Strategic entry in regulated markets

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Abstract

We analyze firms' product line decisions in the presence of entry regulation. We find that pharmaceutical firms prioritize smaller disease markets for a drug's initial regulatory approval and larger markets for its subsequent approvals. These patterns are consistent with a model of strategic entry in which firms—facing high costs of regulation—exploit regulatory loopholes to expand into novel product markets. Drug regulation, in particular, features a loophole where firms can rely on off-label drug use—the practice of using an approved drug for unapproved uses—as a non-regulatory pathway for reaching new markets. These findings raise important considerations for firm managers, highlighting opportunities for utilizing non-regulatory entry pathways to expand into costly product markets, and for regulators, who must balance the trade-off between expedient access to innovative products and the need for sufficient information about their quality.

Keywords: Entry; Regulation; Firm Strategy; Innovation; Health Care; Pharmaceuticals

1 Introduction

In industries with entry regulation, firms must make a series of critical decisions involving which product markets to enter and when. In the pharmaceutical industry where a single drug may have multiple therapeutic uses, manufacturers must decide in which disease markets to seek regulatory approval—a long, costly, and risky process (Adams and Brantner, 2006; Mullard, 2016; Wouters et al., 2020). Consider, for example, the case of Janssen's monoclonal antibody Remicade. In 1998, Janssen sought initial U.S. regulatory approval for Remicade as a treatment for Crohn's disease, despite a successful initial proof-of-concept study in rheumatoid arthritis. This decision was made due to the potential for a quicker path to approval as a treatment for the subset of patients with severe Crohn's who had not responded to conventional therapies (Melsheimer et al., 2019). The example of Remicade reflects a growing trend by pharmaceutical firms transitioning from a strategy of prioritizing large, "blockbuster" disease markets to a "niche buster" one, where they obtain initial regulatory approval for a drug in a small market (Dolgin, 2010; Marselis and Hordijk, 2020).

While such patterns could be due to differences in scientific opportunities (Krieger, 2021), market conditions (Acemoglu and Linn, 2004), or intellectual property protection (Budish et al., 2015), this paper considers an alternative explanation: the role of regulatory loopholes (Anderson and Sallee, 2011). Firms may exploit regulatory loopholes and initially seek approval in small disease markets—because such niche disease markets may require less risky and costly investments—and then rely on non-regulatory pathways to expand into larger disease markets. With this motivation, we investigate the extent to which firms relax regulatory constraints by utilizing non-regulatory pathways to expand into novel product markets. We document evidence that such strategic entry decisions are quantitatively meaningful in the pharmaceutical industry—an important, highly regulated setting—and discuss managerial and policy implications.[1,2]

The decision to circumvent regulatory approval is particularly significant in health care, where entry regulation by the U.S. Food and Drug Administration (FDA) creates a unique set of incentives and disincentives for manufacturers to seek regulatory approval for new uses of approved products (Friedman, 1996). Because firms can only legally market new uses of existing drugs after regulatory approval for each new use, firms have incentives to undergo these so-called supplemental approvals. However, such incentives may be dampened by the high costs of conducting rigorous clinical trials

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[1]The pharmaceutical industry is projected to exceed $1.1 trillion by 2024, making it a noteworthy sector for analysis (IQVIA Institute, 2020).

[2]Anecdotal evidence of pharmaceutical firms' strategic entry decisions has sparked concerns by policy makers and regulators, prompting a reevaluation of existing regulatory policies. See, e.g., Tribble and Lupkin (2017).

to support FDA re-approval. Further, existing FDA drug regulation allows for the use of approved drugs in non-FDA approved ("off-label") uses (Eisenberg, 2005). While firms are not permitted to directly promote off-label drug uses, the potential for off-label drug use presents an alternative, non-regulatory pathway to introduce drugs into new markets.

Underlying our analyses are leading theories suggesting an inverse relationship between the order in which indications (or diseases) are targeted and the size of the corresponding market (Acemoglu and Linn, 2004). In theory, firms would prioritize initial entry into a drug's largest possible market and subsequently focus on expanding into smaller markets through product line extensions. However, when opportunities for circumventing regulation are present—for example, where off-label drug use has the greatest potential—firms may strategically focus on smaller markets (rather than targeting large markets initially). The rationale behind this strategy is that obtaining regulatory approval for niche markets is comparatively easier, primarily due to the ability to conduct smaller clinical trials with the subset of patients who are more likely to respond positively to treatment (Chandra et al., 2019). Under this strategy, firms can rely on off-label markets to effectively expand demand for their drugs instead of investing in the high-quality scientific evidence necessary to pursue formal regulatory approval.

Despite the importance of this issue, there has been relatively little quantitative evidence on regulatory loopholes due to empirical challenges. Our conjecture is that in settings with greater opportunities for off-label drug use, firms are more likely to prioritize smaller markets for regulatory approval. Yet, in practice, we cannot directly measure the potential for off-label drug use. Three features of the market for cancer medicines—the largest pharmaceutical market in terms of spending— allow us to make progress on this issue (IQVIA Institute, 2018). First, the choice between seeking supplemental approval or relying on off-label drug use is highly relevant among cancer drug manufacturers: Among oncology drugs, multiple uses are common and estimates of off-label use range from 50 to 75 percent (Pfister, 2012).[3] Second, cancer treatment, which is organized around the site (e.g., breast) and stage (e.g., metastatic), has provided a tractable way for researchers to measure R&D activity (Budish et al., 2015). Third, for each disease, we are able to utilize genetic information to predict likely off-label disease markets and to determine the size of the opportunity for off-label drug use.

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[3]This is due to favorable off-label reimbursement policies in cancer treatment, as well as other factors (e.g., high disease severity and fewer treatments for rare cancers) encouraging physicians to experiment beyond formally approved uses.

