as Chu and DeVita (2019), but not all regimens included the treatment guidelines are taken in the Medicare or Marketscan data.

As discussed in Section 3.1, several factors prevent us from calculating the regimen introduction externalities directly from the data. First, measuring the change in consumer surplus requires an estimated demand model. Measuring profit changes also requires marginal costs, which we estimate from the bargaining model. Second, there are often multiple regimen introductions in each year for a given cancer, which prevents us from observing the post-introduction prices that would prevail upon introduction of a single regimen. Additionally, idiosyncratic events including patent expiry or generic entry also affect drug prices at each time, again contaminating our observation of post-introduction prices. We use the bargaining model to compute post-introduction prices holding all other primitives constant.

Finally, it is important to note that our estimates of the externalities are computed for the set of regimens that were ultimately introduced, which likely implies selection on being privately worth trialing for the innovator (whether public or private), among other unobserved factors.

5.2 Estimates of Externalities after Regimen Introduction

Table 8 summarizes the externalities after single-drug and combination introduction, computed from the perspective of each firm that would have earned positive profits from that new regimen (firms with at least one branded drug in the combination), i.e., using method 1. We show effects separately for three types of regimens: single drugs, combinations with at least two different firms' branded drugs, and all other combinations.

The introduction of single drugs, for which there is no market expansion effect, results in large business stealing effects on other drugs (not owned by the trial sponsor) on average: negative $40 million per year per new drug. For combinations with at least two firms' branded drugs, market expansion dominates business stealing on average, with the sum of these effects averaging $27 million per year per combination. These externalities are significant compared to the own-profit effect of introducing the combination, which averages $33 million per year. Extrapolated over the average patent length of affected drugs implies positive externalities upwards of $200 million over the life-cycle of each new combination therapy. Figure 5 shows the distribution of the sum of business stealing and market expansion by regimen entry event, where combinations with at least two firms' branded drugs are shown in red and single-drugs are shown in gray. This sum is positive for approximately 80% of combination entry events, indicating that the market expansion effect dominates the business stealing effect.

All types of new regimens also have positive spillovers on consumers and negative spillovers on insurers, and the price adjustment terms in the profit change decomposition are relatively small in magnitude. In sum, the net externality is positive on average for each type of new

Table 8: Average One-Year Externalities by Regimen Type

	Regimen Type		
	Single Drug	**$\geq$ 2 Firms' Branded**	**Other Combinations**
	(1)	(2)	(3)
# Events	92	66	65
Fraction Firm Trials		0.15	0.15
Business Stealing + Market Expansion ($M)	-40.2	27.01	-16.77
Price Adjustment ($M)	-1.9	-0.48	-1.12
Δ CS ($M)	92.77	31.02	35.73
Δ TC ($M)	16.22	23.7	19.79
Net Externality ($M)	6.04	34.65	3.13
Fraction Positive Net Externality	0.43	0.9	0.6
Firm Profit (Innovator) ($M)	58.18	32.58	26.83

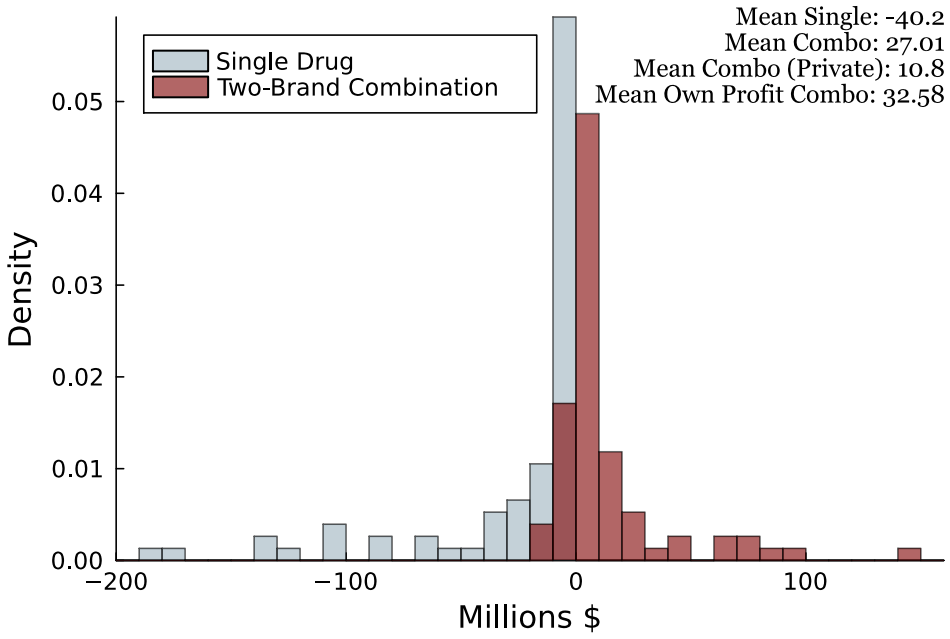
Notes: Table shows summary statistics and estimates of externalities separately for single drugs (1), combinations with at least 2 firms' branded drugs at the time of introduction (2) and all other combination (3). Combinations of this third type include: combinations with at least two branded drugs owned by the same firm, or combinations that consist of at most one branded drug. Externalities and own profit effects are computed separately for each event and from the perspective of each firm that would have earned positive profits from the new regimen (i.e., firms with at least one branded drug in the regimen). # Events is the number of introduction events. Fraction Firm Trials is the fraction of trials for that regimen type that were run by firms (rather than public innovators). Business Stealing + Market Expansion is the mean sum of the business stealing and market expansion terms in the drug profit change decomposition from (3.1), summed over all drugs not owned by the innovating firm. Price Adjustment is the mean change in drug profits due to the price adjustment term from (3.1), summed over all drugs not owned by the innovating firm. Δ CS is the mean change in consumer surplus. Δ TC is the mean change in insurer costs. Net Externality is the mean net externality (summing consumer surplus, insurer costs, and net profit externality). Fraction Positive Net Externality is the fraction of events with positive net externalities. Firm Profit (Innovator) is the mean profit change of the drugs owned by the innovating firm.

regimen, but largest for combinations with at least two firms' branded drugs, at $35 million per year per new combination.

We can also compute the externalities from the perspective of the innovator who ran the trial in the data (i.e., using method 2). Publicly-funded combination trials have large positive profit spillovers on firms on average, shown in Figure 6. Privately funded trials for combinations with at least two branded drugs owned by different firms have a mean sum of business stealing and market expansion externalities of $11 million per year per combination, as annotated on Figure 5.

Together, these results suggest that firms are often under-incentivized to conduct trials for combination therapies because of large positive externalities on other firms and patients. Having quantified the externalities associated with combination innovation, we now derive

Figure 5: Business Stealing + Market Expansion Externalities



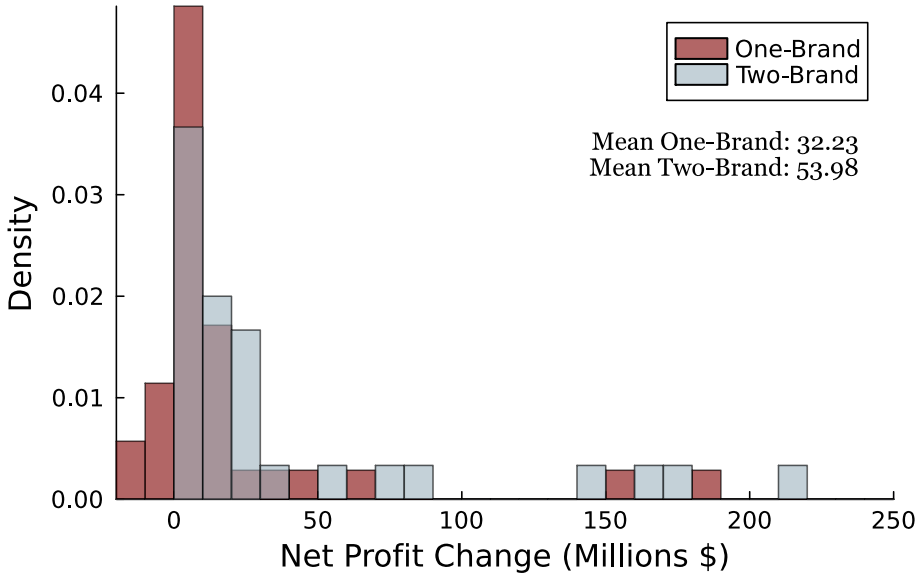
Notes: Figure shows the distribution of the sum of business stealing and market expansion externalities over introduction events. Combination entry events with at least two firms' branded drugs are in red and single-agent entry events are in gray.

the implications of these externalities for innovation decisions by building a dynamic model of combination innovation decisions. We use this model to explore potential policies to support combination innovation.

6 Dynamic Model of Combination Innovation

The results in Section 5 indicate that significant externalities may arise from combination innovation. Analyzing policies to correct these externalities requires imposing additional structure on innovation decisions. In this section, we develop and estimate a dynamic model of combination innovation. We use this model to explore how externalities influence the path of innovation: market expansion externalities create incentives for firms to *free ride* off others' combination innovations, and innovation by public innovators may similarly *crowd out* private combination innovation. We first use the model to recover primitives of the innovation process, including the incentives for free-riding and public crowd-out. Then, in Section 7, we use the model to explore potential policies to support combination innovation.

Figure 6: Public Innovation Profit Spillovers



Notes: Figure shows the distribution of the net profit externality (i.e., spillovers on firms) for combinations trialed by public innovators. Combinations with one-branded drug are in red and combinations with two-branded drugs are in gray.

6.1 Setup

We model the innovation decision for each combination regimen r as a dynamic discrete-choice game. This game involves a set of innovators I: firms with at least one patented drug in the regimen, and a public innovator. Innovators can choose to run a clinical trial for regimen r to learn its quality. We refer to this regimen r as the *focal regimen* of its game. Time is discrete (yearly) with a finite horizon, which allows us to capture the fundamental nonstationarity of the setting arising from individual drug introduction and patent expiry.

At year t, the state variables relevant for the decision to trial focal regimen r are summarized by the vector $s_{rt} \in \mathcal{S}_r$. This state includes information about whether other potential regimens have been trialed and, if so, their revealed qualities. This state space suffers from the curse of dimensionality, and we discuss simplifications to facilitate estimation below.

In each year t until focal regimen r has been trialed, each innovator $i \in I$ takes action a_{rit}: trial the focal regimen, $a_{rit} = 1$, or not, $a_{rit} = 0$. Each action has some i.i.d. (across firms and time) private cost shock $\varepsilon_{rit,a}$, drawn from a Type 1 extreme value distribution, scaled by parameter θ^{ε}. Trialing focal regimen r by innovator i at time t has cost κ_{rit}. We assume this decision represents the cumulative efforts to bring the combination to market, and we abstract

away from any choice of effort (e.g., trial size) conditional on trialing.[78]

A trial is successful with probability χ, where success means that the regimen is of sufficient quality to be taken by patients (i.e., appears in treatment guidelines such as Chu and DeVita, 2019). If trialed successfully, regimen r has quality $\xi_r \sim G_c(\cdot)$, where c is the cancer the regimen is being considered for. The distribution G_c is estimated from our demand model in Section 4.

Each innovator maximizes the discounted sum of flow profits net of trial costs. For a firm, flow profits in state s_{rt} are defined to be its profits from regimens that have been successfully trialed. We model the flow profits of the public innovator as the sum of consumer surplus and weighted firm profits:

$$\pi_{rit}(s_{rt}) = CS(s_{rt}) + \lambda \sum_{i' \neq \text{ public}} \pi_{ri't}(s_{rt}),$$

where the weight on firm profits $\lambda \in [0,1]$ will be estimated.

Equilibrium

For each focal regimen game, we solve for a type-symmetric pure strategy Markov Perfect Equilibrium (MPE), as is common in the literature following Maskin and Tirole (1988) and Ericson and Pakes (1995). Each innovator i's Markov strategy σ_i at time t is a mapping from the current state vector $s_{rt} \in \mathcal{S}_r$ and vector of private shocks ε into a trialing decision: $\sigma_i : \mathcal{S}_r \times \mathbb{R}^2 \to a_i$. The profile of Markov strategies is given by the vector $\sigma = (\sigma_i)_{i \in I}$. As we discretize the state space (discussed below), an equilibrium of the game exists (Doraszelski and Satterthwaite, 2010). However, we cannot guarantee uniqueness since multiple innovators could trial regimens in a particular period.

Note that equilibrium strategies are defined for the focal regimen of each game, and we take the trialing decisions of all other regimens as exogenous. This assumption imposes separability across the different focal regimen games: the state of the focal regimen evolves as a function of equilibrium strategies, while the states of other regimens evolve exogenously. Separability is critical to making the problem computationally tractable, yet preserves the key economic forces our dynamic combination innovation model seeks to capture: externalities on drug owners and patients, the incentive to free ride off others' combination innovation, and public innovation crowd-out. We discuss this assumption and its implications for estimation in further detail in Section 6.2.

[78] We do not model different phases of trials. Combinations are involved in 1.3 different trials (phases) on average. We take the trialing decision for a particular regimen to be the first trial for that regimen in the data.

Timing

For focal regimen r, the game starts when each component drug of the regimen has been trialed in at least one other cancer clinical trial, and ends 5 years past the last patent expiry event.[79] We assume individual drug arrival and patent expiry is exogenous and deterministic. Let t_{r1} denote the first year of the game for focal regimen r and denote the last year t_{rT}. The timing of each year t of the game for focal regimen r is as follows:

(i) The state $s_{rt} \in \mathcal{S}_r$ is observed.

(ii) Equilibrium drug prices are determined via the static price setting game (as estimated in Section 4), and each innovator i realizes variable surplus $\pi_{rit}(s_{rt})$.

(iii) Each innovator i observes private cost shocks $\varepsilon_{rit,a}$ and innovators simultaneously decide whether to trial the regimen or not following strategy profile σ. If an innovator i trials the focal regimen, she pays cost κ_{rit}.

(iv) The state evolves to $s_{rt+1} \in \mathcal{S}_r$ on the basis of the outcome of the focal regimen trial (if applicable) and the exogenous trialing decisions and outcomes of other regimens.

Dynamic Game

The ex-ante choice-specific value function of not trialing focal regimen r by innovator i at time $t < t_{rT}$ at state s_{rt} is given by the following Bellman equation:

$$v_{rit}(s_{rt}, 0) = \pi_{rit}(s_{rt}) + \beta \mathbb{E}_{s_{rt+1}|\sigma}\Big[V_{rit+1}(s_{rt+1})|s_{rt}, 0\Big]. \tag{6.1}$$

The first term is the flow surplus for innovator i. When i is a firm, it only considers its own profits, ignoring the potential externalities on firms (business stealing and market expansion) and patients. The second term is the discounted expected future value V_{rit+1}. This expectation is calculated over potential states in the next period, capturing two key elements: (i) whether another innovator i' trials the focal regimen (following strategy $\sigma_{i'}$) and that trial's outcome (if applicable) and (ii) the exogenous trialing decisions and outcomes of other regimens. The possibility that another innovator may trial the focal regimen creates the incentive to free ride off that innovator's trial. Similarly, trials run by the public innovator may crowd out trials run by a firm.

[79] The regimens trialed in the data are typically trialed within this time horizon. As our demand data end in 2019, we extrapolate the profit functions we estimate in 2019 forward to all remaining years of the game. Alternative ways of extrapolating could include estimating a constant profit decay or growth factor in years before 2019 and applying in future years.

The ex-ante choice-specific value function of trialing focal regimen r by innovator i at time $t < t_{rT}$ at state s_{rt} is

$$v_{rit}(s_{rt}, 1) = \pi_{rit}(s_{rt}) - \kappa_{rit} \times \mathbf{1}_{r \text{ not trialed by } t} + \beta \mathbb{E}_{s_{rt+1}|\sigma}\Big[V_{rit+1}(s_{rt+1})|s_{rt}, 1\Big]. \tag{6.2}$$

The first term is flow surplus minus trial costs, where the costs are paid only if the focal regimen has not been trialed. We model trialing as an absorbing state so that, after trialing, innovators remain in a state in which the focal regimen has been trialed. The second term is the discounted expected future value, conditional on the focal regimen having been trialed. The expectation is again calculated over potential states in the next period, capturing: (i) the outcome of focal regimen trial (if applicable) and (ii) the exogenous trialing decisions and outcomes of other regimens.

At the final year of the game $t = t_{rT}$, innovators do not trial and simply receive flow surplus from the current state.

Conditional Choice Probabilities

Let $Pr^{\theta}(a_{rit}|s_{rit})$ be the conditional choice probability of innovator i taking action $a_{rit} \in \{0, 1\}$ in the focal regimen r game at time t, conditional on parameters θ and state s_{rt}. The conditional choice probability of trialing is then

$$Pr^{\theta}(1|s_{rt}) = \frac{\exp\left(\frac{v_{rit}(s_{rt},1)}{\theta^{\varepsilon}}\right)}{\exp\left(\frac{v_{rit}(s_{rt},0)}{\theta^{\varepsilon}}\right) + \exp\left(\frac{v_{rit}(s_{rt},1)}{\theta^{\varepsilon}}\right)}. \tag{6.3}$$

State Space

The state space summarizes variables relevant to the profitability of trialing the focal regimen. Without further restrictions, it is infinite dimensional: predicting profits requires knowing the states of all other regimens (i.e., indicators of whether regimens have been trialed and resulting qualities). This state space suffers from the curse of dimensionality even if we discretize the quality distribution, so we make an additional simplification to reduce the size of the state space.

We assume each innovator tracks the trialing status (or outcomes) of a subset of potential combination regimens and a "fringe" regimen. The fringe regimen represents trialing outcomes of all other regimens and has a relatively low probability of success. This assumption is similar to those made in oblivious equilibrium models (Weintraub et al., 2008). We denote by $\mathcal{R}_r$ the set of regimens included in the state for focal regimen r, which we refer to as *tracked* regimens.

For focal regimen r being trialed for cancer c, we let the set of tracked regimens include the focal regimen r, the regimens that were ultimately successfully trialed for that cancer c, and a fringe regimen with a relatively low probability that summarizes all remaining regimens. The expectations in (6.1) and (6.2) integrate over the exogenous evolution of these tracked regimens.

We discretize the regimen quality distribution G_c to have N_ξ points. The state is summarized by the quality levels of the tracked regimens, where the quality level is either not trialed, trialed and failed, or trialed and successful with some quality level. The state space $\mathcal{S}_r$ for the focal regimen r game is therefore given by

$$\mathcal{S}_r = \left\{\text{not trialed, trialed and failed, trialed and quality } \xi_1, \ldots, \text{ trialed and quality } \xi_{N_\xi}\right\}^{|\mathcal{R}_r|}. \tag{6.4}$$

6.2 Estimation and Identification

The parameters in the model are the innovation fixed cost κ_{rit}, scale parameter θ^ϵ, profit weight λ, discount rate β, and success rate χ. We estimate a common fixed cost κ, scale parameter θ^ϵ, and profit weight λ via a full-solution method using maximum likelihood. We set a yearly discount rate of .9, and we set the success rate to be the rate observed in the data for each cancer.

The likelihood of a candidate parameter vector $\theta = (\kappa, \theta^\epsilon, \lambda)$ is computed as follows. For each focal regimen $r \in \mathcal{R}$, we approximate the solution to the game at parameters θ (details of this approximation procedure are given in Section 6.3), obtaining ex-ante choice specific value functions (6.1) and (6.2). These functions are used to compute the conditional choice probabilities $Pr^\theta(a_{rit}|s_{rit})$ as defined in (6.3). As is common in the literature on dynamic games, we fix competitor conditional choice probabilities at first-stage estimated values (via multinomial logit) in estimation.[80] This assumption is made to avoid issues with multiple equilibria when iterating over conditional choice probability profiles (Aguirregabiria and Mira, 2010; Sweeting, 2013; Bodéré, 2023). Let $\{(\hat{a}_{rit}, \hat{s}_{rit})\}_{r\in\mathcal{R}, i\in\mathcal{I}, t\in\mathcal{T}}$ denote the set of observations (over regimens, innovators, and time) of action-state tuples in data. Define the log-likelihood function as

$$\sum_{r\in\mathcal{R}, i\in\mathcal{I}, t\in\mathcal{T}} \frac{1}{|\mathcal{R}|\,|\mathcal{I}|\,|\mathcal{T}|} \log\left(Pr^\theta(\hat{a}_{rit}|\hat{s}_{rit})\right). \tag{6.5}$$

We find the θ that maximizes (6.5).

[80] The specification of first-stage CCPs and results are shown in Appendix E.

The estimates of profits and consumer surplus from the introduction of a new regimen (from Sections 4 and 5), combined with observed trialing decisions, are key inputs into identifying the dynamic parameters. For example, conditional on expected profits, a high fixed cost of innovation will lower the CCP of trialing. Similarly, a high weight on aggregate profits in the public innovator's objective will increase the public innovator's CCP of trialing. Finally, the scale parameter is identified since revenues are taken as given when estimating the dynamic model.

We make additional assumptions to ease the computational burden of estimation. First, we estimate the model for focal regimens for colorectal cancer. Colorectal cancer is not unique compared to the other cancers in our sample, but focusing a single cancer alleviates significant computational challenges.[81] Second, we focus on regimens that were trialed in the data rather than considering the full set of potential combinations given a set of available drugs. By focusing on regimens that were ultimately trialed in the data, the model is most useful for understanding the timing of trialing and which innovator runs the trial rather than the extensive margin of which regimens are trialed. Extending the model to consider the extensive margin requires estimating the (unobserved) quality distribution of this larger risk set of potential regimens. Such an extension is possible with more data about the potential quality of regimens as a function of characteristics such as mechanism of action, known interactions, etc., but is beyond the scope of our analysis.[82]

Within each focal regimen, taking the trialing decisions of other regimens as exogenous is critical to the computational tractability of the game. Given the separability across focal regimens, we can parallelize across focal regimens when approximating the game solution. This assumption is also motivated by institutional details: decisions in large pharmaceutical companies are likely decentralized, and a model with strategic interactions within each focal regimen, taking the evolution of other regimens as given, approximates this structure. This is especially true of public innovation decisions, which are made across many hundreds of different publicly-funded research organizations.

We compare alternative ways of estimating the model in Appendix E. The model has the finite dependence property (Arcidiacono and Miller, 2019), and can be estimated through a two-step estimation approach (similar to Scott, 2014). The first step requires non-parametric estimates of the conditional choice probabilities, while the second estimates dynamic parameters using Euler perturbations. While this approach is computationally less demanding than

[81] An extension to all cancers in our data will be included in future drafts.

[82] In future work, we can make progress on this extension by focusing on two-drug combinations and using the results of trials in the NCI ALMANAC to create a risk set of potential combinations based on having promising results in the laboratory tests.

the full-solution method, it is very demanding of data. We explore it in Appendix E, but prefer our current approach given the noise with which the first-stage conditional choice probabilities are estimated in the two-step approach.

6.3 Solution Procedure

For each candidate parameter vector in estimation (and counterfactuals), we apply sieve value function approximation (Arcidiacono et al., 2013), extended to a game rather than single-agent problem, to solve for approximate value and policy functions. This method approximates the integrated (i.e., expected) value function with a non-parametric sieve function of state variables. Applying approximation methods is required to make the problem computationally tractable: despite the assumptions made regarding the number of regimens to track in the state space and the discretized quality distribution, the dimension of the state space is prohibitively large to solve the model exactly via backwards induction.[83]

For notational convenience, define the flow surplus net of trial costs as

$$\Pi_{rit}(s_{rt}, a) = \pi_{rit}(s_{rt}) - a \times \kappa_{rit} \times \mathbf{1}_{r \text{ not trialed by } t}.$$

Let n be the dimension of the sieve. The approximation $\hat{v}_{rit,n}$ to the ex-ante value function for the focal regimen r game for innovator i at time t satisfies

$$\begin{aligned}\hat{v}_{rit,n}(s_{rt}) &= \theta^{\varepsilon} \ln\left(\sum_{a_{rit}\in\{0,1\}} \exp\left(\frac{1}{\theta^{\varepsilon}}\left(\Pi_{rit}(s_{rt}, a_{rit}) + \beta \mathbb{E}\left\{\hat{v}_{rit+1,n}(s_{rt+1})|s_{rt}, a_{rit}\right\}\right)\right)\right) + \tilde{\gamma}, \\ &\approx \mathbb{E}\left\{\max_{a_{rit}\in\{0,1\}} \{v_{rit}(s_{rt}, a_{rit}) + \theta^{\varepsilon}\varepsilon_{rit}(a_{rit})\}\right\},\end{aligned}$$

where the sieve $\hat{v}_{rit,n}(s_{rt})$ is

$$\hat{v}_{rit,n}(s_{rt}) = \omega_{rit,1} w_1(s_{rt}) + \ldots + \omega_{rit,n} w_n(s_{rt}) = \omega_{rit} \cdot W_n(s_{rt}),$$

and $\tilde{\gamma}$ is the Euler-Mascheroni Constant.

The vector of coefficients ω_{rit} characterizes the sieve, along with the set of functions W. These functions are all linear terms of the state space, all quadratic interactions, all cubic interactions, etc., until the dimension of the sieve n is reached.[84] We can recover the coefficients

[83] For example, suppose there are 8 points in the quality distribution in addition to the states of not trialed and trialed and failed. With 10 tracked regimens (including) the focal regimen, there are 10 billion states.

[84] Additional details about the exact construction of the sieve function are given in Appendix E.

of the sieve function via backwards recursion at each t by solving the following program:

$$\hat{\omega}_{rit} = \underset{\omega_{rit}}{\operatorname{argmin}} \sum_{s_{rt} \in \hat{\mathcal{S}}_r} \Bigg[\omega_{rit} \cdot W_n(s_{rt}) - \theta^{\varepsilon} \ln \Bigg(\sum_{a_{rit} \in \{0,1\}} \exp \Bigg(\frac{1}{\theta^{\varepsilon}} \left(\Pi_{rit}(s_{rt}, a_{rit}) + \beta \hat{\omega}_{rit+1} \mathbb{E}\left\{ W_n(s_{rt+1}) | s_{rt}, a_{rit} \right\} \right) \Bigg) \Bigg) - \tilde{\gamma} \Bigg]^2.$$

The sieve function can be used to derive the ex-ante choice value functions (6.1) and (6.2), which in turn give the CCPs in (6.3). When computing counterfactuals, we iterate over CCP profiles until they are consistent.

The key assumption for computational tractability is that we use a subset of states $\hat{\mathcal{S}}_r \subseteq \mathcal{S}_r$ for this approximation. This choice of approximation states $\hat{\mathcal{S}}_r$ is crucial to the accuracy of the approximation. In order to increase accuracy of the approximation around the states in the data and states likely reached in counterfactual simulations, we generate the approximation states as follows, similar to Sweeting (2013). For each state observed in the data, we choose a random subset of tracked regimens (including the focal regimen) and change those regimens' quality levels to random values (using weights based on the likelihood of those quality levels being realized). We repeat until the desired number of approximation states is reached. In our baseline specification, we set $\left|\hat{\mathcal{S}}_r\right| = 15,000$ and $n = 1,000$.

We present results about approximation error from Monte Carlo simulations of the model with a small number of tracked regimens in the state space and quality levels in Appendix E. We can solve this model exactly via backwards induction and compute approximation error for various choices of the number of approximation states and sieve specification. The approximation error is generally small, even for sets of approximation states with relatively small cardinality compared to the dimension of the full state space.

6.4 Parameter Estimates

Table 9 presents estimates of the dynamic parameters. We assume a yearly discount rate of .9, and we observe a 5% success rate for colorectal combination therapies in the data. We estimate trial costs of $28 million, a scale parameter θ^{ε} of 10.91, and a weight on aggregate profits in the public innovator's objective of .25.

Our cost estimates are similar to expected accounting costs of oncology trials. Sertkaya et al. (2016) estimates that oncology trial costs average $4.5 million in Phase I, $11.2 million in

Table 9: Dynamic Model Parameter Estimates

Parameter	Method	Estimate
Cost κ (million \$)	Estimated – Maximum Likelihood	28.0
		(13.19)
Scale θ^{ε}	Estimated – Maximum Likelihood	10.91
		(0.28)
Profit Weight λ	Estimated – Maximum Likelihood	0.25
		(0.23)
Discount Rate β	External Estimate	0.9
Success Rate χ	Estimated – Mean Success	0.05

Notes: Table presents estimates of the dynamic parameters. Each row is a parameter. Column 2 shows the method used to estimate the parameter. Column 3 contains parameter estimates. Standard errors are in parentheses, calculated from bootstrap samples of focal regimens. Note that these standard errors currently only capture variation in estimates of the dynamic game and not the demand or bargaining models.

Phase II, and \$22.1 million in Phase III, totaling \$37.8 million.[85] While similar, our estimate of \$28 million may differ from the sum of these phases for two key reasons. First, as discussed in Section 2.1, successful combinations often do not go through all three phases, often combining Phase I/II or Phase II/III if the component drugs have already been shown to be safe. Our model does not distinguish between stages and instead assumes the innovation costs are the total cost of bringing combinations to market across all phases. Many of the combinations in our data fail after one or two phases, reducing the expected trialing costs. Second, the costs recovered by the model are economic costs rather than accounting costs, so additionally capture the possible opportunity costs associated with not trialing other regimens.

Model Fit: We compare model predicted trial times to the data in Appendix E. The model fit is reasonable with high correlation between model predicted and actual trial times, though our model predicts trials occurring approximately 1.5 years earlier than the data on average.

7 Designing Policy to Support Combination Innovation

In this section, we use the dynamic model to design cost-effective policies to support combination innovation. The policies we consider include research subsidies, varying the amount of public innovation, and varying the direction of public innovation.

[85] Additional external estimates of the accounting costs of a single stage of an oncology trial are approximately \$100,000 per patient (Sertkaya et al., 2014). In our data, combination trials enroll an average of 116 patients (across all phases), implying an average per-phase cost of \$12 million. This estimate is similar to the Phase 2 trial costs cited above.

7.1 Counterfactual Policies

The large set of externalities that arise from combination innovation suggests that private innovation of new combinations is unlikely to yield a socially efficient outcome, perhaps justifying policy intervention. In principle, a social planner could ensure efficient innovation decisions by giving each firm f a subsidy equal to the net externality after it trials a new regimen r^+. But directly implementing this subsidy is impractical, because it requires correct forecasts of the changes in demand, prices, and profits after the introduction of *each* possible regimen by *each* firm. Moreover, such subsidies would need to account for the dynamic effects on patients and firms, which also depend on a correct forecast of the future path of innovation. Given these difficulties, we study a more limited collection of policies that can improve welfare and are simple to implement: a regimen- and firm-independent research subsidy for combination therapy trials and changes in the amount and direction of public innovation.

We note that crafting these policies to balance public and private innovation is particularly important given the large role of public innovation in pharmaceutical markets. Our analysis suggests an important role for public researchers to study combination therapies neglected by firms, particularly those involving only generic drugs. But policies that expand the role of public innovation can also crowd out private innovation, which may be inefficient to the extent that public innovation is more costly (i.e., through the marginal cost of public funds).

We compute counterfactuals by solving the model at the estimated parameters and counterfactual policies and forward simulating the model to predict trial times (and which innovator trials the regimen), described in more detail in Appendix E. To implement a research subsidy we reduce the trial cost κ by some fixed amount. To vary the amount of public innovation, we set the CCPs of public innovation at either lower or higher (exogenous) levels than we estimate. To vary the direction of public innovation, we set the CCPs of public innovation of certain regimens at higher or lower levels than we estimate.

7.2 Results

Table 10 summarizes the effects of counterfactual innovation policies for funding colorectal cancer combination trials.[86] For each counterfactual policy, we compute the total cost to the government of implementing the policy, the change in consumer surplus, the change in firm profits, and the net change in welfare. Figure 7 compares the policy cost to the government with the gains in consumer surplus and firm profits for a subset of the policies we consider.

Research Subsidy: The first set of policies we consider is a constant research subsidy to

[86] In future drafts, we will include extensions to all cancers in our sample.

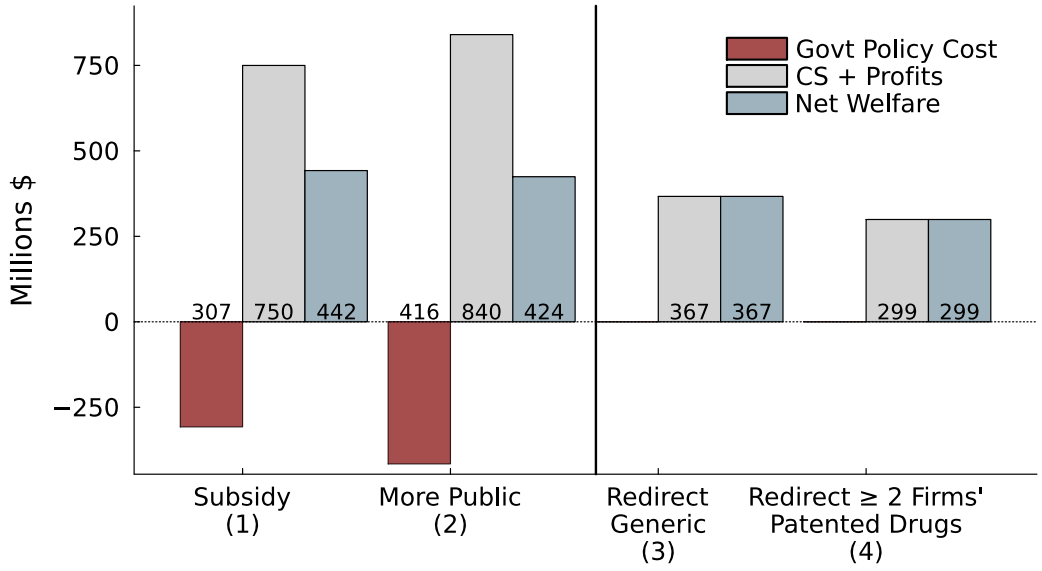
firms for running the trial at a percentage of the estimated trial cost. The government cost of implementing this subsidy consists of two components. First, offering a subsidy may increase the probability of private trialing and result in fewer publicly funded trials relative to baseline. Second, the government must pay a research subsidy on all privately run trials irrespective of success. A 20% subsidy increases total welfare by approximately $442 million ($642 per patient-year), with larger increases in firm profits compared to consumer surplus because of the large transfer that occurs through the subsidy.

Amount of Public Innovation: The next policy we consider varies the probability of public trialing by setting the public innovator's CCPs as exogenous and at higher levels than the estimated levels. For example, the NIH would reduce the threshold for approving grants by some fixed amount. Increasing the probability of the public innovator has two key effects: First, the public innovator is more likely to trial, and therefore more likely to trial earlier. Second, other innovators may be less likely to trial because of the incentive to free-ride and public innovation crowd-out. Increasing public CCPs by 4 percentage points (uniformly across all states) increases total welfare by approximately $424 million ($616 per patient-year). We use 4 percentage points as it gives a similar policy implementation cost to the research subsidy, and we show results for other policies in Table 10. On average, a firm's CCP of trialing decreases by approximately 18% relative to baseline, implying positive but limited public crowd-out.

Direction of Public Innovation: The final set of policies we consider varies the direction of public innovation. As public innovation may crowd out private innovation, it may be possible to redirect public innovation towards combinations that firms are particularly underincentivzed to trial and increase trialing speed while keeping the public budget fixed. We implement this type of directional policy similar to the previous counterfactual, where we set the public innovator's CCPs as exogenous and at either or lower levels than what we estimate, depending on characteristics of the combination.

First, we construct a policy that redirects public innovation towards regimens with at least one generic drug. This type of regimen may feature higher consumer surplus spillovers because of the lower drug prices, and firms may be particularly underincentivzed to trial a regimen when a sufficiently high fraction of component drugs are generic. We reduce public CCPs by a fixed amount for all regimens that do not involve any generic drugs, while we increase public CCPs for regimens that do. It is important to note that in this counterfactual we do not compute the optimal policy for redirecting public innovation based on this regimen characteristic, but rather choose the magnitude of the change in CCPs to deliver similar welfare gains as the previous policies. To obtain a budget neutral policy, we reduce public CCPs by approximately 1 percentage point for regimens that do not involve generic drugs and increase by approximately

Figure 7: Policy Cost and Welfare Gains



Notes: Figures shows estimates of the government policy cost and change in consumer surplus and profits for counterfactual innovation policies.

5 percentage points for those that do. Despite being budget neutral, this policy increases total welfare by $367 million ($533 per patient-year).

The second policy we consider similarly redirects public innovation towards regimens with at least two on-patent drugs owned by different firms. These regimens are likely to have positive market expansion externalities, resulting in reduced firm incentives to trial them relative to what is socially optimal. We decrease public CCPs by approximately 4 percentage points for regimens that have at most one firm's patented drug and increase by approximately 3 percentage points for regimens with at least two firms' patented drugs. This policy is again approximately budget neutral yet increases total welfare by $299 million ($435 per patient-year).

These policies demonstrate that it is possible to obtain similar welfare gains to untargeted subsidies or increases in public innovation at much lower costs by taking advantage the features of the setting that reduce firm incentives to trial certain regimens: missing property rights and market expansion externalities.

8 Conclusion

Market expansion externalities, missing property rights for combinations, and the incentive to free ride off others' combination innovation are forces that tend to reduce the private value of combination innovation below its social value.