FIGURE 1: MEAN MARKET SIZE BY INDICATION ORDER
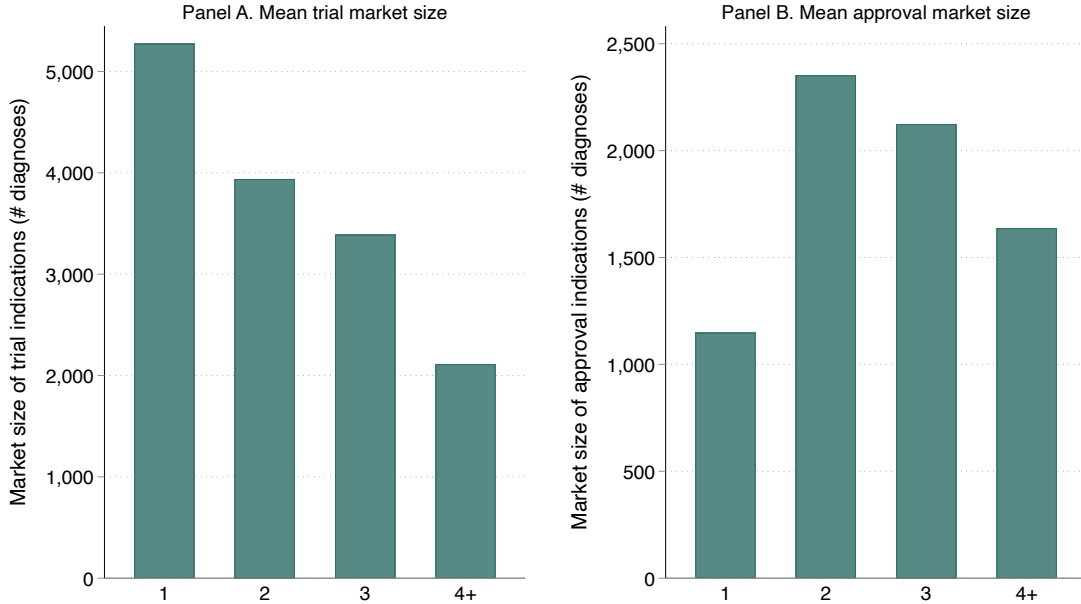
NOTES: This figure shows the mean market size by indication order for both research investments (clinical trials in Panel A) and commercialization investments (FDA approvals in Panel B) for cancer drugs approved from 1990-2016. Market size is measured by new diagnoses for an indication in the Surveillance, Epidemiology, and End Results (SEER) data. Trial indications are given by cancer sites and approval indications are given by cancer site-stages.

To explore the factors influencing the choice and timing of firms' product line decisions in the presence of entry regulation, we construct a dataset of all cancer drug approvals between 1990 and 2016, matched to comprehensive clinical trial information. Our measure of market size comes from measuring disease prevalence using cancer registry data. We isolate the potential for firms' strategic behavior by noting that product line decisions occur at both the research and commercialization stages. Each stage involves its own set of incentives, with entry regulation more likely to shape decisions at the commercialization stage. Our dataset allows us to distinguish between investments in these two stages, with product line investments measured via either clinical trials (research investments) or formal regulatory approvals from the FDA (commercialization investments).

Motivating our subsequent analyses, Figure 1 plots mean market size by indication order for both research and commercialization investments, where indication order specifies the indications in which a given drug is tested (or approved) first, second, third, and so forth. Panel A shows that, on average, firms initially test their drugs in the largest possible market and then in successively smaller markets. In contrast, consistent with our expectation that off-label drug use provides a

non-regulatory pathway for entry into new diseases, Panel B shows that firms prioritize the smallest market for initial approval and then seek subsequent approvals in larger markets.

After controlling for detailed disease and time fixed effects, the difference between research and commercialization investments in their relationships with indication order persist: Research investments have a strictly negative indication order-market size relationship, while commercialization investments have a non-negative one. Further, accounting for competition, regulatory incentives, and intellectual property protection does little to minimize this difference. For example, Budish et al. (2015) note that firms have reduced incentives to pursue treatments for early-stage cancers due to longer development times and shorter subsequent patent terms for such treatments post-launch. If early-stage cancers have larger market sizes, the relationship between indication order and market size may be due to firms' concerns regarding monopoly exclusivity periods. We control for measures of intellectual property protection and find they have minimal impact in explaining the discrepancy between research and commercialization investments.

Instead, we address this gap by presenting evidence from two empirical tests that indicate firms strategically utilize off-label markets as a means to circumvent regulation. First, we examine the indication order-market size relationship after accounting for the size of potential off-label disease markets. To do this, we construct a novel index of disease similarity between cancer sites, based on genomic sequencing data. Using this index, we can approximate an indication's total market size, including off-label drug use. After accounting for the size of expected off-label markets, we recover a strictly negative and significant relationship between approval indication order and market size. As such, our results are consistent with a model of strategic entry: Pharmaceutical firms prioritize smaller therapeutic indications for regulatory approval, knowing that they can rely on off-label drug use as a non-regulatory pathway to expand demand.[4]

Second, we expand our analyses to diseases outside oncology and exploit variation across diseases in their propensity for off-label use. Using findings from the medical literature to identify disease categories with high and low levels of off-label drug use, we find that the approval indication order-market size correlation is significantly less negative among drugs first approved for high off-label diseases and very strongly negative for those approved in low off-label diseases.[5] This

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[4]Appendix A formalizes a model of strategic entry explaining why firms may prioritize smaller indications in their commercialization investments.

[5]Therapeutic areas with low off-label propensity include antidiabetics, antihypertensives, and antihyperlipidemics, and therapeutic areas with high off-label propensity include oncology, anticonvulsants, psychiatry, and antiasthmatics.

provides further support of the hypothesis that firms strategically circumvent regulatory approval in therapeutic areas where expected off-label drug use is high.

Finally, we consider the managerial and policy implications of our findings. First, we note that our findings shed light on opportunities for non-regulatory entry strategies for firms. This approach can be particularly beneficial for firms facing substantial financial constraints or operating in regulatory environments characterized by uncertainty. In a back-of-the-envelope calculation, we find that pharmaceutical firms can enter the market 9.3 months quicker by seeking a drug's initial regulatory approval in a small market relative to a large one, translating to $117.2 million dollars in value from clinical trial savings and revenues over this time. Second, for regulators, this raises questions on whether and when firms are actively avoiding regulatory processes and the corresponding impacts to consumers.[6] Regulators must strike a balance between expediting consumer access to new products and ensuring their quality via rigorous and potentially lengthy testing and examination. This is of particular importance in the pharmaceutical sector, where numerous drugs are recommended and used off-label for important health conditions—for example, the use of aspirin prophylaxis for coronary disease in certain high-risk patient populations—yet off-label drug use without sufficient evidence is also associated with higher rates of adverse events (Eguale et al., 2016; Richardson, 2016; Wittich et al., 2012). We find that substantial R&D investment currently goes towards off-label markets; policies restricting off-label use would need to weigh the benefit of firms potentially pursuing regulatory approval for some of these markets against the cost of firms discontinuing that R&D investment and consumers being unable to use the drug in other markets.

This research contributes to four strands of literature. First, a vast body of prior work across marketing, strategy, and economics has studied firm decisions regarding product line extensions and brand proliferation in a range of industries, including automobiles, cell phones, food products, personal computers, and retail (e.g., Barroso and Giarratana, 2013; Bayus and Putsis Jr, 1999; Ellison and Ellison, 2011; Fan and Yang, 2020; Fowler, 2019; Kadiyali et al., 1999; Kekre and Srinivasan, 1990; Morgan and Rego, 2009; Ren et al., 2019; Schmalensee, 1978).[7] These papers—

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[6] A *New England Journal of Medicine* perspective piece highlights potential concerns associated with regulatory loopholes in pharmaceuticals: "When newer, more expensive drugs are used off-label, it increases health care costs. It undermines the incentives for manufacturers to perform rigorous studies—and instead subtly encourages them to game the system by seeking approval for secondary indications for which clinical trials are less complicated and less expensive. And off-label use may discourage evidence-based practice" (Stafford, 2008).