Table 10: Policy Counterfactual Summary

Counterfactual	**Policy Cost (Govt)** Millions $	**Δ CS** Millions $	**Δ Profits** Millions $	**Δ Welfare** Millions $
Research Subsidy 20%	307	255	495	443
More Public + 1 pp	116	5	120	9
More Public + 2 pp	155	124	292	261
More Public + 3 pp	337	151	507	321
More Public + 4 pp	416	200	640	424
More Public + 5 pp	571	241	837	507
Redirect Generic	0	160	207	367
Redirect $\geq$ 2 Firms' Patented Drugs	0	113	186	299

Notes: Table shows estimates of the government policy cost and change in consumer surplus and profits for counterfactual innovation policies. Column 1 is the cost to the government of implementing the policy. Column 2 is the change in consumer surplus. Column 3 is the change in profits. Column 4 is the change in total welfare (summing the government policy cost and change in consumer surplus and profits). Values are in millions of dollars, rounded to the nearest million.

This paper presents descriptive evidence consistent with underinvestment in combinations because of these forces, develops an empirical framework to quantify combination innovation externalities, and evaluates alternative innovation funding policies in the context of cancer drug combination therapies. Market expansion externalities often dominate business stealing, showing that there is often underinvestment in combination therapies. Redirecting public innovation towards combinations that firms are particularly underincentized to trial—those with the potential for large consumer surplus spillovers, such as combinations of generic drugs, and market expansion externalities—minimizes free-riding and public crowd-out and provides a set of relatively simple innovation funding policies that increase total welfare yet are budget neutral.

This analysis focuses on particular aspects of combination innovation, leaving other important features for future research. Mergers and acquisitions of drugs in the early stages of development may play a key role in the shaping the risk set of potential combinations and the amount and direction of combination innovation. And underinvestment in combination therapies suggests potential inefficiencies in the amount, and direction, of innovation in new drugs themselves. Technology (e.g., artificial intelligence) that helps screen potential combinations for predicted success probabilities and externalities could be an important tool in correcting the amount and direction of innovation.

Moving beyond pharmaceuticals, the efficiency of combination innovation will depend

critically on the nature of product market competition, the possibility of joint ventures, and the particular property rights institutions. The empirical framework in this paper can be extended to match alternative institutions and provide evidence of how these features shape the efficiency of combination innovation.

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A Data Construction Details

A.1 Cancer Drugs

We use three main sources of data about cancer drugs and characteristics.

GlobalData: We access GlobalData's Drug Database via MIT's institutional subscription.[87] This database is similar to other databases used in papers about pharmaceutical demand and supply, such as Pharmaprojects and Cortellis. We harmonize firm names across different drugs that they own, and we collapse ownership to the parent level (i.e., assign all drugs owned by subsidiaries to their parent company).

Drugs@FDA: We supplement the GlobalData drug database with marketing and other regulatory information from Drugs@FDA.[88] We count the number of generic competitors for each drug in a year as the total number of Abbreviated New Drug Application's (ANDA) filed cumulatively for that drug up to that year. More than one firm can be listed on each ANDA, but each is typically producing a different dosage.

SEER CanMED: We obtain HCPCS codes for marketed drugs from the CanMED: HCPCS database.[89] HCPCS codes often change overtime, so finding historical HCPCS codes is important to using historical Medicare and Marketscan data.

A.2 Clinical Trials

We obtain all metadata from all clinical trails on ClinicalTrials.gov.[90]

A.2.1 Identifying Cancer Clinical Trials

We use the list of oncology Medical Subject Headings (MeSH) terms and free text keywords in Califf et al. (2012) to subset to oncology clinical trials. We define an oncology clinical trial to be a trial with at least one MeSH term or condition that is in the list from Califf et al. (2012). We then manually make a crosswalk between the list of MeSH terms and cancer types in Chu and DeVita, 2019. The mapping is many-to-one (one MeSH term may map to many cancer types in Chu and DeVita (2019)), and each clinical trial may have more than one MeSH term.

[87] The database is described here: https://www.globaldata.com/marketplace/pharmaceuticals/pipeline-marketed-drugs/. We received an extract of all drugs classified as oncology drugs on October 31, 2023.

[88] The data is available here: https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-data-files. We downloaded the full database on October 3, 2023.

[89] The data is available here: https://seer.cancer.gov/oncologytoolbox/canmed/hcpcs/. We downloaded the full database on October 4, 2023.

[90] The data is available here: https://classic.clinicaltrials.gov/api/gui/ref/download_all. Our extract is from January 12, 2023.

Appendix Table A.1 summarizes the number of trials we observe for each cancer type in Chu and DeVita (2019), where we count a trial for a specific cancer type if any of the MeSH codes map to that type of cancer.

Table A.1: Clinical Trial Counts By Cancer

Cancer	# Trials	Fraction Combo	Fraction Industry
Hodgkin Lymphoma	2784	0.62	0.34
Breast Cancer	2624	0.65	0.31
Acute Lymphoblastic Leukemia	2469	0.6	0.32
Non-Small Cell Lung Cancer	2341	0.64	0.45
Prostate Cancer	1576	0.52	0.32
Brain Cancer	1532	0.48	0.2
Multiple Myeloma	1233	0.69	0.38
Malignant Melanoma	1201	0.64	0.34
Colorectal Cancer	991	0.7	0.31
Head and Neck Cancer	895	0.57	0.24
Pancreatic Cancer	760	0.73	0.26
Ovarian Epithelial Cancer	726	0.65	0.37
Renal Cell Carcinoma	642	0.55	0.41
Kaposi Sarcoma	562	0.53	0.22
Hepatocellular Carcinoma	456	0.49	0.37
Carcinoid and Neuroendocrine Tumors	434	0.55	0.21
Bladder Cancer	352	0.55	0.32
Gastric Cancer	304	0.76	0.33
Myelodysplastic Syndrome	263	0.5	0.41
Endometrial Cancer	258	0.57	0.22
Non-Hodgkin Lymphoma	240	0.64	0.15
Esophageal Cancer	179	0.73	0.18
Cervical Cancer	175	0.51	0.21
Biliary Tract Cancer	155	0.64	0.32
Malignant Mesothelioma	151	0.54	0.27
Thyroid Cancer	145	0.43	0.23
Osteogenic Sarcoma	89	0.43	0.24
Soft Tissue Sarcoma	75	0.49	0.33
Basal Cell Carcinoma	69	0.16	0.51
Gastrointestinal Stromal Tumor	67	0.34	0.55
Merkel Cell Carcinoma	66	0.48	0.47
Acute Myeloid Leukemia	60	0.63	0.4
Ovarian Germ Cell Tumor	59	0.69	0.03
Small Cell Lung Cancer	57	0.7	0.4
Anal Cancer	33	0.64	0.12
Waldenström's Macroglobulinemia	30	0.53	0.1
Chronic Lymphocytic Leukemia	27	0.81	0.37
Thymoma	25	0.44	0.08
Adrenocortical Carcinoma	24	0.42	0.21
Chronic Myeloid Leukemia	21	0.38	0.14
Cancer of Unknown Primary	13	0.85	0.08
Testicular Cancer	7	0.43	0.0
Hairy Cell Leukemia	2	0.5	0.5

Notes: Table shows the number of drug trials run by cancer. Fraction Combo is the fraction of trials for that cancer that are for combinations. Fraction Industry is the fraction of trials for that cancer that have an industry lead sponsor.

A.2.2 Extracting Drug Information from Clinical Trials

We use the OpenAI GPT-4o API to extract drugs used in the control and treatment arm(s) of each trial. The query we use is as follows:

```
request_all = "What drugs are used in the treatment versus control arms of
    the clinical trial described below? We provide the trial title and
    summary below. If a trial does not use drugs, just say 'none' for both
    the treatment and control arms.

You should return a list with 2 elements separated by semicolons: the word '
    treatment:' followed by the drug(s) used in the treatment arms of the
    trial (separated by commas), and the word 'control:' followed by the
    drug(s) (write none if none are used) used in the control arm (separated
     by commas).

Example outputs:
treatment: cisplatin; control: placebo
treatment: oxaliplatin, bevacizumab; control: none
treatment: none; control: none

####
The trial title is: '$(trial_title)'.
The trial brief summary is: '$(trial_brief_summary)'.
The trial full summary is: '$(trial_summary)'.
###"

output_instructions = "Desired output format is: treatment: drug1, drug2...;
     control: drug3, drug4..."

body = JSON.json(
    Dict(
    "model" => "gpt-4o",
    "messages" => [Dict("role" => "user", "content"=> request_all),
                   Dict("role" => "system", "content"=> output_instructions)
                       ],
    "temperature" => 0.0)
    )

url = "https://api.openai.com/v1/chat/completions"
```

query.jl

A.2.3 Clinical Trial Sample Restrictions

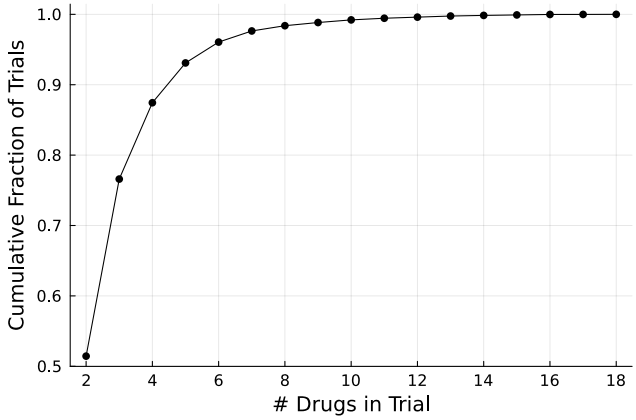
After extracting the drugs used in a trial, we subset to trials that trial at least one drug (rather than only trialing e.g., a radiation or surgical treatment). We further subset to trials with at least one location in the US in order to focus on trials for treatments that are most likely

to be used in the US, which our drug demand usage data covers.

A.2.4 Classifying Combination Clinical Trials

We define a combination trial to be a trial that tests at least two drugs together in a treatment arm of the trial. We do not count a single drug plus some other treatment (e.g., radiation or surgery) as a combination trial. We also do not count a trial as a combination trial if the control arm is a combination but the treatment arm is a monotherapy. Figure A.1 plots the CDF of the number of component drugs in combination therapies.

Figure A.1: Combination Trials by # of Drugs



Notes: Figure shows the CDF of the number of drugs involved in combination trials.

A.2.5 Merging Clinical Trial Drugs with GlobalData and Drugs@FDA

Given the extracted drug names from the trial, we then merge these drug names with the drug-level dataset we create from GlobalData and Drugs@FDA. Importantly, GlobalData provides an extensive list of aliases for each drug, include names used in early-stage clinical trials. We check all possible aliases when merging. Table A.2 shows summary statistics for merging drugs reported in clinical trials with drugs reported in GlobalData.

Table A.2: Clinical Trial GlobalData Drug Merge Rates by # Drugs in Trial

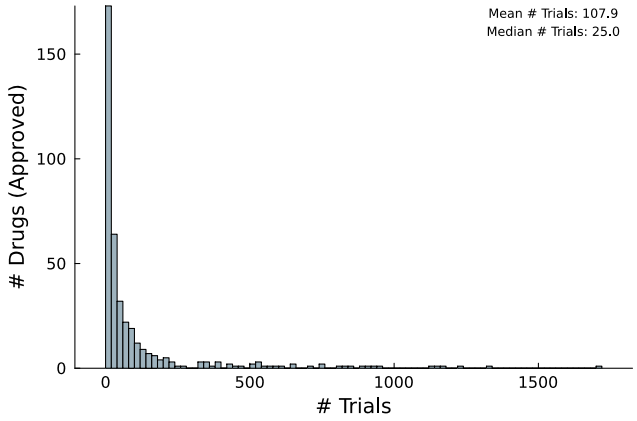
# Drugs	# Trials	Avg Frac Drugs Merged	Frac Merged All Drugs
1 Drug	11959	0.8	0.8
2 Drugs	8537	0.89	0.82
3 Drugs	4175	0.88	0.77
4 Drugs	1800	0.85	0.68
5 Drugs	938	0.86	0.64
All	28555	0.85	-

Notes: Table shows summary statistics of the merge rates between drugs in the clinical trial data and drugs in GlobalData. Each row (except for the last) presents summary statistics subsetting to clinical trials that have a certain number of drugs. # Trials gives how many trials satisfy that condition (e.g., have a certain number of drugs), Avg Frac Drugs Merged is the average (over trials) fraction of drugs in a trial that merge to GlobalData, and Frac Merged All Drugs is the fraction of trials for which *all* drugs in a trial merge.

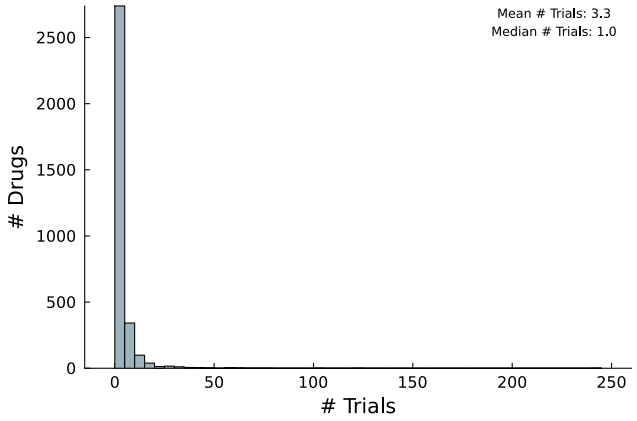
A.2.6 Trials per Drug

Figure A.2: Number of Trials Involving a Drug

(a) Approved Drugs

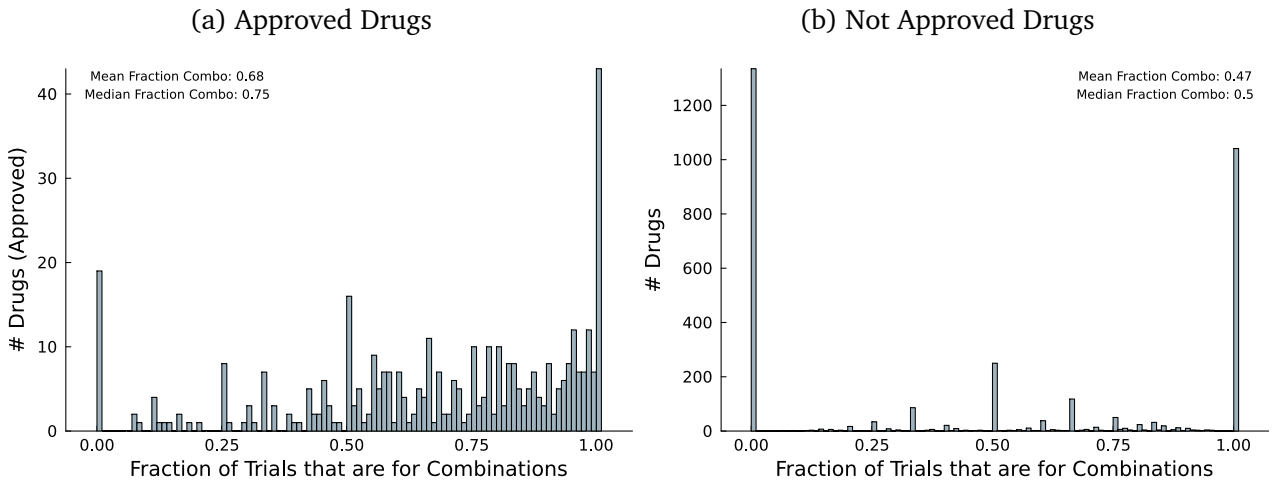


(b) Not Approved Drugs



Notes: Figure shows the distribution of the number of trials that is a drug is involved in (in the treatment arm), separately for approved and not approved drugs.

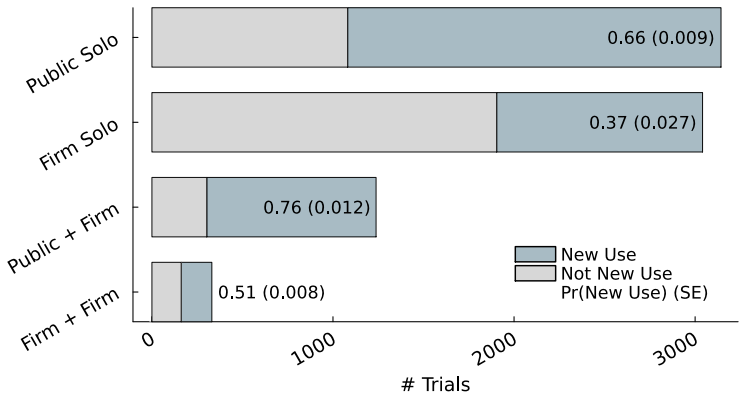
Figure A.3: Fraction of Trials for Combinations



Notes: Figure shows the distribution of the fraction of trials that is a drug is involved in that are for combinations (in the treatment arm), separately for approved and not approved drugs.

A.2.7 Trials for New Uses

Figure A.4: Clinical Trials by Funding Type

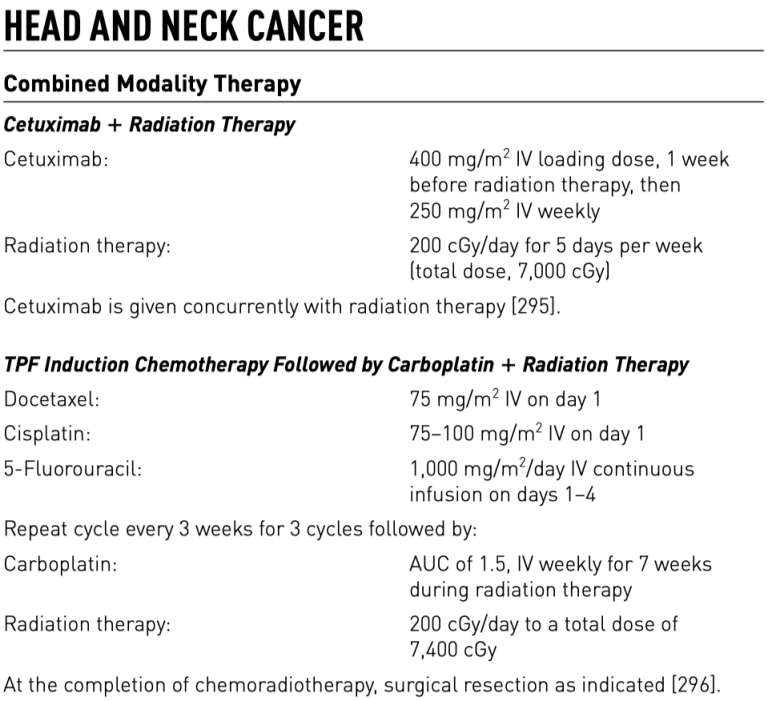


Notes: Figure shows the counts of fractions of single drug trials for the initial condition versus new conditions, separately by different trial sponsors.

A.3 Cancer Regimens

Figure A.5 shows an example of how regimens are recorded in Chu and DeVita (2019). Table A.3 summarizes the number of regimens available for each cancer, the number of drugs used in each regimen, and the publication year of related scientific papers.