[7] In pharmaceuticals, Ellison and Ellison (2011) find increased product line extensions (changes in a drug's dosage, formulation, or administration route) in larger markets and Fowler (2019) demonstrates a strategic delay in the timing of these extensions, with firms introducing them as expected generic entry nears. Our study of product line decisions focuses on a drug's introduction into different therapeutic markets.

studying the determinants of brand proliferation and corresponding impacts to both firm performance and industry structure—focus on product line decisions as indicated by those products actually introduced to the market. Our data allow us to extend this literature by looking at firm decisions at two different stages of the innovation process—research and commercialization—and thereby explore the factors driving changes in product line decisions over this entire process.

Second, this paper relates to existing research on first-mover advantages (Lieberman and Montgomery, 1988, 1998; Robinson et al., 1994) and niche markes (Adner and Levinthal, 2002; King and Tucci, 2002; Pepall, 1992). We add to this literature by quantifying the extent to which pharmaceutical manufacturers can shorten drug development and approval times via niche market entry—allowing for potential first-mover advantages—and provide an estimate of the dollar benefit to firms of such a strategy. While existing work on niche market strategy focuses on its potential for such advantages as differentiation from competitors, increased sales, and the opportunity for market learning and technology development, we highlight an additional rationale for pursuing a smaller, selective market: to circumvent regulatory processes.

Third, we contribute to a growing set of papers on the measurement (Radley et al., 2006; Stafford, 2008), drivers (Dubois et al., 2023; Larkin et al., 2014; McKibbin, 2023; Shapiro, 2018) and consequences of off-label drug use (Bradford et al., 2018; Tuncel, forthcoming). Most closely related to this work, Dubois et al. (2023) show how policy changes on off-label promotion and prescribing influence firms' decisions to submit drug uses for formal approval. We build on these papers by developing an ex-ante measure of off-label markets that does not rely on access to health care claims data. We also provide, to our knowledge, the first empirical evidence using early and late-stage drug development data to clarify how pharmaceutical firms incorporate off-label use in their strategic research and commercialization decisions.

Finally, we add to the broader literature on how entry regulation influences firms' incentives for innovation in health care markets (Acemoglu and Linn, 2004; Berger et al., 2021; Blume-Kohout and Sood, 2013; Danzon and Keuffel, 2014; Dubois et al., 2015; Grennan and Town, 2020; Maini and Pammolli, 2023; Stern, 2017). Our work makes two key contributions relative to this body of literature. First, we offer the first comprehensive empirical analysis of the impact of FDA regulation on firms' within-drug market entry strategies. Second, while much of the literature has highlighted that firms facing high regulatory costs may lower their investment in R&D, we offer a more nuanced picture: We demonstrate that firms may turn to regulatory loopholes to enter new product markets.

Across a variety of industries, the belief that firms may seek to exploit regulatory loopholes to circumvent costly entry regulation has fueled considerable policy attention. For example, in the transportation industry, ride-sharing apps such as Uber and Lyft have been able to bypass city taxicab regulations by arguing they are technology platforms and not transportation providers (Posen, 2015). Similarly, in the financial industry, financial technology ("fintech") companies like PayPal refrain from certain activities, such as holding customer funds or making loans, to avoid being regulated as banks (Douglas, 2016; Vives, 2019). While such strategic entry decisions have been widely discussed, there is relatively little empirical evidence that documents this activity (see Maini and Pammolli (2023) for a recent contribution). This article aims to address this gap.

The paper proceeds as follows. Section 2 describes the institutional background behind pharmaceutical entry regulation and off-label drug use in the United States. Section 3 outlines the data, including construction of our disease similarity index, and provides summary statistics. Section 4 gives the empirical results, and Section 5 discusses managerial and policy implications. Section 6 concludes.

2 Institutional background

2.1 Pharmaceutical entry regulation in the United States

Current drug regulation is rooted in the Federal Food, Drug, and Cosmetic Act of 1938 (FD&C Act), which requires that manufacturers generate evidence of safety and efficacy as a pre-condition for marketing their products. Drug development typically begins with extensive preclinical laboratory research that involves testing a new drug candidate on animals and human cells. Once complete, the manufacturer completes an Investigational New Drug Application (IND) that outlines its plan of action with respect to human testing in clinical trials. After the IND is approved by regulators, the manufacturer begins the most expensive aspect of drug development: human testing of drugs in a series of clinical trials in which costs increase with each subsequent phase. Drugs that successfully demonstrate safety in Phase I trials proceed to Phase II trials in which their efficacy is tested in a few hundred patients. If successful, the drugs move to Phase III trials in which their efficacy is tested in several thousand patients. Upon successfully completing Phase III trials, the sponsor will submit a New Drug Application (NDA) to the FDA for final approval. The entire process is long (often taking between 8 and 12 years), costly (typically costing a manufacturer between $300 million and $2.6 billion), and risky (only 9 percent of drugs that receive an IND ultimately receive

regulatory approval) (Adams and Brantner, 2006; CSDD, 2014; Danzon and Keuffel, 2014; DiMasi, 2001; DiMasi et al., 2003; Wouters et al., 2020).

Importantly, the development and review process is indication-specific—i.e., a drug receives regulatory approval for a specific use. As a result, manufacturers aiming to shift out the potential applicability of drugs at the time of first approval must decide whether to: (a) conduct additional trials for the purpose of seeking subsequent FDA approvals for further indications or (b) support exploratory studies that expand off-label use.

Under the FD&C Act, the FDA considers an approved drug with an unapproved use to be "an unapproved new drug with respect to that use" (FDA, 2014). Consequently, to expand a drug's label to include a new use, the manufacturer must submit a new IND, undertake additional efficacy clinical trials, and submit a supplemental New Drug Application (sNDA). The amount of resources involved depends on the similarity between the original and new use (FDA, 1998a). If the original and new use are closely related, for instance, manufacturers seeking approval for new uses may skip Phase I trials and rely on fewer Phase II trials. Examples include a new stage of the same disease or the same disease in a new population. With less evidence for the FDA to review, average approval times are shorter for sNDAs for new indications and new patient populations relative to NDAs (DiMasi, 2013; DiMasi et al., 1996; DiMasi and Lasagna, 1991). Despite this, the sNDA process is still considered expensive and time-consuming (Wittich et al., 2012). Further, evidentiary standards of safety and efficacy for original and supplemental indications are similar, setting a high bar for subsequent trials. Indeed, an analysis of efficacy trials for sNDA approvals found that rates of use of active comparators and clinical outcome endpoints were comparable to those of trials supporting NDAs (Wang and Kesselheim, 2015). Additionally, firms typically must still run at least one Phase III trial for which costs can run between $11.5 million and $52.9 million (Sertkaya et al., 2016).

The costs and risks of drug development also vary across indications. To the best of our knowledge, there are no publicly available data estimates of drug development costs and risks by indication size. However, some quantitative evidence suggests that smaller indications may be less costly and risky than larger indications: On average, drugs treating orphan diseases (defined as those affecting less than 200,000 people in the U.S.) experience a shorter regulatory review period than non-orphan diseases (Seoane-Vazquez et al., 2008). Firms conducting clinical trials for orphan diseases often rely on biomarkers to target the patient subgroups that are most responsive to treatment (Chandra et al., 2019; Michaeli et al., 2023). Given that patient recruitment and enrollment costs constitute a

major portion of clinical trial costs (Sertkaya et al., 2016), the enrollment of a smaller, yet more responsive set of patients could lead to reduced costs and risks for smaller indications.

2.2   Off-label drug use

The practice of using health care technologies and treatments for unapproved uses is legal and common, with estimates ranging from 20 to 39 percent across all diseases (Conti et al., 2013; Molitor and Agha, 2012; Stafford, 2008).[8] Such off-label use is particularly common among treatments for cancer, cardiovascular diseases, and psychiatric diseases. There are several reasons for off-label use (Wittich et al., 2012). First, FDA-approved therapies might not exist for the treated population. Second, physicians might substitute within a class of medications if one medication is approved for a particular use and others are not. Finally, the features of two conditions might be similar and physicians may use one approved drug for both. For example, off-label psychiatric drug use is common in children because mental illnesses are difficult to diagnose and children are rarely included in clinical trials for drug approval (Lee et al., 2012). Many mental illnesses share the same symptoms, motivating physicians to use one drug approved for a particular condition to treat another.[9]

While the FDA recognizes that off-label use can be clinically appropriate under some circumstances, the agency is concerned that research outside of the FDA's control is less rigorous and that the information disseminated from such trials may pose a public health risk (FDA, 2014). As a result, the FDA aims to dissuade firms from circumventing the supplemental regulatory approval process by banning the direct promotion of drugs for off-label uses, arguing that doing so would violate the FD&C Act provisions which prohibits the introduction of "misbranded" drugs.

Despite this, evidence suggests that manufacturers may use certain types of clinical evidence as a means to promote off-label uses.[10] Further, the agency's policy towards off-label advertising has gradually loosened and been challenged over time, lowering the costs of off-label promotion (FDA, 2014). Manufacturers are currently permitted to respond to unsolicited questions about off-label

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[8]For example, expandable metal mesh stents approved for biliary stenting in cancer are also used for renal artery stenosis.

[9]The prevalence of off-label use depends on a physician's propensity to prescribe a drug with limited evidence of safety and efficacy. In practice, physicians who engage in off-label use are rarely accused of medical malpractice. The process of informed consent does not require physicians to disclose that a drug is being used off-label. Further, off-label use is not necessarily negligent if the off-label use is included in the current standard of practice.

[10]The U.S. Department of Justice has charged and fined several major major companies with illegal off-label promotion, including Eli Lilly ($1.4 billion in 2009); Pfizer ($2.3 billion in 2009); GlaxoSmithKline ($3 billion in 2012); and Abbott ($1.6 billion in 2012).

uses from health care professionals and to disseminate information describing off-label uses from peer-reviewed journal articles, textbook chapters, and clinical practice guidelines (Avorn et al., 2015). Most recently, Amarin, a manufacturer of a prescription fish-oil pill, was alleged to have provided doctors with clinical evidence of off-label uses. After a federal court ruling that attempts to prohibit such marketing violated the First Amendment, the manufacturer reached a settlement with the FDA allowing it a pathway for continued off-label promotion.[11]

3 Data and summary statistics

To understand pharmaceutical firms' strategic entry decisions, we evaluate product line investments associated with drugs initially approved for oncology. Focusing on cancer conditions allows us to categorize diseases into cancer sites (e.g., breast) and stages (e.g., metastatic). This enables us to roughly measure the similarity between the approved use and the new use under investigation (i.e., whether the original and new use are in different cancer sites and stages).

Our sample is the set of cancer drugs first approved by the FDA between 1990 and 2016. For these 129 drugs, we obtain detailed product line investment data on clinical trials and supplemental drug approvals. With these data, we can thus distinguish between product line decisions occurring at two distinct stages: the research stage (measured via clinical trials) and the commercialization stage (measured via FDA approvals). We then investigate the relationship between market size and indication order for both research and commercialization investments. Further, we examine the role of competition, regulatory incentives, and intellectual property protection in influencing this relationship. Finally, we repeat our analyses incorporating off-label market size, using an index of disease similarity based on gene sequencing efforts to measure potential off-label drug use for a given indication. We summarize the data supporting these analyses below.

3.1 Product line investments

3.1.1 Clinical trials (research investments)

To proxy for research investments, we collect information on each drug's clinical trials. In particular, we focus on supplemental clinical trials from the Clarivate Analytics Cortellis Clinical Trials Intelligence Global database. We include as supplemental trials all trials starting after the first pivotal trial start date for the initial approval; pivotal trials are those used to support regulatory

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[11]http://www.raps.org/Regulatory-Focus/News/2016/03/08/24501/FDA-Amarin-Propose-to-Settle-Landmark-Off-Label-Marketing-Case/

approval in an NDA. Data limitations prevent us from categorizing clinical trial conditions to the stage level. As a result, our trial analysis is conducted at the drug-site level.[12]

3.1.2 Drug approvals (commercialization investments)

Our measure of commercialization investments comes from identifying for each drug its set of supplemental drug approvals from the Clarivate Analytics Cortellis Competitive Intelligence Global ("Cortellis") database and the FDA's Drugs@FDA database. It should be noted that FDA-approved indications are typically more granular than the cancer site-stage; a drug can receive multiple approvals for the same cancer site-stage. For instance, Letrozole was originally approved for "advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy." It was later approved for "first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer." In both cases, the approval was for the cancer site "breast" and the cancer stage "metastatic."

3.2 Market size

As a proxy for market size, we collect data on the number of new diagnoses associated with each cancer's site and stage (Budish et al., 2015). Data comes from the Surveillance, Epidemiology, and End Results (SEER) database, available from the National Cancer Institute (NCI). We focus on 5-year lagged averages of market size, where we caclulate these lags relative to either the trial start year or the indication approval year.

3.3 Regulatory incentives

To capture regulatory incentives associated with subsequent product line investments, we compile data on whether the drug ever received an orphan drug designation. This designation aims to lower the cost of development by providing tax credits for clinical trials and offers additional intellectual property exclusivity for drugs that receive approval for rare diseases.[13]

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[12] For consistency, we also conduct our drug approvals analysis at the drug-site level and find similar results.

[13] For more details, see https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/d esignating-orphan-product-drugs-and-biological-products.