Figure A.5: Chu and DeVita (2019) example



HEAD AND NECK CANCER

Combined Modality Therapy

Cetuximab + Radiation Therapy

Cetuximab:	400 mg/m^2 IV loading dose, 1 week before radiation therapy, then 250 mg/m^2 IV weekly
Radiation therapy:	200 cGy/day for 5 days per week (total dose, 7,000 cGy)

Cetuximab is given concurrently with radiation therapy [295].

TPF Induction Chemotherapy Followed by Carboplatin + Radiation Therapy

Docetaxel:	75 mg/m^2 IV on day 1
Cisplatin:	75–100 mg/m^2 IV on day 1
5-Fluorouracil:	1,000 mg/m^2/day IV continuous infusion on days 1–4

Repeat cycle every 3 weeks for 3 cycles followed by:

Carboplatin:	AUC of 1.5, IV weekly for 7 weeks during radiation therapy
Radiation therapy:	200 cGy/day to a total dose of 7,400 cGy

At the completion of chemoradiotherapy, surgical resection as indicated [296].

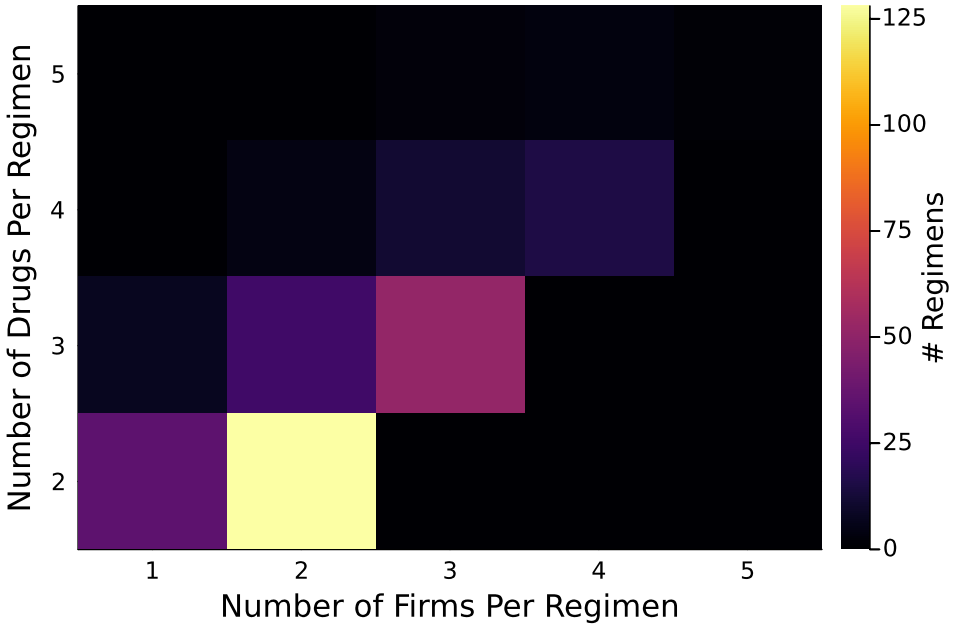
Notes: Figure shows example example treatment regimens for head and neck cancer, taken from Chu and DeVita (2019).

Table A.3: Cancer Regimen Summary

Cancer	# Regimens	Mean # Drugs	Min # Drugs	Max # Drugs	Unique # Drugs	Average Paper Year
adrenocortical	2	3.0	2	4	5	2012.0
anal	5	1.8	1	2	6	2007.6
basal cell	2	1.0	1	1	2	2013.5
biliary tract	9	1.67	1	2	6	2004.56
bladder	20	1.9	1	4	18	2004.3
brain	10	1.7	1	3	8	2003.2
breast	70	2.04	1	5	35	2003.99
unknown primary	8	2.5	2	3	11	2001.25
carcinoid and neuroendocrine	10	1.5	1	2	12	2004.0
cervical	21	1.9	1	4	15	2003.19
colorectal	39	2.51	1	5	20	2006.33
endometrial	15	1.93	1	4	14	2001.33
esophageal	12	2.25	1	3	9	2004.75
gastric	22	2.32	1	3	13	2004.82
gastrointestinal stromal tumor	5	1.0	1	1	5	2008.4
head and neck	20	2.05	1	4	13	1999.85
hepatocellular	10	1.4	1	3	12	2006.4
kaposi sarcoma	9	1.33	1	3	11	1995.44
all	17	2.76	1	6	22	1999.12
aml	21	1.67	1	3	19	2002.67
cll	23	1.61	1	3	16	2001.65
cml	10	1.1	1	2	10	2002.9
hairy cell leukemia	3	1.0	1	1	3	1989.33
non-small cell lung	51	1.86	1	3	28	2006.76
small cell lung	12	1.92	1	3	10	1997.0
hodgkin lymphoma	18	3.06	1	8	24	2001.17
non-hodgkin lymphoma	44	3.39	1	11	38	2000.82
primary cns lymphoma	5	2.6	1	6	8	2008.0
malignant melanoma	18	1.44	1	3	17	2005.56
malignant mesothelioma	11	1.73	1	3	8	2004.82
merkel cell	4	2.0	1	3	7	1999.0
multiple myeloma	27	2.26	1	4	16	2005.63
myelodysplastic syndrom	5	1.2	1	2	6	2007.0
osteogenic sarcoma	4	3.25	2	4	7	1997.5
ovarian epithelial	26	1.5	1	3	18	2003.0
ovarian germ cell	1	3.0	3	3	3	2004.0
pancreatic	13	2.08	1	4	10	2003.0
prostate	27	1.48	1	3	21	1999.56
renal cell	16	1.31	1	2	14	2007.38
soft tissue sarcoma	15	2.07	1	5	15	2004.2
testicular	12	2.92	1	5	12	1993.67
thymoma	6	2.83	2	4	11	2000.33
thyroid	8	1.12	1	2	8	2004.25
waldenstrom's macroglobulinemia	5	2.6	1	3	6	2007.0
Total	691	1.99	1.13636	3.52273	193	2003.19

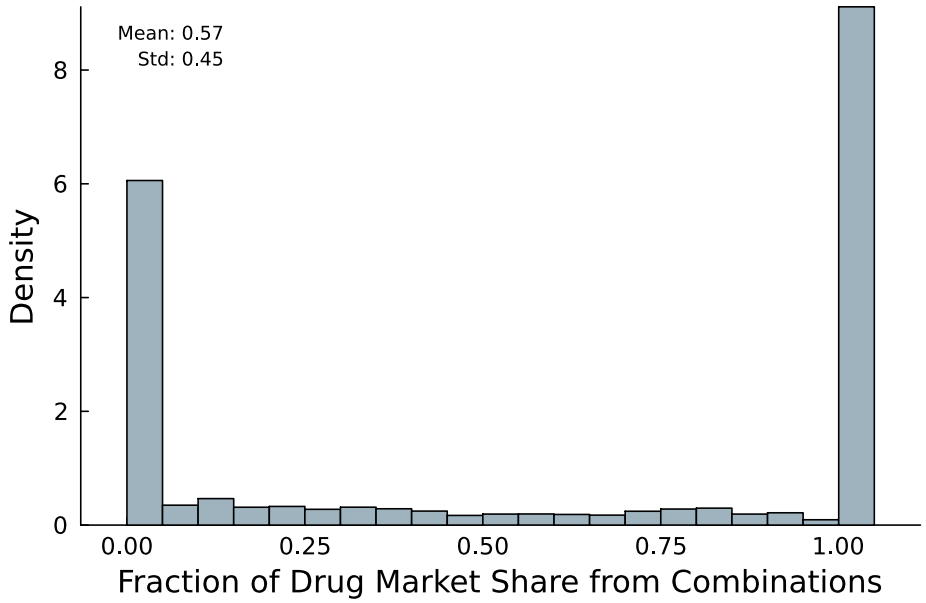
Notes: Table shows summary statistics of recommended regimens in Chu and DeVita (2019). We drop regimens that are missing paper publication years. # regimens is the number of recommend regimens for that cancer. Mean # Drugs is the average number of drugs in a regimen for that cancer. Min # Drugs and Max # Drugs are the minimum and maximum number of drugs in a regimen for that cancer, respectively. Unique # Drugs is the total number of unique drugs used in regimens for that cancer. Average Paper Year is the average paper publication year for the pivotal study for regimens for that cancer.

Figure A.6: Number of Firms, Drugs Per Regimen in Chu and DeVita (2019)



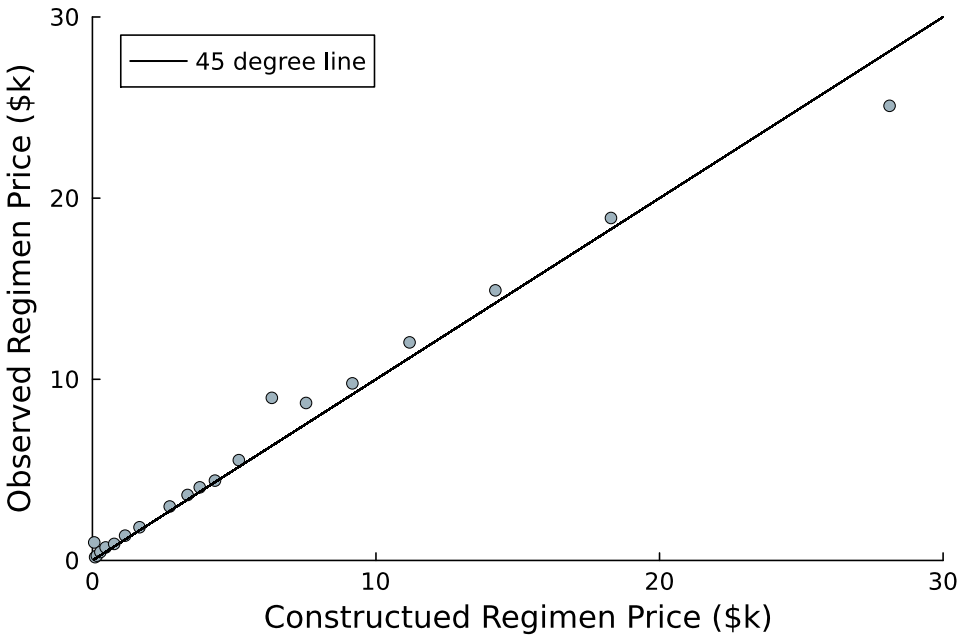
Notes: Figure shows the number of firms and drugs per regimen in Chu and DeVita (2019).

Figure A.7: Fraction of Drug Market Share from Combinations



Notes: Figure shows the density of the fraction of a drug's market share (within time, cancer tuples) that comes from combination regimens. A drug's market share is calculated as the sum of market shares of regimens the drug is a component of.

Figure A.8: Observed versus Constructed Regimen Price



Notes: Figure shows a binscatter of the relationship between observed regimen prices and constructed regimen prices. Constructed regimen prices are calculated from average drug prices then summed to the regimen level, while observed prices sum over drugs and then average. This figure demonstrates the lack of price discrimination based on use in a particular regimen or not.

Table A.4: Observed versus Constructed Regimen Price

	Constructed Regimen Price
(Intercept)	-0.050
	(0.058)
Observed Regimen Price	0.953
	(0.006)
N	3,550
R^2	0.875

Notes: Table shows the relationship between observed regimen prices and constructed regimen prices. Constructed regimen prices are calculated from average drug prices then summed to the regimen level, while observed prices sum over drugs and then average. This table demonstrates the lack of price discrimination based on use in a particular regimen or not.

A.4 Claims Data

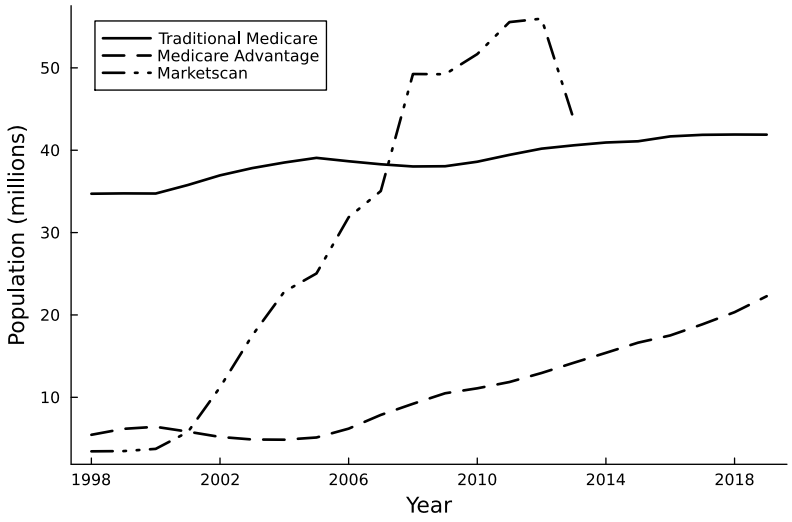
This section describes how we use microdata from CMS and Marketscan to construct cancer patient treatment regimen usage and prices.

A.4.1 Populations

Figure A.9 displays counts of patients in the Medicare and Marketscan data. The solid line and dashed line show the total number of beneficiaries enrolled in Traditional Medicare and Medicare Advantage, respectively, calculated using the Master Beneficiary Summary File. We use a 20% random sample of the beneficiaries, where we observe claims for patients enrolled in Traditional Medicare. The dash-dotted line shows the number of patients we observe in the Marketscan data, calculated using the Annual Summary Enrollment file.

In order to make our demand system representative of the US population, we scale the counts of Traditional Medicare patients (and their drug usage etc.) to meet match the total number of Traditional Medicare and Medicare Advantage patients. We scale up the counts of Marketscan patients to meet the residual US population.

Figure A.9: Number of Enrollees by Insurance Type



Notes: Figure shows the number of individuals enrolled in Traditional Medicare and Medicare Advantage, and the number of individuals we observe in the Marketscan data.

A.4.2 Identifying Cancer Patients

To identify cancer patients, we use the 42 types of cancer identified by Chu and DeVita (2019). In the Medicare and Marketscan data, patients are assigned ICD 10 codes after 2015, and ICD 9 before 2015, to indicate diagnoses. We consider codes C00-D48 (neoplasms), and in particular codes C00-D09 (malignant and in situ neoplasms), leaving out codes D10-D36 (benign neoplasms) and D37-D48 (neoplasms of uncertain or unknown behavior). We manually assign each code to a set of relevant Chu and DeVita (2019) cancer types. The mapping is one to many (e.g., one ICD 10 code can map to many Chu and DeVita (2019) cancer types). In

these cases, the diagnosis codes do not allow us to distinguish between different types of cancers. An important example of this is lung cancer, where the diagnosis codes do not distinguish between non-small and small-cell lung cancer.

To convert between ICD 9 and ICD10 codes, we use the NBER ICD9 to ICD10 crosswalk.[91]

We use the 20% sample of Medicare beneficiaries for years 1998-2019. A beneficiary is defined to have a type of cancer in a year if a claim is submitted with a primary diagnosis of that cancer in either the inpatient, outpatient, or carrier files. We use the 100% sample of the Marketscan dataset. A beneficiary is defined to have a type of cancer in a year if a claim is submitted with a primary diagnosis code of that cancer in either the outpatient, inpatient services, or inpatient admissions files.

Table A.5 shows counts of patients by year for the Medicare and Marketscan datasets.

[91] Available here: https://www.nber.org/research/data/icd-9-cm-and-icd-10-cm-and-icd-10-pcs-crosswalk-or-general-equivalence-mappings. These files were downloaded on January 21, 2023.

Table A.5: Patient Counts by Cancer

Cancer	Median Patients Per Year	
	Medicare	Marketscan
Prostate	205,334	47,097
Head and Neck	110,665	26,738
Colorectal	71,295	27,008
Bladder	54,078	13,270
Basal Cell Carcinoma	53,614	118,782
Non-Hodgkin Lymphoma (NHL)	46,927	26,732
Breast	43,554	41,182
Small Cell Lung (SCLC)	29,755	11,404
Non-Small Cell Lung (NSCLC)	29,755	11,404
Osteogenic Sarcoma	26,327	12,208
Malignant Melanoma	20,618	17,930
Renal Cell Carcinoma	19,976	10,119
Chronic Lymphocytic Leukemia (CLL)	19,397	4,942
Hepatocellular Carcinoma	18,718	7,697
Malignant Mesothelioma	18,625	11,072
Anal	18,467	8,244
Endometrial	17,299	9,243
Multiple Myeloma	16,274	4,920
Biliary Tract	16,128	7,077
Brain	14,552	10,754
Hodgkin Lymphoma	14,369	13,088
Ovarian Germ Cell Tumor	12,410	10,616
Ovarian Epithelial	12,410	10,616
Pancreatic	11,338	3,597
Gastric	7,821	2,993
Central Nervous System (CN)	5,548	3,526
Chronic Myeloid Leukemia (CML)	5,496	2,789
Acute Myeloid Leukemia (AML)	5,092	3,414
Acute Lymphoblastic Leukemia (ALL)	4,965	3,990
Esophageal	3,976	1,577
Cervical	3,059	13,833
Hairy Cell Leukemia	2,995	1,210
Waldenstrom Macroglobulinemia (WM)	2,133	576
Testicular	1,158	5,308
Adrenocortical Carcinoma	1,094	1,492
Kaposi Sarcoma	713	610
Thyroid	661	822
Thymoma	456	321
Merkel Cell Carcinoma	451	293

Notes: Table shows counts of patients by cancer, taking a median over years.

A.4.3 Calculating Regimen Market Shares

Table A.6 shows the average number of drugs cancer patients take that are not included in the regimen they are assigned to.

Table A.6: Regimen Procedure – Extra Drugs

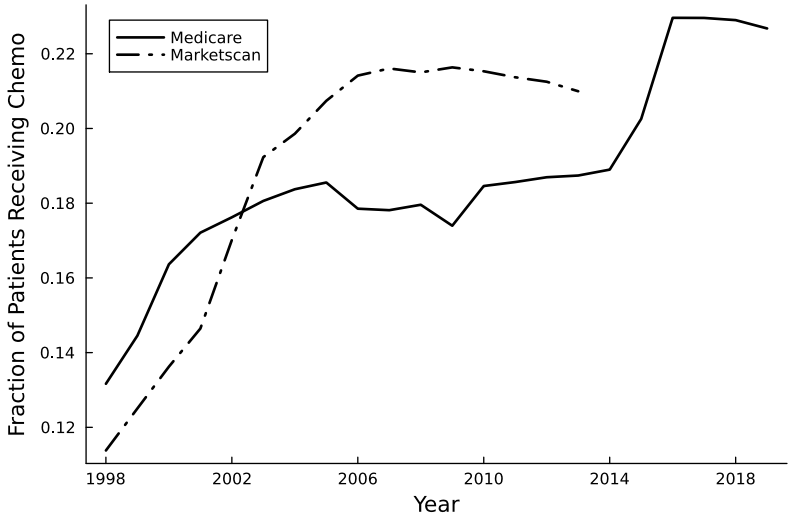
Cancer	Extra Drugs
Prostate	0.18
Head and Neck	0.36
Colorectal	0.72
Bladder	0.11
Non-Hodgkin Lymphoma (NHL)	1.14
Breast	0.23
Non-Small Cell Lung (NSCLC)	0.12
Chronic Lymphocytic Leukemia (CLL)	0.13
Hepatocellular Carcinoma	0.36
Malignant Mesothelioma	0.15
Endometrial	0.39
Multiple Myeloma	0.33
Biliary Tract	0.1
Brain	0.15
Hodgkin Lymphoma	0.5
Ovarian Epithelial	0.18
Pancreatic	0.16
Gastric	0.28
Esophageal	0.13
Mean	0.3

Notes: Table shows the average number of "extra" drugs patients take in addition to drugs in their assigned regimens, by cancer.