3.4 Intellectual property protection

We also incorporate information on intellectual property (IP) protection using data from the FDA's Orange Book and the United States Patent and Trademark Office (USPTO).[14] We create two controls for IP protection: primary and potential IP protection. Primary IP protection measures the months from each trial start (or approval) date to when the drug's primary IP expires. The primary IP on a drug is generally considered the strongest form of IP protection, with almost certain enforcement.[15] Potential IP protection measures from each trial start (or approval) to when the final IP on the drug expires.[16]

3.5 Off-label drug use

The next step in our analysis is to construct an ex-ante measure of potential off-label drug use for each indication. To do so, we rely on cancer genome sequencing, an advance in medical technology which systematically catalogues the genetic aberrations underlying different types of cancer. By comparing the DNA sequences of cancer cells to those of normal tissue, genomic sequencing researchers are able to characterize the genetic mutations likely driving the progression and growth of specific cancers and determine similarities across different cancer types (Weinstein et al., 2013). We use genetic sequencing data to characterize the similarity between different diseases and to define a drug's expected off-label cancer sites. For example, cancer mapping efforts have revealed the occurrence of same genetic mutations underlying both ovarian and breast cancer (TCGA Research Network, 2011). This suggests that ovarian cancer may be an off-label cancer site for a drug approved for breast cancer (Pleasance et al., 2022). This approach is similar in spirit to research conducted by the bioinformatics community using genetic sequencing data to aid drug repurposing efforts (Cheng et al., 2019; Tanoli et al., 2021).

We obtain information on gene-cancer pairings that result from large-scale cancer mapping efforts from the publicly accessible COSMIC Cancer Gene Census (CGC) database (Sondka et al., 2018; Tate et al., 2018).[17] The COSMIC team curates cancer genome data from hundreds of genetic

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[14]Drugs are protected by two types of IP rights: patents granted by the USPTO and regulatory exclusivities granted by the FDA.

[15]We consider the primary IP expiration to be the latter of either the molecule patent or the new chemical entity exclusivity expiration. For those trials taking place before a drug's initial launch, we assume the firms have an ex-ante expectation of what this primary IP expiration will be. For trials taking place after the primary IP has expired, we consider this measure to be zero.

[16]For trials occurring before a drug's initial launch, we consider the patents and exclusivities in effect at launch to calculate this measure. For all trials after launch, we consider the patents and exclusivities in effect at the trial start date.

[17]For more details, see https://cancer.sanger.ac.uk/census.

sequencing studies and literature to catalogue the set of genes containing mutations that are causally associated with cancer. In the CGC, each gene (e.g., BRCA2) is presented with the set of cancers (e.g., breast cancer, ovarian cancer) where mutations in that gene are likely contributors to the disease's development.

3.5.1 Similarities between cancer sites

Using the CGC data, we then estimate the similarity between cancer sites using the extent of overlap between the sets of genetic mutations associated with each cancer type. In the spirit of Krieger et al. (2022), we quantify the similarity between two different cancer sites by calculating the Tanimoto distance (Jaccard coefficient). This measure calculates the distance between each set of genetic mutations associated with each of the cancer sites. For example, the similarity index s between cancer sites A and B is the intersection of A and B's genetic mutations divided by the union of these mutations:

$$s_{A,B} \equiv \frac{|A \cap B|}{|A \cup B|} = \frac{|A \cap B|}{|A| + |B| - |A \cap B|} \tag{1}$$

A similarity index of 0 implies that a pair of cancer sites are not closely related and have no common mutations, while a measure of 1 implies that they are closely related and have exactly the same set of mutations. Figure 2 shows a heat map of our similarity index across all 79 cancer sites in our sample. Among different cancer sites, the mean index is 0.04 with a standard deviation of 0.13. As an example, Appendix B provides the mutations for breast and ovarian cancer, including their overlapping mutations, and shows the calculation of their similarity index. Breast and ovarian cancer have a similarity index of 0.09.

We use the similarity index to determine the expected off-label market size for each indication. This calculation is based on the market size for cancer sites related to indication i, weighed by the similarity index:

$$\textit{Off-Label Market Size}_{i,t} = \sum_{j \neq i} s_{i,j} \textit{Market Size}_{j,t} \tag{2}$$

Here, indication i has an off-label market size at time t that is defined as the weighted sum of the market sizes of all other cancer sites j ($j \neq i$) at time t, where the weight is the similarity index between cancer sites i and j. To see this, consider a simple example between three cancer sites, A, B, and C. Assume that cancer site B has a similarity with cancer site A ($s_{A,B} = 0.09$) and similarity with cancer site C ($s_{B,C} = 0.01$). Suppose that at time t, the market size for cancer site A is 100

FIGURE 2: SIMILARITY INDEX HEAT MAP
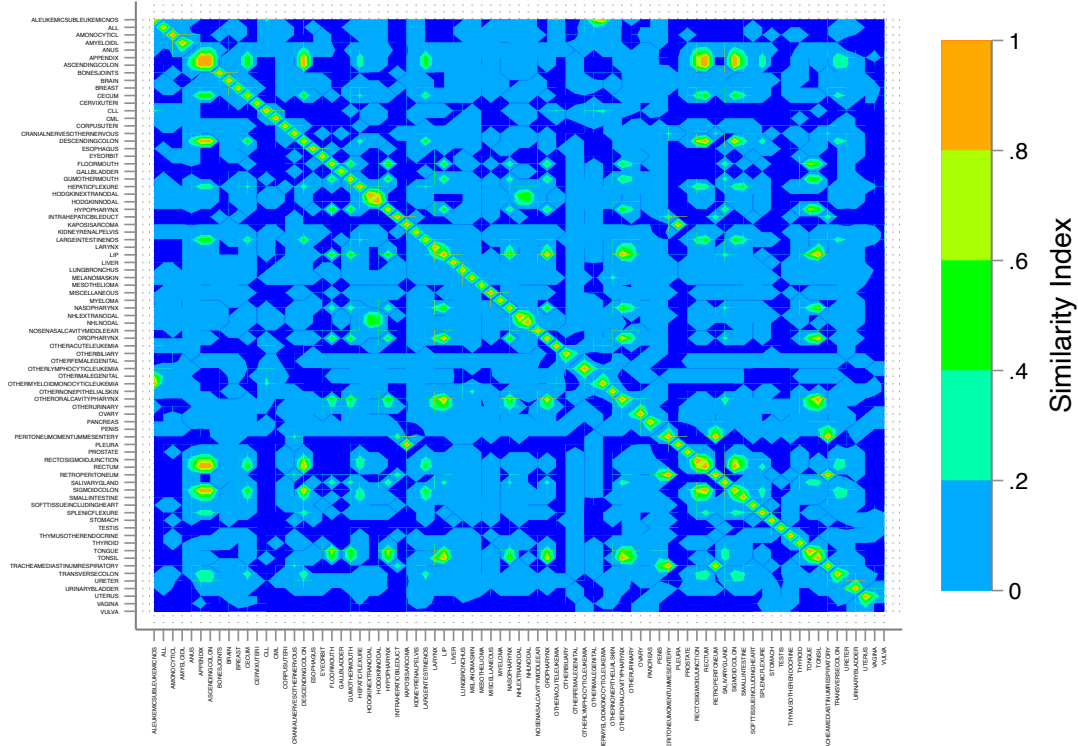
NOTES: This figure shows a heat map of our similarity index across all 79 cancer sites in our sample.

and the market size for cancer site C is 20. At time t, the off-label market size for a drug initially approved in cancer site B is $(0.09 \times 100) + (0.01 \times 20) = 9.2$.

Before continuing, we note that there are limitations to this approach. One key limitation is the potential underestimation of off-label drug markets. This may be due to the fact that off-label drug use may be driven by factors unrelated to genetic similarities across cancer sites, such as costs and the quality of existing evidence (Stafford, 2008). In addition, the evidence from the CGC may not fully capture the true level of overlap across cancer sites: The creators of the CGC describe it as being a "conservative but high-confidence list" of genes associated with cancer, raising questions about the possibility of false negatives when deciding which gene-cancer associations to include in the database.[18]

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[18]The CGC's cancer experts apply a strict criteria when determining the set of gene-cancer associations to include in the database. For more information, see https://www.sanger.ac.uk/data/cancer-gene-census/.

Nevertheless, we confirm the robustness of our approach by showing that our results remain largely unchanged when using alternative similarity measures. These alternative measures are generated by directly using cancer genome sequencing data from 168 large-scale mapping studies. Following the bioinfomatics literature, we focus on genetic mutations that occur at a high frequency within each mapping study, where we consider a genetic mutation as "high frequency" within a cancer if it occurs in the top 10 percent, top 20 percent, or top 30 percent of the most frequently occurring mutations (see Section 4.2).

3.6   Summary statistics

Table 1 presents some basic summary statistics of our sample of 129 oncology drugs approved between 1990 and 2016. The average drug is tested in 46 different trial indications (cancer sites) and receives FDA approval in 4 unique approval indications (cancer site-stages). Across the sample, 64 percent of drugs have received an orphan drug designation. Across all drug-indications, mean primary IP protection remaining at the time of approval is 124 months (10.3 years) and mean potential IP protection is 174 months (14.5 years). The maximum primary IP protection remaining is 277 months (23.1 years) and the maximum potential IP protection is 346 months (28.8 years). Mean off-label market size (7,534 diagnoses) is more than 4.5 times the mean market size of trial indications (1,640 diagnoses) and 7.5 times that of approval indications (985 diagnoses).

TABLE 1: SUMMARY STATISTICS

|	Mean	SD	Min	Max	N
Drug level					
Number of Unique Trial Indications	46	23	2	78	111
Number of Unique Approval Indications	4	6	1	35	129
Share with Orphan Disease Drug Designation	0.64	0.48	0	1	113
Drug-trial indication level					
Market Size of Trial Indications (Diagnoses)	1,640	3,251	5	17,915	5,100
Drug-approval indication level					
Primary IP Protection (Months)	124	55	0	277	513
Potential IP Protection (Months)	174	51	44	346	513
Market Size of Approval Indications (Diagnoses)	985	1,749	2	9,104	428
Potential Off-Label Market (Diagnoses)	7,534	9,690	0	32,122	518

NOTES: This table shows summary statistics for our dataset of cancer drugs approved from 1990-2016. The level of observation is the drug for number of trial indications, number of approval indications, and share with orphan drug designation; the level of observation is the drug-trial indication for market size of trial indications; and the level of observation for all other summary statistics is the drug-approval indication.

4 Empirical results

4.1 Product line investments and market size

Figure 3 plots the relationship between product line investments and market size for our oncology sample; Panels A and B illustrate key differences between the timing of research and commercialization investments. Panel A documents that trial indication order is strongly negatively correlated with market size. This fact is consistent with previous literature suggesting that firms prioritize research in conditions with larger market sizes. Contrasting this, Panel B documents that approval indication order has a non-negative relationship with market size. That is, firms do not prioritize approvals in larger markets. This fact is consistent with the hypothesis that due to the potential for off-label markets and the relative ease of obtaining approval for conditions with smaller market sizes (e.g., firms may seek to obtain orphan drug status), firms strategically seek first approval for indications with smaller markets.

FIGURE 3: PRODUCT LINE INVESTMENTS AND MARKET SIZE
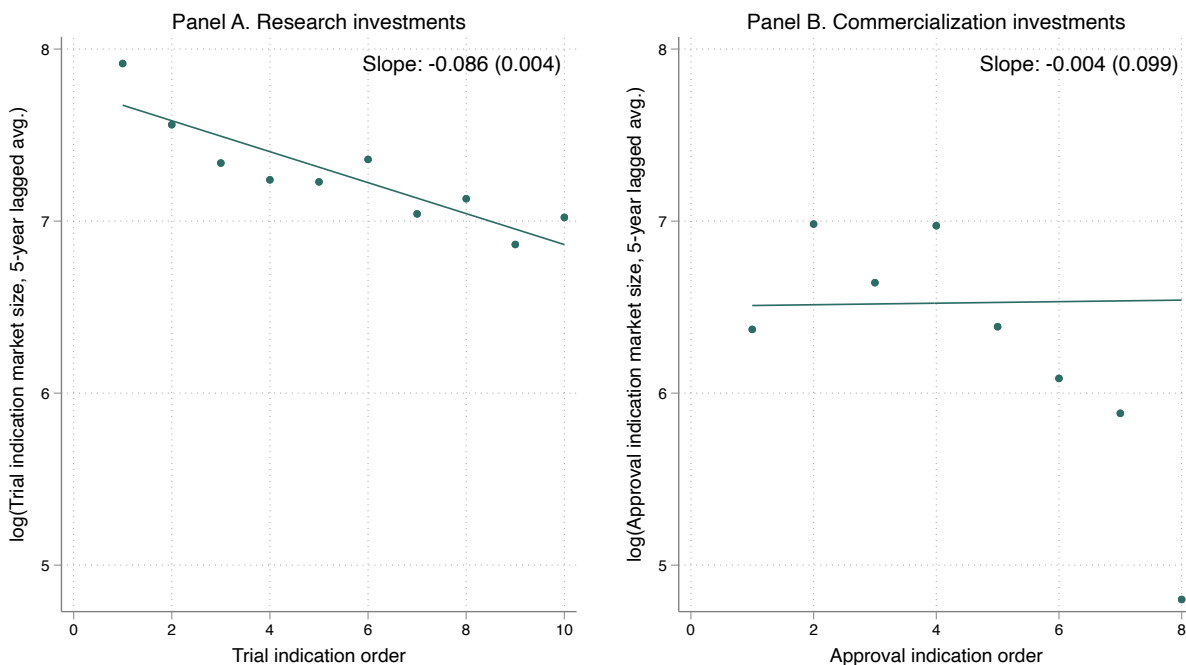
NOTES: This figure shows the relationship between product line investments and market size for cancer drugs approved from 1990-2016. The level of observation is the drug-indication order. Panel A shows the relationship between trial indication order and market size; number of observations is 1,656. Panel B shows the relationship between approval indication order and market size; number of observations is 187. Market size is measured by new diagnoses for an indication in the SEER data; we consider the log of the 5-year average market size relative to either the trial start year (Panel A) or approval year (Panel B). Each marker represents binned averages for a given indication order. For ease of interpretation, we display up to the 10th indication.