A.4.4 Outside Option

Figure A.10 shows the fraction of patients identified to have a particular type of cancer that take cancer drugs in a given year. We take the mean over the cancers, and plot this trend separately for Medicare and Marketscan patients.

Figure A.10: Fraction of Patients Taking Cancer Drugs



Notes: Figure shows the fraction of cancer patients taking drugs. We take a mean over cancers.

A.4.5 Patient Regimen Summary Statistics

Table A.7 presents summary statistics at the patient level about patient characteristics and regimen usage, separately for each cancer in our estimation sample.

Table A.7: Regimen - Patient Summary Statistics

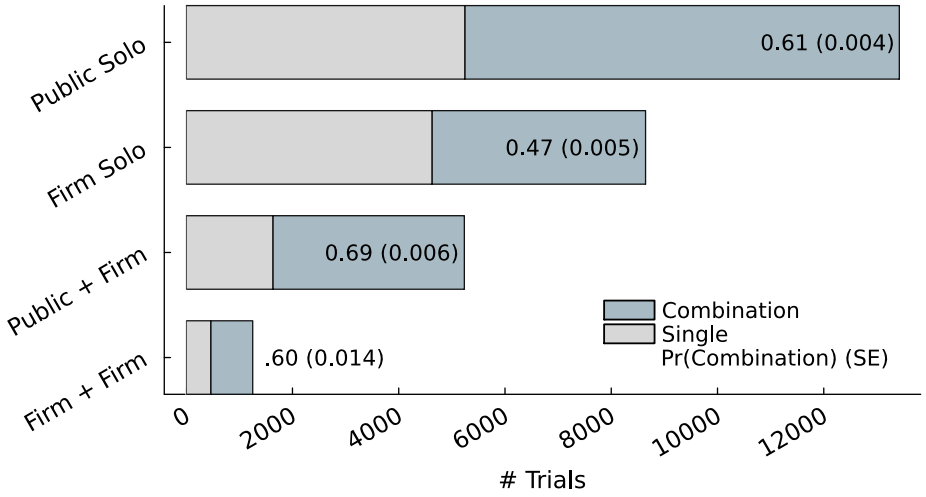
Cancer	Mean Age	Total Regimen Days (Mean)	Total Regimen Days (Std)	Regimen Days (Mean)	Regimen Days (Std)	Num Regimens (Mean)	Num Regimens (Std)
Biliary Tract	92.6	133	91	120	81	1.1	0.3
Bladder	91.6	170	138	126	95	1.3	0.7
Brain	81.2	184	181	167	165	1.1	0.4
Breast	89.5	355	365	213	261	1.7	1.1
Chronic Lymphocytic Leukemia	88.8	282	325	182	218	1.5	0.9
Colorectal	77.6	266	242	152	128	1.8	1.2
Endometrial	91.0	198	189	160	154	1.2	0.5
Esophageal	88.3	131	90	113	68	1.2	0.4
Gastric	85.4	168	134	128	94	1.3	0.6
Head and Neck	78.3	150	139	117	100	1.3	0.6
Hepatocellular	89.5	145	155	128	136	1.1	0.4
Hodgkin Lymphoma	85.2	153	123	143	103	1.1	0.3
Malignant Mesothelioma	85.6	146	113	117	88	1.2	0.6
Multiple Myeloma	77.5	469	541	226	289	2.1	1.5
Non-Hodgkin Lymphoma	77.8	261	265	201	215	1.3	0.6
Non-Small Cell Lung	76.3	199	195	128	119	1.6	0.9
Ovarian Epithelial	81.4	346	315	154	129	2.2	1.5
Pancreatic	77.7	201	172	141	119	1.4	0.8
Prostate	78.0	430	530	287	376	1.5	0.9

Notes: Table includes summary statistics for patients about demographic characteristics and regimen usage by cancer.

B Facts

B.1 Who Funds Combination Innovation

Figure B.1: Clinical Trials by Funding Type



Notes: Figure shows the number of trials run by different sponsors broken in combination (blue) and single drug trials (gray) and the fraction of that sponsor's trials that are for combinations (black number). Robust standard errors are in parentheses on each bar, which come from a trial-level regression of an indicator for being a combination trial on sponsor type.

Table B.1: Probability of Combination Trialing

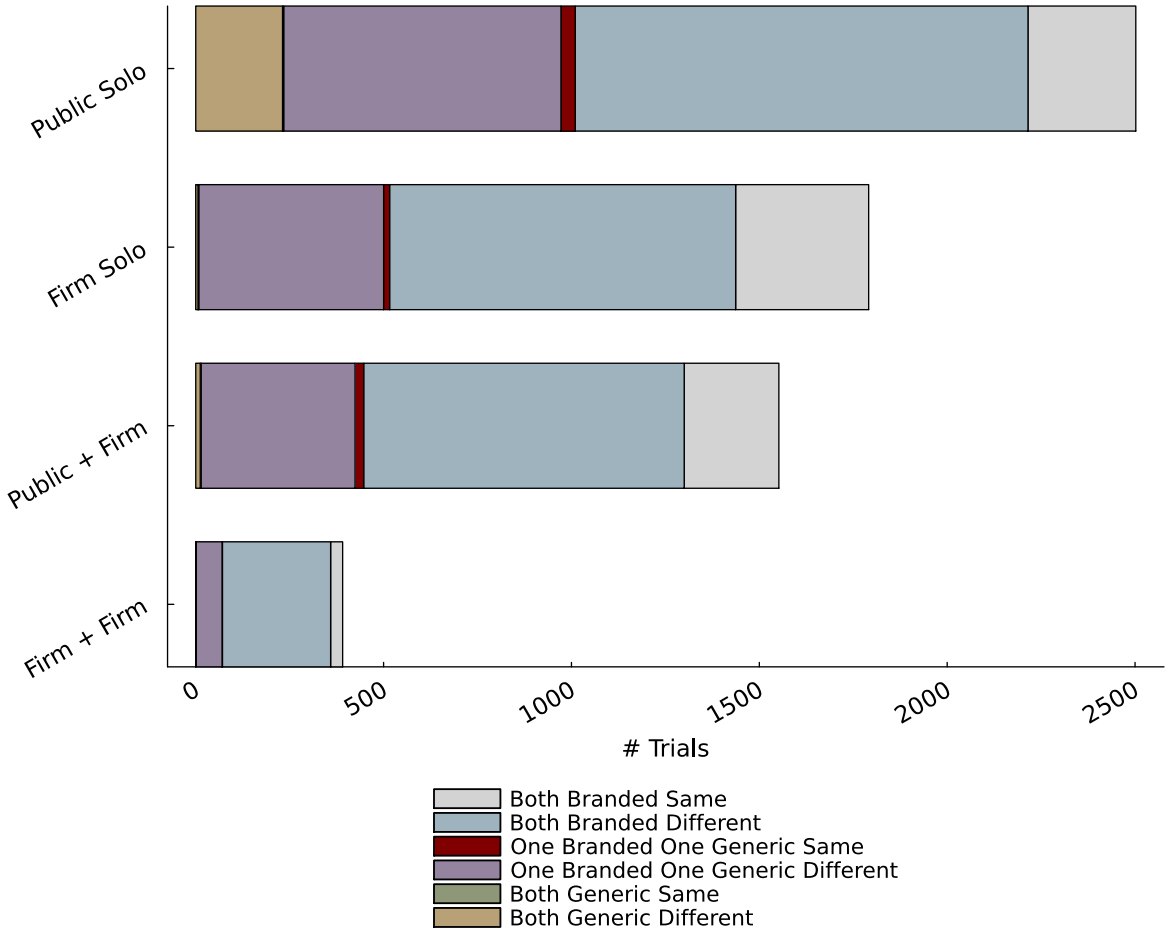
	Combination Indicator			
	(1)	(2)	(3)	(4)
Sponsor Type: Firm + Firm	0.632	0.651	0.013	0.046
	(0.014)	(0.014)	(0.014)	(0.040)
Sponsor Type: Firm Solo	0.465	0.479	-0.139	-0.074
	(0.005)	(0.006)	(0.007)	(0.032)
Sponsor Type: Public + Firm	0.689	0.685	0.074	0.089
	(0.006)	(0.007)	(0.008)	(0.050)
Sponsor Type: Public Solo	0.609	0.600		
	(0.004)	(0.005)		
Cancer Type Fixed Effects			Yes	Yes
Trial Submission Year Fixed Effects			Yes	Yes
N	28,555	21,807	28,555	26,485
R^2	0.593	0.590	0.060	0.333
Within-R^2			0.025	0.013
Year Restriction	None	Post 2007	None	None
Weights	None	None	None	Enrollment

Notes: Table shows estimates of a trial-level regression of an indicator for being a combination trial on indicators for different multi-sponsor types. The first column includes the full sample of clinical trials, while the second checks robustness with respect to only including trials run after 2007. The third column additionally conditions on cancer type (the first type of cancer reported in the trial) and trial submission year. We choose the "Public Solo" group as the base. The fourth column additional weights be number of enrolled patients (e.g., trial size). Robust standard errors are in parentheses.

B.2 What is the Direction of Combination Innovation

B.2.1 Levels

Figure B.2: Two-Drug Trials by Type



B.2.2 Baseline Regression Tables

Table B.2: Relative Probability of Trialing 2 Drugs Together by Drug Ownership Status – Private

	Trial Run (Normalized), Private
Both Branded, Same	10.86546
	(0.938387)
Both Branded, Diff	0.46238
	(0.019609)
Brand and Generic	1.02547
	(0.051401)
N	33,356,609
R^2	0.000094

Notes: Table shows estimates of Equation (3.3). Robust standard errors are in parentheses.

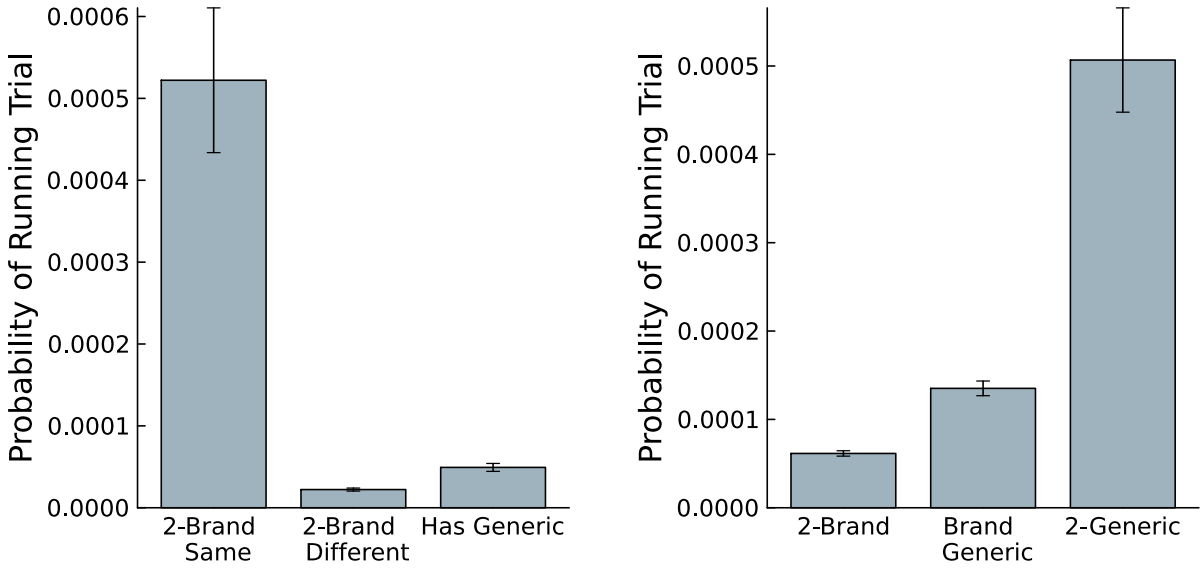
Table B.3: Relative Probability of Trialing 2 Drugs Together by Drug Ownership Status – Public

	Trial Run (Normalized), Public
Both Branded	0.61313
	(0.015553)
One Branded, One Generic	1.34790
	(0.042284)
Both Generic	5.05438
	(0.300375)
N	33,356,609
R^2	0.000132

Notes: Table shows estimates of Equation (3.3) for public innovators. Robust standard errors are in parentheses.

B.2.3 Baseline Regression Tables, Not Normalized

Figure B.3: Relative Probability of Trialing 2 Drugs Together by Drug Ownership Status



(a) Firm

(b) Public

Notes: Figure shows estimated γ_k coefficients of Equation (3.3) where we do not normalize the trialing indicator. Private innovators (firms) are on the left panel, and public innovators on the right. 95% confidence intervals for the regression coefficients calculated from robust standard errors are displayed on each bar. Regression tables and additional robustness checks are given in Appendix B.

B.2.4 Extended Regression Results

$$\begin{aligned}\frac{\text{Trial Now}_{rft}}{\beta^{\text{unif}}\left(L_{ft}\right)} = \gamma_1 \,&\text{Both Branded Same}_{rft} + \gamma_2 \,\text{Both Branded Different}_{rft} \\ &+ \gamma_3 \,\text{One Branded One Generic Same}_{rft} + \gamma_4 \,\text{One Branded One Generic Different}_{rft} \\ &+ \gamma_5 \,\text{Both Generic Same}_{rft} + \gamma_6 \,\text{Both Generic Different}_{rft} + \varepsilon_{rft}. \qquad \text{(B.1)}\end{aligned}$$

Table B.4: Relative Probability of Trialing 2 Drugs Together by Drug Ownership Status – Private

	Trial Run (Normalized), Private
Both Branded, Same	10.86546
	(0.938387)
Both Branded, Diff	0.46238
	(0.019609)
Branded and Generic, Same	1.76066
	(0.556746)
Branded and Generic, Diff	1.00675
	(0.053207)
Both Generic, Same	0.80991
	(0.809899)
Both Generic, Diff	1.13274
	(0.210338)
N	33,356,609
R^2	0.000094

Notes: Table shows estimates of Equation (B.1) for private innovators. Robust standard errors are in parentheses.

Table B.5: Relative Probability of Trialing 2 Drugs Together by Drug Ownership Status – Public

	Trial Run (Normalized), Public
Both Branded, Same	7.69509
	(0.546655)
Both Branded, Diff	0.54049
	(0.014677)
Branded and Generic, Same	4.81012
	(0.636962)
Branded and Generic, Diff	1.29260
	(0.041737)
Both Generic, Same	4.65828
	(1.344416)
Both Generic, Diff	5.07348
	(0.308113)
N	33,356,609
R^2	0.000183

Notes: Table shows estimates of Equation (B.1) for public innovators. Robust standard errors are in parentheses.

B.2.5 Intra-Firm Complementarity

Using data from the NCI-ALAMANC, A Large Matrix of Anti-Neoplastic Agent Combinations, from Holbeck et al. (2017) we can compare whether two-drug combinations that are owned by the same firm have the same efficacy as measured by laboratory tests on human tumor cell lines (NCI-60) of all pairwise combinations of a large set of marketed cancer drugs ($\approx$ 100 drugs, leading to $\approx$ 5000 combinations) for various dosages.

We first look at the effect of being owned by the same firm on tumor growth rates. The results are in Table B.7. While the coefficient on the indicator of being owned by the same firm is negative (indicating the tumor decreasing in size), it is relatively small in magnitude compared to the mean growth rate, and reduces in magnitude even further when including drug fixed effects. Figure B.4 shows the distribution of combination score (a measure of how effective the combination is overall and relative to single-agent therapies, and find similar results), separately for combinations consisting of drugs owned by the firm or not.

Table B.6: NCI Almanac Tumor Growth Rates

	Percent Growth		
	(1)	(2)	(3)
(Intercept)	72.771		
	(0.028)		
Same Firm	-1.300	-1.301	-0.667
	(0.166)	(0.163)	(0.152)
Cell and Panel Fixed Effects Fixed Effects		Yes	Yes
Drug 1 Fixed Effects			Yes
Drug 2 Fixed Effects			Yes
N	2,578,833	2,578,833	2,578,833
F	61.189	63.811	19.383
Within-R^2		0.000	0.000
Adjusted R^2	0.000	0.057	0.235

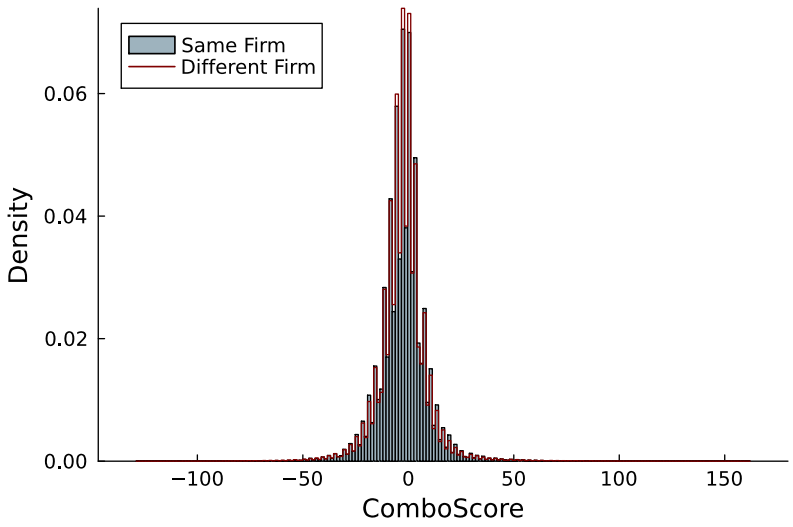
Notes: Table shows estimates of a regression of tumor growth rate (percentage) of a specific combination on an indicator of whether the combination consists of two drugs owned by the same firm.

Table B.7: NCI Almanac ComboScore

	ComboScore		
	(1)	(2)	(3)
(Intercept)	-2.438		
	(0.008)		
Same Firm	0.175	0.174	-0.166
	(0.042)	(0.042)	(0.043)
Cell and Panel Fixed Effects Fixed Effects		Yes	Yes
Drug 1 Fixed Effects			Yes
Drug 2 Fixed Effects			Yes
N	2,578,833	2,578,833	2,578,833
F	17.387	17.385	14.801
Within-R^2		0.000	0.000
Adjusted R^2	0.000	0.005	0.041

Notes: Table shows estimates of a regression of combination score (higher scores are better) of a specific combination on an indicator of whether the combination consists of two drugs owned by the same firm.

Figure B.4: Distribution of ComboScore



Notes: Figure shows the distribution of combination scores, separately for combinations consisting of drugs owned by the firm or not. Each distribution is normalized to show a density.

B.2.6 Multi-Brand Combination Trials

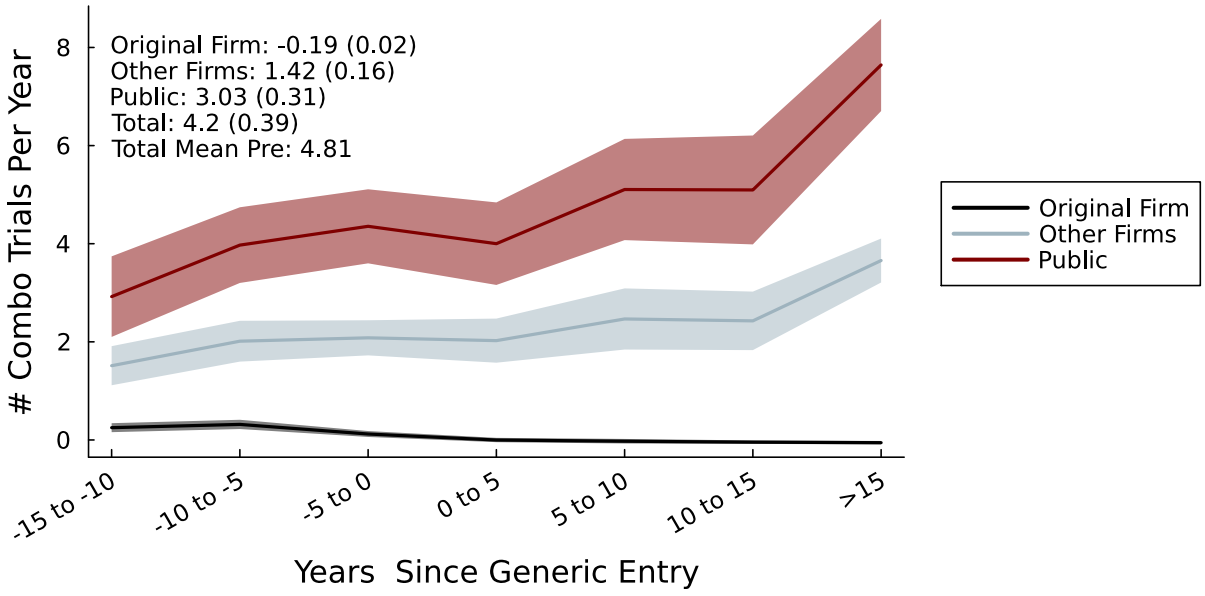
For two-drug combination trials consisting of branded drugs owned by different firms, the firm that has the drug furthest from patent expiry is significantly more like to run the clinical

trial (64% of trials) than the firm with the "newer" drug (36% of trials).

B.3 When Does Combination Innovation Occur

We present results from an alternative specification of Equation 3.4 where we omit drug fixed effects.

Figure B.5: Combination Trials and Generic Entry



Notes: Figure includes dynamic estimates of Equation 3.4 without drug fixed effects.

Table B.8: Combination Trials and Generic Entry Regression

	Original Firm	Public	Other Firms	Total Trials
	(1)	(2)	(3)	(4)
Generic Indicator	-0.172	3.207	1.505	4.291
	(0.020)	(0.277)	(0.142)	(0.350)
Year Fixed Effects	Yes	Yes	Yes	Yes
N	3,882	3,882	3,882	3,882
Mean Pre	0.229	3.894	1.462	4.815

Notes: Table shows coefficient on Generic Indicator in Equation (3.4), excluding drug fixed effects. # Trials (Total) is the total number of combination trials a drug is used in within a year. # Trials Firm is the number of combination trials run by the original owner of the drug in a year. # Trials Other Firm is the number of combination trials run by other firms (i.e., not the original owner of the drug) in a year. Generic Indicator is an indicator of whether drug d is generic at time t (i.e., has had generic entry). Robust standard errors are in parentheses.

C Demand

C.1 Instrument Details

Table C.1: Instrument First Stage – Medicare

	Regimen Price ($k)
# Entrants	-0.27509
	(0.006316)
Generic Entry Time	-0.15212
	(0.010108)
Regimen Fixed Effects	Yes
Year Fixed Effects	Yes
N	34,751
F	1488.304852
First-stage F statistic	
Within-R^2	0.079509
Adjusted R^2	0.893844

Notes: Table shows estimates of the instrument first-stage (the relationship between regimen price and the instrument) for Medicare patients.

Table C.2: Instrument First Stage – Marketscan

	Regimen Price ($k)
# Entrants	-0.27509
	(0.006316)
Generic Entry Time	-0.15212
	(0.010108)
Regimen Fixed Effects	Yes
Year Fixed Effects	Yes
N	34,751
F	1488.304852
First-stage F statistic	
Within-R^2	0.079509
Adjusted R^2	0.893844

Notes: Table shows estimates of the instrument first-stage (the relationship between regimen price and the instrument) for Marketscan patients.

C.2 Micro Moments

We calculate micro moments in the data as follows. Let $\hat{Z}$ denote the set of demographic bins. For each $\hat{z} \in \hat{Z}$ calculate the average characteristic of the taken inside regimens as

$$\bar{p}_{\hat{z}t} = \frac{\sum_{r \in \mathcal{R}_t} s_{\hat{z}rt} p_{rt}}{\sum_{r' \in \mathcal{R}_t} s_{\hat{z}r't}} \tag{C.1}$$

$$\overline{\text{fraction biologic}}_{\hat{z}t} = \frac{\sum_{r \in \mathcal{R}_t} s_{\hat{z}rt} \mathbf{1}_{r \text{ biologic}}}{\sum_{r' \in \mathcal{R}_t} s_{\hat{z}r't}} \tag{C.2}$$

$$\overline{\text{fraction combo}}_{\hat{z}t} = \frac{\sum_{r \in \mathcal{R}_t} s_{\hat{z}rt} \mathbf{1}_{r \text{ combo}}}{\sum_{r' \in \mathcal{R}_t} s_{\hat{z}r't}} \tag{C.3}$$

We then calculate the covariance between $\hat{z}$ and and each of these average characteristics (weighted by the number of patients in that bin).

In the model, these moments are calculated similarly, but instead of observing $s_{\hat{z}rt}$ directly, we impute $s_{\hat{z}rt}$ from $s_{\hat{r}t}$ and the integration weights of the demographic bins. These quantities are simple to compute in the model.

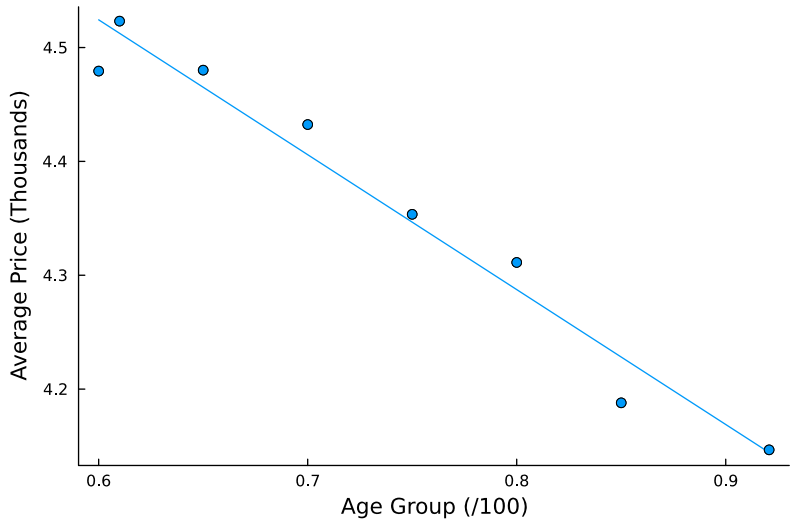
Micro moment targets are show in Table C.3. Additional patterns are displayed below.

Table C.3: Micro Moment Targets

Micro Moment	**Medicare**	**Medicare Dual**	**Marketscan**
$\text{Cov}(a_{it}, p_{rt})$	-0.0157	-0.0157	0.0217
$\text{Cov}(a_{it}, \mathbf{1}_{r \text{ combo}})$	-0.0076	-0.0076	0.0008
$\text{Cov}(a_{it}, \mathbf{1}_{r \text{ biologic}})$	-0.004	-0.004	0.0004

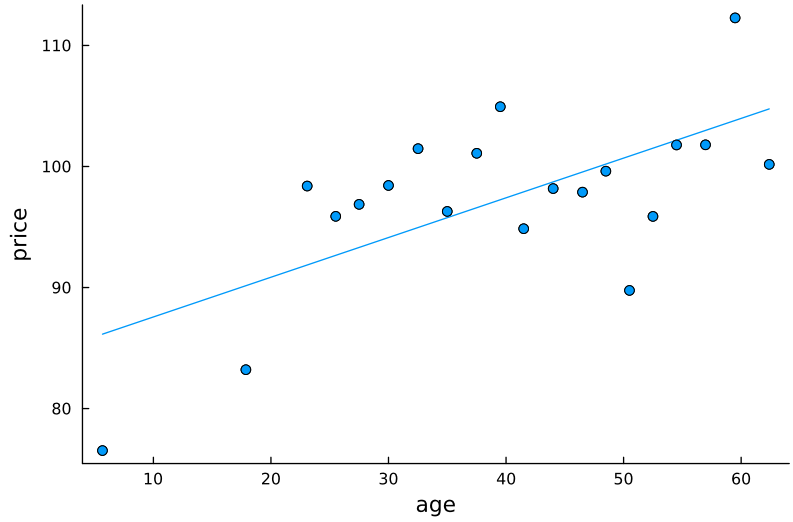
Notes: Table shows micro moment targets by insurance type. Prices are in thousands of dollars and age is divided by 100. These patterns are shown in detail in Appendix C.

Figure C.1: Regimen Price and Patient Age – Medicare



Notes: Figure shows a binscatter of regimen price on age for Medicare patients. Dataset is (share, age-group) monthly average characteristics (conditional on inside good).

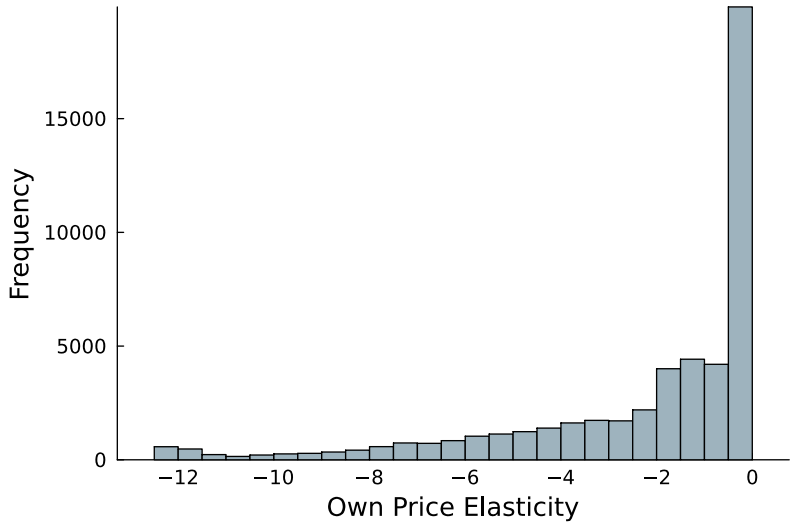
Figure C.2: Regimen Price and Patient Age – Marketscan



Notes: Figure shows a binscatter of regimen price on age for Marketscan patients. Dataset is patient-level monthly regimen usage (conditional on inside good).

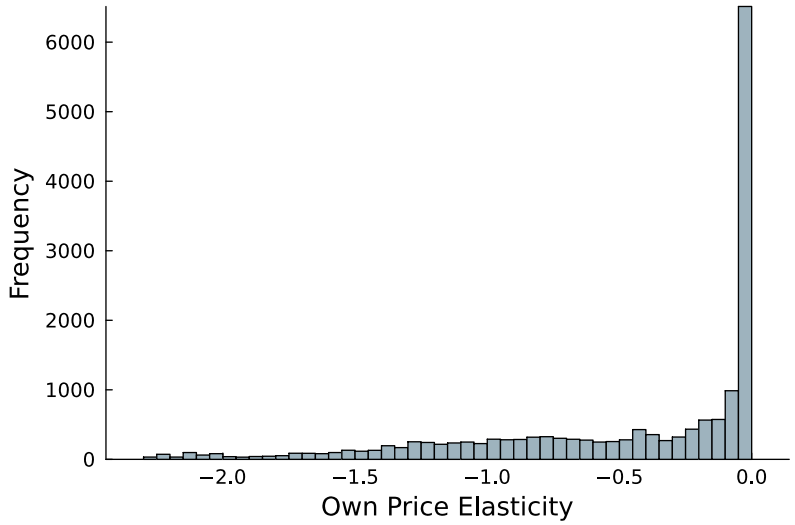
C.3 Additional Results

Figure C.3: Distribution of Own Price Elasticities – Medicare



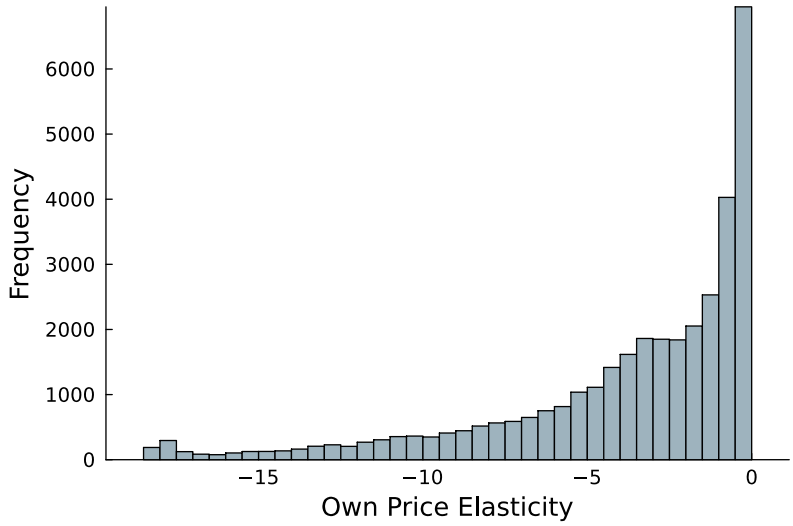
Notes:. Figure shows the distribution of own-price elasticities of demand for Medicare patients.

Figure C.4: Distribution of Own Price Elasticities – Medicare Dual



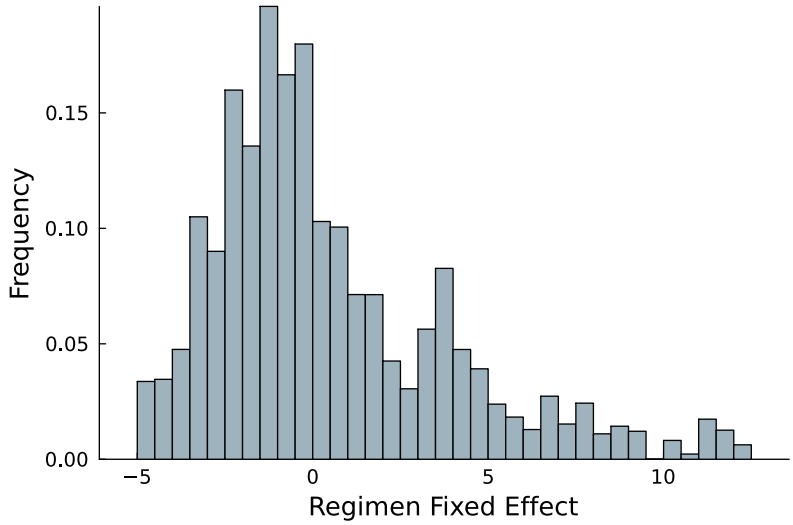
Notes:. Figure shows the distribution of own-price elasticities of demand for Medicare dual-enrolled patients.

Figure C.5: Distribution of Own Price Elasticities – Marketscan



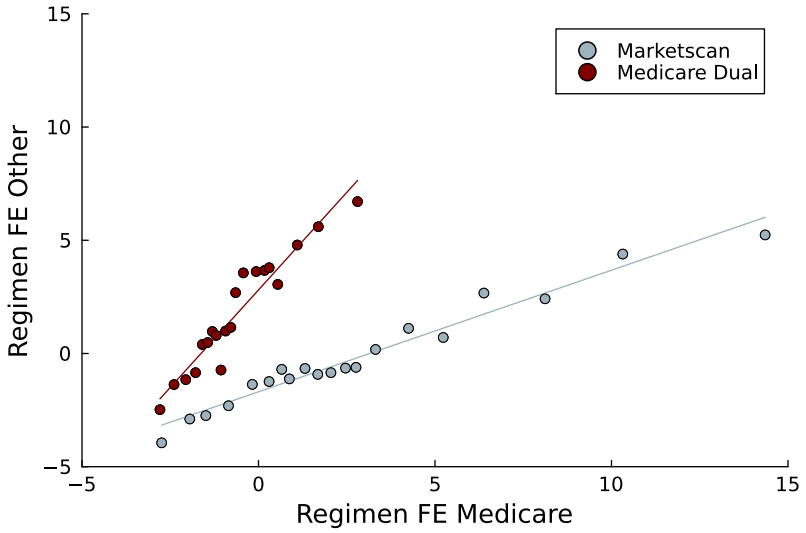
Notes: Figure shows the distribution of own-price elasticities of demand for Marketscan patients.

Figure C.6: Distribution of Regimen Fixed Effects – Medicare



Notes: Figure shows the distribution of regimen fixed effects for Medicare patients.

Figure C.7: Regimen Fixed Effect Comparison Across Insurance Types



Notes: Figure shows binscatters of the relationship between the regimen FEs estimated in the Medicare sample versus the Marketscan and Medicare Dual samples.

Table C.4: Regimen Fixed Effect Comparison Across Insurance Types

	Regimen FE Medicare	
	(1)	(2)
(Intercept)	-1.688	2.807
	(0.042)	(0.068)
Regimen FE Marketscan	0.536	
	(0.008)	
Regimen FE Medicare Dual		1.741
		(0.045)
N	2,444	1,604
R^2	0.634	0.482

Notes: Tables shows regressions of the relationship between the regimen FEs estimated in the Medicare sample versus the Marketscan and Medicare Dual samples.