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Table 2 formalizes this relationship between indication order and market size. For drug d and indication order i, we estimate the following:

$$MarketSize_{d,i} = \alpha + \beta_1 IndicationOrder_{d,i} + \gamma X_{d,i} + \epsilon_{d,i} \tag{3}$$

Our outcome variable $MarketSize$ is the natural log of the lagged 5-year average market size associated with indication order i for drug d. The coefficient on $IndicationOrder$ is our main estimate of interest. We investigate this relationship by conditioning on a series of controls X, including: initial approval year for the drug; its indication group; competition, meaning the number of drug approvals in the same indication in the past five years; regulatory incentives, meaning whether the drug has ever received an orphan drug designation; and the measures of intellectual property protection described in Section 3. Each of these controls may influence the relationship between indication order and market size. For example, Budish et al. (2015) highlight that firms have reduced incentives to pursue research for early-stage cancers relative to late-stage ones, due to longer development times and shorter resulting patent terms post-launch for early-stage cancers. This has implications for our findings: If early-stage cancers have larger market sizes, the relationship between indication order and market size may be driven, in part, by patent-related factors. To account for this, we include detailed controls for each drug's primary and potential intellectual property protection. All estimates are from ordinary least squares (OLS) models.

Column (1) of Table 2 reports the raw correlation between trial indication order and market size. The estimated coefficient implies that a 1-unit increase in trial indication order is associated with a 9-percent decrease in market size. Column (2) shows that this negative relationship between trial indication order and market size persists once all controls are included, and the relationship remains significant at the 1-percent level. Columns (3) and (4) repeat these same regressions for approvals instead of trials. Column (3) confirms that approval indication order has a non-negative and insignificant relationship with market size. Once all controls are included in Column (4), the relationship becomes negative, but remains quantitatively small and insignificant. That is, the inclusion of these controls does not meaningfully shift the relationship between approval indication order and market size. We interpret this to mean that such factors as initial approval year, indication group, competition, regulatory incentives, and intellectual property protection do not explain the

	Research investments		Commercialization investments	
	(1)	(2)	(3)	(4)
Indication order	-0.0860***	-0.0846***	0.00448	-0.0442
	(0.00415)	(0.00614)	(0.0995)	(0.141)
Mean of dep. var.	6.842	6.820	6.513	6.522
Observations	1,656	1,570	187	182
Controls:				
Initial approval year	no	yes	no	yes
Indication group	no	yes	no	yes
Competition	no	yes	no	yes
Regulatory incentives	no	yes	no	yes
Intellectual property	no	yes	no	yes

NOTES: This table shows the relationship between indication order and market size for cancer drugs approved from 1990-2016. The level of observation is the drug-indication order. The first two columns look at research investments (clinical trials), and the second two columns look at commercialization investments (FDA approvals). Market size is measured by new diagnoses for an indication in the SEER data. The outcome variable is the log of the 5-year average market size associated with indication order. Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1.

gap between the timing of research versus commercialization investments and their relationship to market size.[19]

4.2 Incorporating Off-Label Drug Use

To understand how the possibility of strategic market expansion via off-label drug use may influence indication order, we carry out the first of two empirical tests. Using the disease similarity index based on overlapping gene mutations described in Section 3.5, we consider in Table 3 *total* market size, including potential off-label markets, as our outcome of interest. For reference, Columns (1) and (3) repeat the specifications from Table 2, with focal indication market size as the outcome variable and including all controls, for trials and approvals, respectively. Column (2) then regresses total market size on indication order plus all controls for our trial sample. We see that the relationship between indication order and market size becomes more negative, with an increase in indication

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[19]Appendix Table D1 demonstrates the robustness of these results under an alternative specification where we use an indicator for the first indication as our main explanatory variable instead of indication order.

	Research investments		Commercialization investments	
	Focal market size (1)	Total market size (2)	Focal market size (3)	Total market size (4)
Indication order	-0.0846***	-0.102***	-0.0442	-0.189*
	(0.00614)	(0.00670)	(0.141)	(0.107)
Mean of dep. var.	6.820	7.738	6.522	8.649
Observations	1,570	1,570	182	182
Initial approval year	yes	yes	yes	yes
Indication group	yes	yes	yes	yes
Competition	yes	yes	yes	yes
Regulatory incentives	yes	yes	yes	yes
Intellectual property	yes	yes	yes	yes

NOTES: This table shows the relationship between indication order and market size for cancer drugs approved from 1990-2016. The level of observation is the drug-indication order. The first two columns look at research investments (clinical trials), and the second two columns look at commercialization investments (FDA approvals). The outcome variable in Columns (1) and (3) is focal market size while the outcome variable in Columns (2) and (4) is total market size, including potential off-label markets; for both variables, we consider the log of the 5-year average market size associated with indication order. Focal market size is measured by new diagnoses for an indication in the SEER data, while total market size is measured by new diagnoses for the focal indication plus a proportion of new diagnoses for any potential off-label indications, with the proportions given by our disease similarity index. Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1.

order associated with a 10-percent decrease in total market size. Column (4) repeats this exercise for our approval sample. In contrast to Column (3), where there is a small negative and insignificant relationship between indication order and focal market size, once we account for off-label markets the relationship becomes highly negative and statistically significant. A 1-unit increase in indication order is associated with a 19-percent decline in total market size.[20] We confirm that these results are robust to using different measures of total market size that are generated with alternative similarity measures (see Appendix Table D3). These results suggest that pharmaceutical firms do prioritize larger indications once we factor in potential off-label markets. That is, they strategically invest in formal regulatory approval for smaller (focal) indications, anticipating a non-regulatory approach

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[20]Appendix Table D2 shows the robustness of these results using the alternative specification where an indicator for first indication is the main explanatory variable.

(off-label drug use) that allows them to expand demand for their products to other indications without formal approval.

4.3 Off-label heterogeneity across therapeutic areas

As a second empirical test of strategic expansion via off-label drug use, we extend our analyses to additional therapeutic areas outside oncology. While a focused examination of cancer markets allows us to analyze indications in detail, by extending our analysis to a more broad array of diseases, we are able to identify settings (at the disease level) where off-label use is more or less prevalent.

For this analysis, we categorize diseases using ICD-9 (International Classification of Disease) codes. We then use diagnosis data from the Medical Expenditure Panel Survey (MEPS) from 1996 to 1997 to generate ICD-9 level measures of market size. Drug approval data for all drugs first approved between 1998 and 2021 come from Cortellis.