Table C.5: Regimen Fixed Effect Comparison – Complementarities – Colorectal Cancer

Drug 1	**Drug 2**	**Drug 3**	**Drug 4**	**Regimen FE**
regorafenib				7.59
nivolumab				6.72
pembrolizumab				5.35
oxaliplatin	fluorouracil	leucovorin	bevacizumab	4.88
irinotecan	cetuximab			4.77
cetuximab	bevacizumab	irinotecan		4.06
panitumumab				3.84
cetuximab				3.78
irinotecan	fluorouracil	leucovorin	bevacizumab	3.69
irinotecan	fluorouracil	leucovorin	cetuximab	3.59
cetuximab	bevacizumab			3.47
fluorouracil	leucovorin	bevacizumab		2.59
oxaliplatin	fluorouracil	leucovorin		2.08
irinotecan	fluorouracil	leucovorin	panitumumab	1.76
irinotecan				0.86
oxaliplatin	fluorouracil	levoleucovorin		0.71
fluorouracil	leucovorin			0.54
irinotecan	fluorouracil	leucovorin		0.44
fluorouracil	oxaliplatin			-0.22
fluorouracil				-0.34
irinotecan	oxaliplatin	fluorouracil	leucovorin	-0.51
fluorouracil	levoleucovorin			-0.52
capecitabine				-3.1

Notes: Table shows estimated regimen fixed effects ξ_r for colorectal cancer. Supersets of drugs often have higher fixed effects that the subsets of drugs, indicating complementarity.

Table C.6: Regimen Fixed Effect Comparison – Complementarities – Breast Cancer

Drug 1	Drug 2	Drug 3	Drug 4	Regimen FE
palbociclib	fulvestrant			10.6
everolimus	exemestane			10.15
palbociclib	letrozole			9.48
docetaxel	carboplatin	pertuzumab	trastuzumab	7.6
ado-trastuzumab emtansine				5.81
trastuzumab				2.61
anastrozole				1.86
eribulin				1.77
docetaxel	carboplatin	trastuzumab		1.73
paclitaxel	bevacizumab			1.53
trastuzumab	paclitaxel			1.51
fulvestrant				1.2
letrozole				1.15
tamoxifen				1.05
trastuzumab	docetaxel			0.72
trastuzumab	vinorelbine			0.17
exemestane				0.16
trastuzumab	gemcitabine			-0.36
docetaxel				-0.47
paclitaxel				-0.51
doxorubicin	cyclophosphamide			-0.73
docetaxel	cyclophosphamide			-0.96
gemcitabine				-0.99
carboplatin	paclitaxel			-1.33
cyclophosphamide	methotrexate	fluorouracil		-1.65
megestrol				-1.87
doxorubicin	cyclophosphamide	docetaxel		-1.87
vinorelbine				-1.88
doxorubicin	cyclophosphamide	paclitaxel		-2.02
carboplatin	docetaxel			-2.08
fluorouracil	epirubicin	cyclophosphamide		-2.49
docetaxel	doxorubicin			-2.92
gemcitabine	paclitaxel			-3.16
doxorubicin				-3.17
cyclophosphamide	doxorubicin	fluorouracil		-3.21
doxorubicin	paclitaxel			-3.83

Notes: Table shows estimated regimen fixed effects ξ_r for breast cancer. Supersets of drugs often have higher fixed effects that the subsets of drugs, indicating complementarity.

D Bargaining

D.1 Consumer Surplus Weight

We describe two sets of reasons why the insurer might weight consumer surplus with some weight $\rho > 1$ in its objective.

Patient Price Misperception: The first can be microfounded by patient misperceptions of drug costs. Suppose the insurance market is competitive, so that insurers must offer some minimum level of consumer surplus CS^*. For simplicity, assume there is one drug with demand $x(p)$. The insurer chooses premium Φ and drug price p. The consumer pays $p^c(p)$, but perceives price to be $\mu p^c(p)$ (e.g., as suggested by Abaluck Gruber). The insurer's objective is

$$\max_{\Phi,p} \quad \Phi - (p - p^c(p))x(p) \quad \text{s.t.} \quad -\Phi + \int_0^{x(p^c(p))} x^{-1}(s)ds - \mu \times p^c(p)x(p^c(p)) = CS^* \tag{D.1}$$

We can simplify

$$\int_0^{x(p^c(p))} x^{-1}(s)ds = \int_{p^c(p)}^{\infty} x(s)ds + p^c(p)x(p^c(p)) \tag{D.2}$$

Substituting for Φ, the objective function becomes

$$\max_{p} \quad \int_{p^c(p)}^{\infty} x(s)ds + p^c(p)x(p) - \mu p^c(p)x(p) - (p - p^c(p))x(p) - CS^* \tag{D.3}$$

Suppose $p^c(p) = \zeta p$ (i.e., constant coinsurance rate). Then the objective can be further simplified as

$$\max_{p} \quad \int_{p^c(p)}^{\infty} x(s)ds + (\zeta - \mu\zeta - (1-\zeta))px(p) - CS^* \tag{D.4}$$

$$= \quad \int_{p^c(p)}^{\infty} x(s)ds + (\zeta(2-\mu) - 1)px(p) - CS^* \tag{D.5}$$

$$= \quad \int_{p^c(p)}^{\infty} x(s)ds + \frac{(\zeta(2-\mu)-1)}{1-\zeta}(1-\zeta)px(p) - CS^* \tag{D.6}$$

Suppose $\zeta = .2$ and $\mu = .8$. This gives a weight of .95 on insurer costs. This weight is decreasing in μ and ζ. Other reasons that might decrease μ (i.e., lower consumer expectation of cost):

- underestimating sickness / duration of treatment
- overestimating probability of getting high cost drugs (i.e., overestimating probability of prior authorization) – think of as making ex-post cost smaller than expected
- physicians steering to high-cost drugs

Patient Value Misperception: A second reason for $\rho > 1$ could be that consumers themselves "overweight" the (expected) consumer surplus from these drugs. If a patient overweights the probability she will need to take drugs for a cancer, or overweights the value of those drugs (i.e., because of advertising), then in order to get the consumer to choose a particular insurance plan, the insurer might as well.

D.2 Estimation Procedure Details

Define $\Delta V_{ft} = \mathrm{V}_{\iota t}(\mathcal{R}_t, p_t) - \mathrm{V}_{\iota t}\left(\mathcal{R}_t \setminus \mathcal{R}_{ft}, p_t\right)$ as the disagreement payoff for firm f at time t. The first-order condition of the Nash Bargaining problem of firm f in Equation 5.1 for p_{dt}, where $d \in \mathcal{D}_{ft}(\mathcal{R}_t)$ is

$$0 = \gamma_f \frac{1}{\pi_{ft}} \frac{\partial \pi_{ft}}{\partial p_{dt}} + \left(1 - \gamma_f\right) \frac{1}{\Delta V_{ft}} \frac{\partial V_t}{\partial p_{dt}}. \tag{D.7}$$

The derivatives are given by

$$\frac{\partial \pi_{ft}}{\partial p_{dt}} = \sum_{\iota} \sum_{c \in \mathcal{C}} M_{\iota ct} \sum_{d' \in \mathcal{D}_{ft}} \sum_{r \in \mathcal{R}_{ct}(d')} \left\{ \left(p_{d't} - mc_{d't}\right) \frac{\partial s_{\iota rt}}{\partial p_{dt}} + s_{\iota rt} \mathbb{1}\left[d = d'\right] \right\} \tag{D.8}$$

Given a bargaining weight, we can invert the FOCs for the vector of marginal costs $(mc_{dt})_{d \in \mathcal{D}}$. When firms are single-product, marginal costs are given by

$$mc_{dt} = \frac{\gamma_f \Delta V_t \sum_{\iota} \sum_{c} M_{\iota ct} \sum_{r \in \mathcal{R}(d)} \left(s_{\iota rt} + p_{dt} \frac{\partial s_{\iota rt}}{\partial p_{dt}} \right) + (1 - \gamma_f) \frac{\partial V_t}{\partial p_{dt}} \sum_{\iota} \sum_{c} M_{\iota ct} \sum_{r \in \mathcal{R}(d)} p_{dt} s_{\iota rt}}{\gamma_f \Delta V_t \sum_{\iota} \sum_{c} M_{\iota ct} \sum_{r \in \mathcal{R}(d)} \frac{\partial s_{\iota rt}}{\partial p_{dt}} + (1 - \gamma_f) \frac{\partial V_t}{\partial p_{dt}} \sum_{\iota} \sum_{c} M_{\iota ct} \sum_{r \in \mathcal{R}(d)} s_{\iota rt}} \tag{D.9}$$

When firms own multiple drugs, we can solve for marginal costs by inverting the stacked first-order conditions.

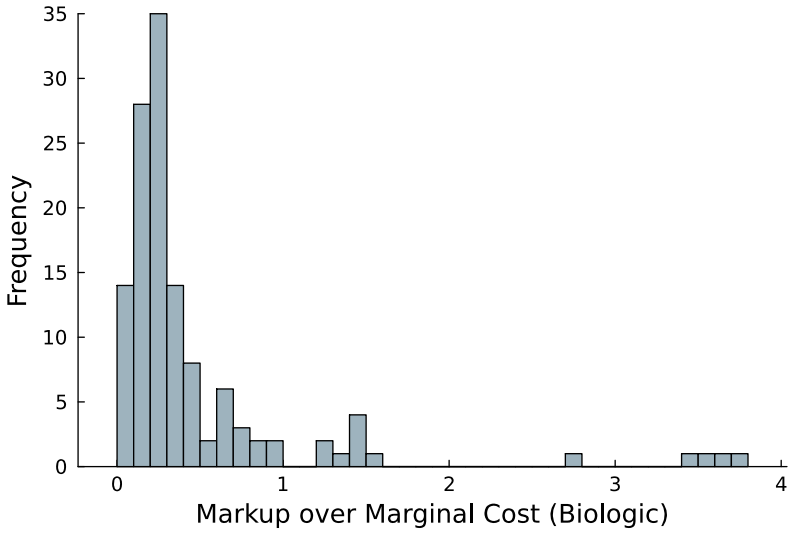
D.3 Solving for Equilibrium Prices

The first-order condition in Equation D.7 may be numerically ill-conditioned when $\pi_{ft} \downarrow 0$ or $\Delta V_{ft} \downarrow 0$, so we instead solve using the transformed FOC

$$0 = \gamma_f \frac{\partial \pi_{ft}}{\partial p_{dt}} \Delta V_{ft} + \left(1 - \gamma_f\right) \frac{\partial V_t}{\partial p_{dt}} \pi_{ft}. \tag{D.10}$$

D.4 Additional Results

Figure D.1: Biologic Drug Markups



Notes: Figure shows the distribution of markups (calculated as margin over marginal cost) of biologic drugs.

Table D.1: Bargaining Weight Robustness

ρ	γ	γ **SE**	**Markup**	**Markup SD**
8.04	0.69	0.29	0.25	0.44
2.5	1.0	0.0	0.11	0.37
5.0	0.89	0.51	0.22	0.41
10.0	0.52	0.14	0.26	0.44

Notes: Table shows how the manufacturer bargaining varies with the consumer surplus weigh ρ. The first row contains our baseline estimates. The remaining rows fix ρ and different levels and estimate the bargaining weight. Model implied markups are computed for each specification.

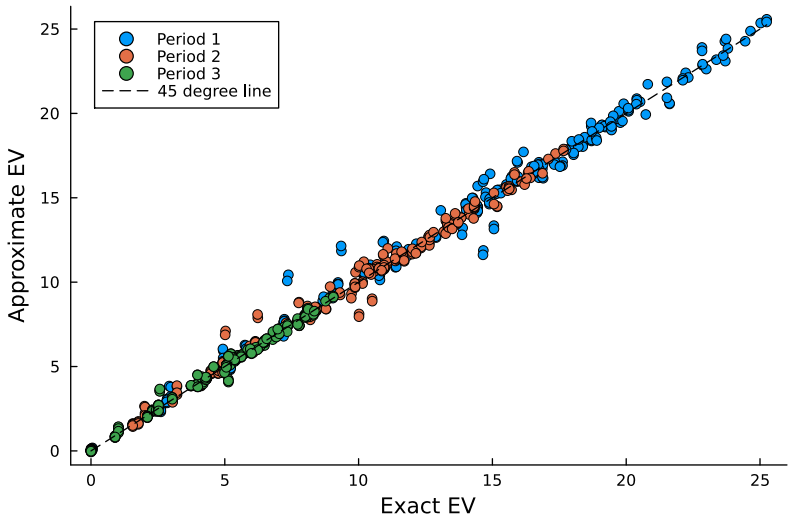
E Dynamic Model

E.1 Model Solution Details

E.1.1 Approximation Error Monte Carlo

We compare the exact and approximate expected value functions (over states) for a model with 3 periods, 9 potential regimens, and 4 quality states for each regimen (not trialed, trialed and failed, trailed and success with low quality, and trialed and success with high quality). Solving the model exactly requires evaluating over 250,000 states each period. We choose small number of states ($\approx$ 5000) for the approximation. Figure E.1 shows the relationship between the exact expected value function versus the approximation value function. We observe minimal approximation error. Importantly, the error does significantly increase in earlier periods of the game.

Figure E.1: Exact EV versus Approximate EV



Notes: Figure shows the relationship between the exact expected value function and the approximate expected value function, by period.

E.2 Computing Counterfactuals

For focal regimen r, set s_{r0} to be the initial state in data. For each simulation, we proceed as follows. For each t until the model predicts trialing of the focal regimen:

(i) Compute flow surplus for each innovator at s_{rt}.

(ii) Compute the ex-ante choice-specific value functions for each innovator using the sieve computed at the counterfactual parameters.

(iii) Draw random variables to determine state transition:

(a) Draw uniform random variables to determine trialing decisions of each innovator using the conditional choice probabilities that are derived from the ex-ante choice-specific value functions.

(b) Draw uniform random variables to determine the trialing decisions of tracked (non-focal) regimens.

(c) Draw uniform random variables to determine trial success and random variables from quality distribution G to determine trial outcomes of non-focal and focal regimens (if applicable).

(iv) Update the state.

We repeat this procedure a large number of times (250) for each focal regimen and compute average trial times (and fraction of trials by each innovator) over these repetitions.

E.3 Estimation Sample

Table E.1: Dynamic Model Regimens: Summary Statistics

	Public Trial Mean	**Public Trial** Std Dev	**Private Trial** Mean	**Private Trial** Std Dev
Time to First Trial	5.65	3.91	4.44	3.49
Start Year	2003.96	5.15	2007.74	5.68
Number of Drugs	2.63	0.73	2.49	0.67
Success Indicator	0.01382		0.00947	
Number of Regimens	5138		4014	

Notes: Table shows summary statistics of the regimens included in the dynamic model.

E.4 Model Fit

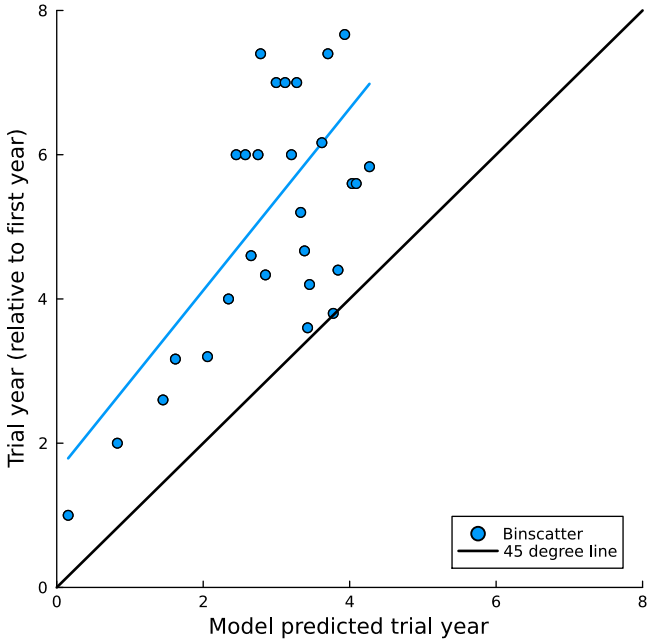


Figure E.2: Model Fit - Trial Year

Notes: Figure shows the relationship between the trial year in the data and the model predicted trial year through a binscatter.

E.5 Nonparametric CCP Estimation

We produce first-stage estimates of conditional choice probabilities by regressing trialing decisions on functions of state variables, separately for public innovators (Table E.2) and private firms (Table E.3). We focus on the timing of the trial, summary statistics of other regimens (e.g., number of untested regimens in the state), and cancer fixed effects.

Table E.2: Public CCPs

	action				
	(1)	(2)	(3)	(4)	(5)
(Intercept)	0.040	0.357	0.366	0.366	0.306
	(0.003)	(0.020)	(0.020)	(0.020)	(0.023)
Time since first year	0.023				
	(0.001)				
Time since first year (0-5)		-0.286	-0.260	-0.260	-0.262
		(0.020)	(0.020)	(0.020)	(0.020)
Time since first year (5-10)		-0.137	-0.125	-0.125	-0.131
		(0.020)	(0.020)	(0.020)	(0.020)
Time since first year (10-15)		-0.077	-0.071	-0.071	-0.076
		(0.022)	(0.021)	(0.021)	(0.021)
Number of untested regimens in state			-0.011	-0.011	-0.015
			(0.001)	(0.001)	(0.001)
Time since generic (owned drug in regimen)				-0.002	-0.002
				(0.002)	(0.002)
cancer: bladder					0.045
					(0.017)
cancer: breast					0.098
					(0.013)
cancer: cll					0.070
					(0.013)
cancer: colorectal					0.087
					(0.015)
cancer: head and neck					0.053
					(0.014)
cancer: hepatocellular					0.028
					(0.016)
cancer: hodgkin lymphoma					0.052
					(0.013)
cancer: multiple myeloma					0.095
					(0.014)
cancer: non-hodgkin lymphoma					0.074
					(0.013)
cancer: non-small cell lung					0.108
					(0.014)
cancer: ovarian epithelial					0.077
					(0.015)
cancer: pancreatic					0.068
					(0.014)
cancer: prostate					0.058
					(0.014)
N	30,759	30,759	30,759	30,759	30,759
R^2	0.053	0.055	0.063	0.063	0.067

Notes: Table shows CCP estimates for public innovators.

Table E.3: Private CCPs

	action				
	(1)	(2)	(3)	(4)	(5)
(Intercept)	0.021	0.005	0.009	0.009	-0.002
	(0.001)	(0.005)	(0.005)	(0.005)	(0.006)
Time since first year	-0.001				
	(0.000)				
Time since first year (0-5)		0.015	0.027	0.027	0.028
		(0.005)	(0.005)	(0.005)	(0.005)
Time since first year (5-10)		0.011	0.016	0.016	0.015
		(0.005)	(0.005)	(0.005)	(0.005)
Time since first year (10-15)		0.001	0.004	0.004	0.003
		(0.006)	(0.006)	(0.006)	(0.006)
Number of untested regimens in state			-0.005	-0.005	-0.008
			(0.000)	(0.000)	(0.000)
Time since generic (owned drug in regimen)				-0.001	-0.001
				(0.000)	(0.000)
cancer: bladder					0.004
					(0.004)
cancer: breast					0.039
					(0.003)
cancer: cll					0.011
					(0.003)
cancer: colorectal					0.023
					(0.004)
cancer: head and neck					0.007
					(0.004)
cancer: hepatocellular					0.013
					(0.004)
cancer: hodgkin lymphoma					0.001
					(0.003)
cancer: multiple myeloma					0.031
					(0.004)
cancer: non-hodgkin lymphoma					0.013
					(0.003)
cancer: non-small cell lung					0.047
					(0.003)
cancer: ovarian epithelial					0.014
					(0.004)
cancer: pancreatic					0.015
					(0.004)
cancer: prostate					0.001
					(0.004)
N	74,430	74,430	74,430	74,430	74,430
R^2	0.001	0.001	0.010	0.010	0.020

Notes: Table shows CCP estimates for private innovators.

E.6 Alternative Estimation Procedure: Euler Perturbations

This section derives estimating equations for exploiting finite dependence to estimate the model via Euler perturbations.

E.6.1 Estimation Equations

Let $p_{rft}(s_{rt})$ be the CCP for focal player given state s_{rt} (focal regimen r, focal player f, time t), and let $p_{rftc}(s_{rt})$ be the (aggregate) CCP of competitors.

Compare two sequences of *planned* trialing actions for an agent

(i) $(0,1,1,\ldots)$

(ii) $(1,1,1,\ldots)$

Then compare choice-specific *conditional* value functions for these choices, and observe that the game ends up in same state by period $t+2$:

$$v_{rft}(s_{rt};0,1) = \pi_{rft}(s_{rt}) + \beta\mathbb{E}\left[\pi_{rft+1}(s_{t+1}|f \text{ doesn't trial at } t) + (1-p_{rftc}(s_t))\kappa_{rft+1}\right] + \beta^2\mathbb{E}\left[v_{rft+2}(s_{t+2};1)\right],$$
$$v_{rft}(s_{rt};1) = \pi_{rft}(s_{rt}) - \kappa_{rft} + \beta\mathbb{E}\left[\pi_{rft+1}(s_{t+1}|f \text{ trials at } t)\right] + \beta^2\mathbb{E}\left[v_{rft+2}(s_{t+2};1)\right].$$

Subtracting these terms gives

$$\begin{aligned} v_{rft}(s_{rt};1) - v_{rft}(s_{rt};0,1) = &-\kappa_{rft} + \beta\mathbb{E}\left[\pi_{rft+1}(s_{t+1}|f \text{ trials at } t)\right] \\ &- \beta\mathbb{E}\left[\pi_{rft+1}(s_{t+1}|f \text{ doesn't trial at } t) + (1-p_{rftc}(s_t))\kappa_{rft+1}\right]. \end{aligned}$$

This leads to a two-step estimation approach. The first step is to nonparametrically estimate CCPs. In the second step, we use the recovered CCPs and the Hotz-Miller inversion to estimate dynamic parameters:

$$\ln\left(\frac{p_{rft}(s_{rt})}{1-p_{rft}(s_{rt})}\right) = \frac{1}{\theta^{\epsilon}}\left(v_{rft}(s_{rt};1) - v_{rft}(s_{rt};0)\right).$$

Notice however the choice-specific conditional value function $v_{rft}(s_{rt};0,1)$ is not the same as the choice-specific value function $v_{rft}(s_{rt};0)$. However, we can estimate the difference between

these terms. We have that

$$\begin{aligned} V_{rft}(s_t) &= \theta^{\epsilon}\mathbb{E}\left[\ln\left(\exp\left(\frac{1}{\theta^{\epsilon}}v_{rft}(s_t;0)\right)+\exp\left(\frac{1}{\theta^{\epsilon}}v_{rft}(s_t;1)\right)\right)\right] \\ &= v_{rft}(s_t;1)-\theta^{\epsilon}\ln p_{rft}(s_{rt}) \\ &= v_{rft}(s_t;0)-\theta^{\epsilon}\ln(1-p_{rft}(s_{rt})) \end{aligned}$$

and

$$\begin{aligned} v_{rft}(s_{rt};0) &= \pi_{rft}(s_{rt})+\beta\mathbb{E}\left[V_{rft+1}(s_{t+1})\right] \\ &= \pi_{rft}(s_{rt})+\beta\mathbb{E}\left[v_{rft+1}(s_{t+1};1)-\theta^{\epsilon}\ln p_{rft+1}(s_{t+1})\right] \end{aligned}$$

and

$$\begin{aligned} v_{rft}(s_{rt};0,1) &= \pi_{rft}(s_{rt})+\beta\mathbb{E}\left[\pi_{rft+1}(s_{t+1}|f \text{ doesn't trial at } t)+(1-p_{rftc}(s_t))\kappa_{rft+1}\right]+\beta^2\mathbb{E}\left[v_{rft+2}(s_{t+2};1)\right] \\ &= \pi_{rft}(s_{rt})+\beta\mathbb{E}\left[(1-p_{rftc})v_{rft+1}(s_{t+1}|f \text{ trials});1)+p_{rftc}(v_{rft+1}(s_{t+1}|f \text{ doesn't trial};1))\right] \\ &= \pi_{rft}(s_{rt})+\beta\mathbb{E}\left[v_{rft+1}(s_{t+1};1)+p_{rftc}\kappa_{rft+1}\right] \end{aligned}$$

This gives

$$\begin{aligned} v(s_{rt};1)-v(s_{rt};0) &= v(s_{rt};1)-(v(s_{rt};0,1)+\text{correction}) \\ &= -\kappa_{rft}+\beta\mathbb{E}\left[\pi_{rft+1}(s_{t+1}|f \text{ trials at } t)\right]-\beta\mathbb{E}\left[\pi_{rft+1}(s_{t+1}|f \text{ doesn't trial at } t)+(1-p_{rftc}(s_t))\kappa_{rft+1}\right] \\ &\quad +\beta\mathbb{E}\left[\theta^{\epsilon}\ln p_{rft+1}(s_{t+1})+p_{rftc}(s_{rt})\kappa_{rft+1}\right] \end{aligned}$$

This is a similar result to Arcidiacono and Ellickson (2011) (and applied, in, e.g., Scott, 2014), but with a correction for free-rider problem: there is some probability of ending up in trialed state but not actually having to run trial.

We can then apply the standard rational expectations assumption. Under the assumption of rational expectations, the conditional expectation of CCPs and profits at $t+1$ is equal to the realized variables minus an expectational error. We assume this error is orthogonal to state variables at period t. That expectational error will be included in the regression error term.

The second step estimation equation is then

$$\ln\left(\frac{p_{rft}(s_{rt})}{1-p_{rft}(s_{rt})}\right)-\beta\ln p_{rft+1}(s_{rt+1})=$$
$$\frac{1}{\theta^{\epsilon}}\Big(-\kappa_{rft}+\beta\pi_{rft+1}(s_{rt+1}|f \text{ trials at } t)-\beta\pi_{rft+1}(s_{rt+1}|f \text{ doesn't trial at } t)+\beta p_{rftc}(s_{rt})\kappa_{rft+1}$$
$$-\beta(1-p_{rftc}(s_{rt}))\kappa_{rft+1}+\text{expectation error}\Big)$$
$$=\frac{1}{\theta^{\epsilon}}\Big(\beta\pi_{rft+1}(1-p_{rftc}(s_{rt}))+\kappa_{rft}(-1+\beta(2p_{rftc}(s_{rt})-1))\Big)+\text{expectation error}$$

F Institutional Details

F.1 Clinical Trial Cost Components

Table F.1: Clinical Trial Cost Components

Cost Component	Cost Group	Mean Percent
Data Management Costs	Administrative	1.0
Cost Per IRB Approvals	Administrative	0.9
Cost of IRB Amendments	Administrative	0.0
Administrative Staff Costs	Administrative	19.6
Patient Recruitment Costs	Patient Recruitment	2.3
Patient Retention Costs	Patient Recruitment	0.2
Clinical Procedure Total	Clinical Procedure	19.2
SDV Costs	Site	6.8
RN/CRA Costs	Site	7.4
Physician Costs	Site	5.8
Central Lab Costs	Site	8.4
Site Recruitment Costs	Site	2.6
Site Retention Costs	Site	12.9
Site Monitoring Costs	Site	12.9

Notes: Table shows estimates of clinical trial cost components (as a percentage of total cost) from Sertkaya et al. (2014). The cost of drugs used in the trial would be recorded under the category "Clinical Procedure Total," which also likely includes costs associated with administering the drugs.

F.2 Contracting Frictions

The development of cancer drug combination therapies faces several significant contracting frictions that hinder collaboration between firms and the ability of firms to internalize innovation externalities through Coasian bargaining.

One major challenge is the uncertainty surrounding the commercial potential of combination regimens. This uncertainty complicates negotiations between firms, often leading to a "hold up" problem where each party tries to extract more value than their contribution warrants. As Humphrey et al. (2011) notes, this can result in negotiations being viewed as a "zero-sum exercise" with perceived economic winners and losers.

Intellectual property (IP) concerns also pose substantial barriers to collaboration. Companies are often reluctant to combine their drugs with those from other firms due to worries about potential IP violations and liabilities. This extends to concerns about "secondary IP" that might arise from unexpected therapeutic benefits of drug combinations. As a result, firms tend to prefer developing combinations using only their own drugs, as it simplifies the IP landscape:

- "One company might have a candidate therapy that would make sense to test with a drug from a different firm. But because the two firms hold the patents to each separately, both parties might worry about future liabilities, intellectual property (IP) rights, and secondary IP (that is, IP issues that might arise from unexpected new therapeutic benefits from combining the drugs)" (Deng, 2015).
- "They would rather do it with two of their own drugs, because it makes life easy" (Institute of Medicine et al., 2012).
- "A major impediment to companies sharing their cell lines and drug candidates preclinically is intellectual property issues, while others stressed that intellectual property rights impede clinical trials of combination cancer therapies" (Institute of Medicine et al., 2012).

Another significant friction arises from the potential for adverse effects in combination therapies. Companies fear that unexpected negative outcomes in combination trials could harm the development prospects of their individual drugs. This risk is particularly acute for drugs still in the investigational stage:

- "There was a day, years ago, when the only drugs worth testing were coming from CTEP [NCI's Cancer Therapy Evaluation Program]," said Johnson. But these days, most drugs come from companies, whose corporate cultures—and in particular, their legal departments—render them reluctant to collaborations with potential competitors" (Goldman, 2003).
- "Such combination trials are relatively easy when the compounds are all owned or licensed by one company, but what about combining an investigational drug with another investigational drug from a different company? Companies developing one or both compounds have real concerns—not the least of which is the fear of fortuitous bad reactions. "Suppose we did a combination trial," Johnson mused, "and had some catastrophic result—like the first three patients just up and died within 2 hours of being treated. That would put a cold chill on both drugs. That's the conundrum that companies face" (Goldman, 2003).

Antitrust concerns and pricing issues further complicate the landscape. Some companies express reluctance to engage in collaborative R&D due to perceived antitrust risks (Institute of Medicine et al., 2012):

- "Some drug companies have expressed reluctance to conduct collaborative R&D on investigational drugs with other companies because of concerns about violating antitrust

laws" (Institute of Medicine et al., 2012).

Additionally, competition laws in various jurisdictions can prevent manufacturers from agreeing on pricing strategies for combination treatments without impacting standalone drug prices, limiting their ability to optimize pricing for different use cases. Podkonjak et al. (2021) highlights this friction in the UK, and similar institutional details also apply to the US context:

- "UK competition law, enforced by the Competition Markets Authority (CMA), prevents individual manufacturers agreeing prices for their treatments as part of an agreement for splitting revenues from combination treatments, where this has the effect of also impacting prices for the treatments when sold on a standalone basis. It also prohibits the exchange of pricing or other sensitive commercial information that could have the effect of limiting competition between the manufacturers when supplying their treatments on a standalone basis" (Podkonjak et al., 2021) (statement for UK, but something similar true in US).

F.3 Exclusivity

A drug is protected from competition through two mechanisms: patents and FDA "data exclusivity." A firm can directly patent a drug (more precisely an "active moiety," the part of a drug responsible for the physiological effect) after discovery, in which case it has the sole right to manufacture and market the drug for 20 years, with the exception of the Bolar exemption which protects the rights of others to use the drug in research. It can further apply for patents related to other formulations and indications at any time that would extend the firm's exclusive right to market the drug for these new purposes, but would not interfere with generic competition under the original formulation or indications.

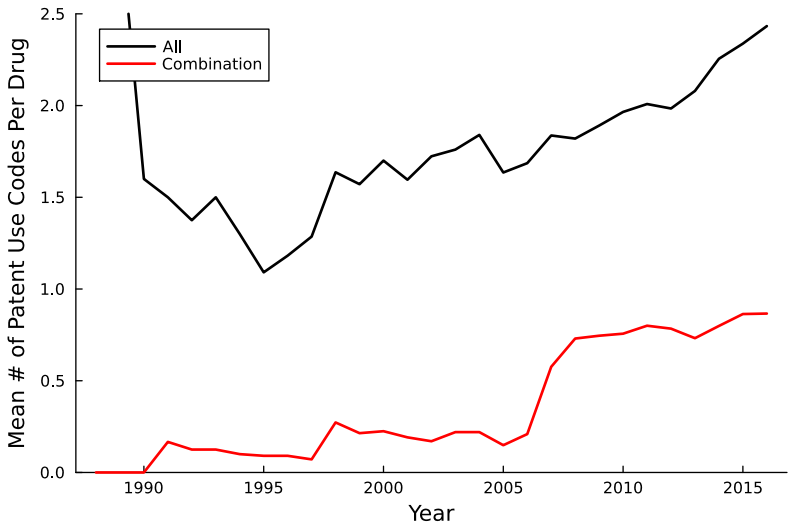
The FDA's data exclusivity provisions function similarly: The firm(s) applying for New Chemical Entity (NCE) exclusivity must submit a New Drug Application (NDA) describing the drug and the clinical trials used to verify the drug's safety and efficacy for a given formulation and indication. A successful NDA gives the firm(s) an exclusive right to market the drug in the US for 5 years, unless another firm undertakes duplicate clinical trials that verify safety and efficacy. (In practice, the latter does not occur either because a drug with an NDA is also under patent protection or because the time and expense needed to conduct clinical trials would exceed the profits that could be earned before the expiry of the initial NDA.) Note that the FDA requires the NDA applicant to have "conducted or sponsored the study by providing 50 percent of the funding or by purchasing exclusive rights to the study." While a given drug is still under NCE exclusivity, the "exclusive firm(s)" can conduct additional trials to show safety and effi-

cacy for new formulations and indications, including the use of the drug in combination with others. These additional trials allow the firm(s) to apply for New Clinical Investigation (NCI) exclusivity, which protects the right to market the drug according to its new uses for an additional 3 years regardless of the patent or NCE exclusivity term. Other firms can also conduct clinical trials and attempt to receive NCI exclusivity while NCE exclusivity is still in force, but this would again be precluded by patent protection and may require additional clinical trials if data produced for the original NDA is needed to establish safety/efficacy. For these reasons, we expect other firms to apply for NCI exclusivity only after patent protection and the original NCE exclusivity period have lapsed.

It is not clear how valuable additional "method-of-use" patents or NCI exclusivity provisions are for firms after the original patent and NCE exclusivity have lapsed. In principle, off-label use allows doctors to prescribe generic versions of a drug for use in combinations or for indications that have only been tested using the branded version of a drug, though insurance reimbursement restrictions may affect this. There is some concern that method-of-use patents or NCI exclusivity provisions may have a chilling effect on generic entry after the original patent and NCE exclusivity have lapsed if the entrants take any action to market the drug for new uses, but it is not clear how important this is (Strohbehn et al., 2021; Feldman, 2022; Tu and Sarpatwari, 2023). In general, it appears that firms only have incentives to conduct new clinical trials for their own drugs that are still under original patent or NCE exclusivity protection.

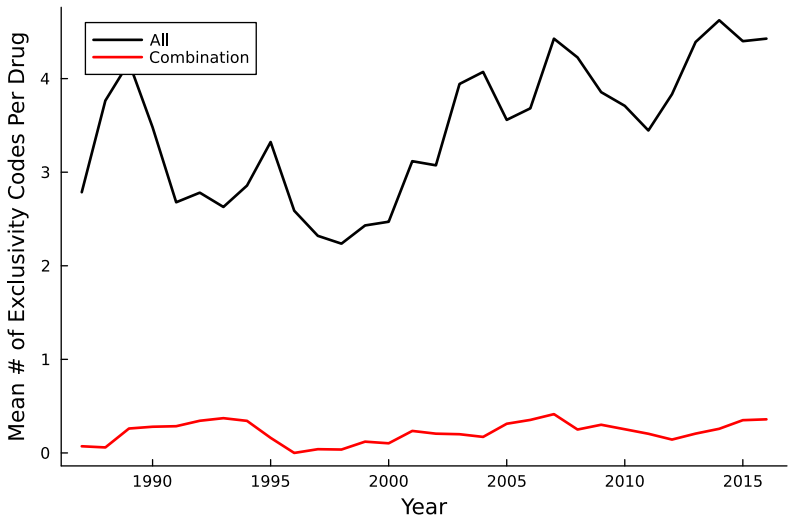
We make a first attempt at understanding the prevalence of patenting for combinations by using data from Durvasula et al. (2023) to extract patents and exclusivity extensions associated with combinations. We first subset to patents and exclusivity instances that pertain to oncology drugs. We count the mean number of patent use codes and exclusivity codes that a particular drug has per year, and we calculate the same means for patents and exclusivity that pertain to combinations. We say a particular patent use code or exclusivity code is associated with combinations if it includes more than one drug in the description or says the word combination (or close variants). There is an increasing number of patents for each drug associated with combinations (Figure F.1), but these patents do not seem to translate into explicit exclusivity extensions by the FDA (Figure F.2).

Figure F.1: Patent Use Codes and Combinations



Notes: Figure shows the mean number of patent use codes per drug by year in total and that are associated with combinations.

Figure F.2: Exclusivity Codes and Combinations



Notes: Figure shows the mean number of exclusivity codes per drug by year in total and that are associated with combinations.

F.4 Clinical Trials

ClinicalTrials.gov defines a "sponsor" as the entity that initiates the study, while a "collaborator" is any organization other than the sponsor that provides support (funding, design, implementation, data analysis, or reporting). The legal definition of "sponsor" is provided in

21 CFR 50.3:

"A person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators."

The Food and Drug Administration Amendments Act of 2007 requires that clinical trial information submissions include the sponsor, but not collaborators (42 CFR 11). It is not clear how extensive reporting of collaborators is.