From Radley et al. (2006) and Stafford (2008), we identify disease categories associated with high and low levels of off-label drug use. Diseases categories associated with high levels of off-label drug use include oncology, anticonvulsants, psychiatry, and antiasthmatics. Diseases categories associated with low levels of off-label drug use include antidiabetics, antihypertensives, and antihyperlipidemics. Figure 4 shows that the indication order-market size correlation is less negative among drugs first approved for diseases with a high off-label propensity relative to drugs first approved for low off-label diseases. That is, for drugs in therapeutic areas with low off-label propensity, firms do not have the option of expanding into other markets via off-label use, leading them to prioritize larger markets in their formal regulatory approvals. In contrast, for drugs in therapeutic areas with high off-label propensity, firms can rely on off-label drug use to expand into additional markets and hence, we observe a less negative relationship. This provides additional support for the conjectured role of off-label drug use in shifting firms' market entry strategies.

FIGURE 4: COMMERCIALIZATION INVESTMENTS AND MARKET SIZE ACROSS DISEASES, BY PROPENSITY FOR OFF-LABEL DRUG USE
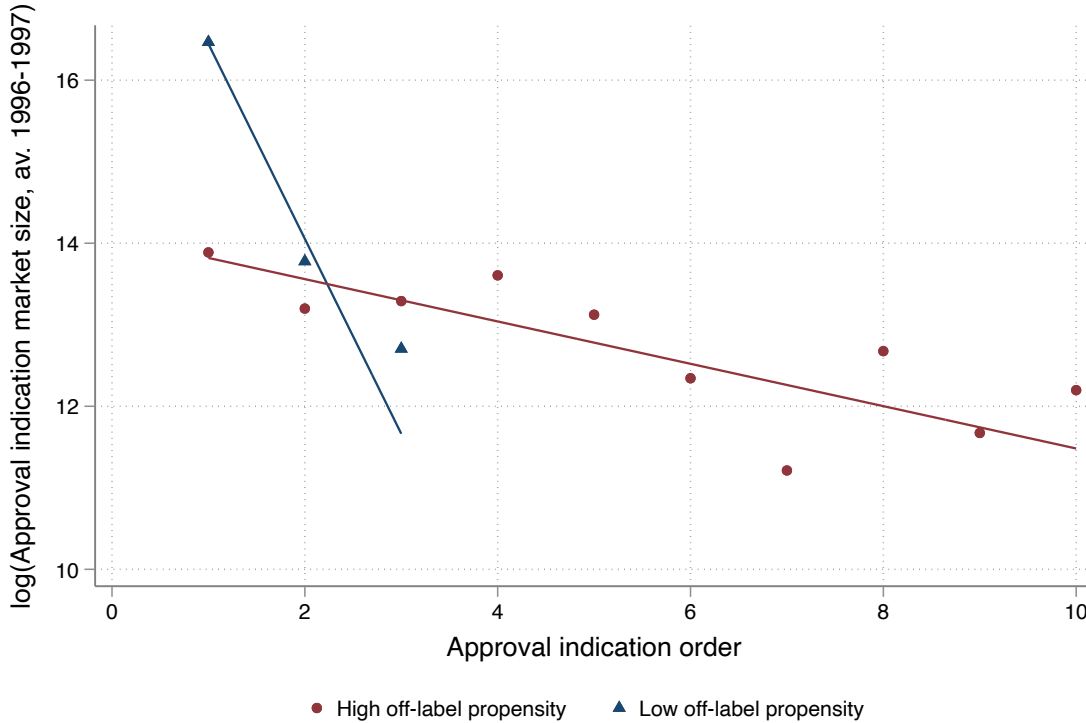
NOTES: This figure shows the relationship between commercialization investments (FDA approvals) and market size for approved drugs across several disease categories from 1998-2021, by propensity for off-label drug use. The level of observation is the drug-indication order, where an indication corresponds to an ICD-9 code. Number of observations is 1,108 (877 under high off-label propensity and 231 under low off-label propensity). Market size is measured by indication (ICD-9) prevalence in the MEPS data; we consider the log of the average market size between 1996 and 1997. Each marker represents binned averages for a given indication order. For ease of interpretation, we display up to the 10th indication.

4.4 Mechanisms: Conducting trials for regulatory versus off-label purposes

The above analyses provide evidence of firms' strategic investment in smaller disease markets for initial regulatory approval, knowing they can expand demand into larger disease markets via off-label drug use. A possible concern with this interpretation would be if the gap between research and commercialization investments were due to scientific rationales rather than strategic ones. To address this concern, we explore the characteristics of trials likely conducted for off-label versus regulatory purposes. We consider a drug's "off-label indications" to be those tested in clinical trials but for which the firm does not seek regulatory approval; "regulatory indications" are ones receiving FDA approval. Note that it is possible our designation of "off-label indications" captures indications
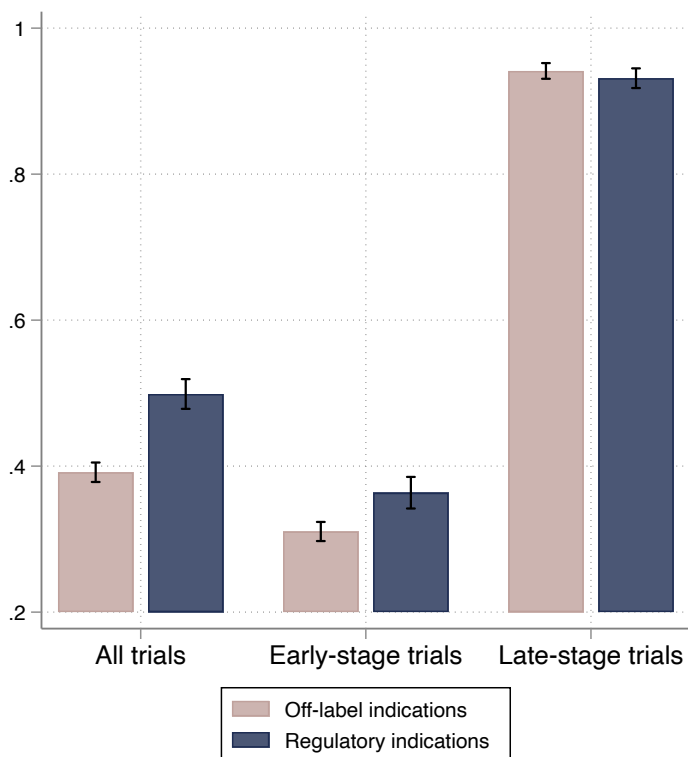
NOTES: This figure shows differences in trial quality for off-label versus regulatory indications for cancer drugs approved from 1990-2016. Trial quality is measured as the share of trials that are randomized and controlled. Bars give means, while capped ranges provide 95-percent confidence intervals.

discontinued due to scientific reasons—for example, a drug is found to be ineffective in treating a particular indication. However, if the gap between research and commercialization investments were purely due to scientific rationales rather than economic ones, then we would expect to see no difference in trial quality between indications with regulatory approval and those without.

Figure 5 depicts mean trial quality for regulatory and off-label indications, with quality measured as the share of trials that are randomized and controlled. We see that trials conducted for regulatory indications are of significantly higher quality on average. Looking at all trials, we see that those conducted for regulatory indications have a higher rate of being randomized and controlled (50 percent), relative to trials for off-label indications (39 percent). The difference between these means is statistically significant at the 1-percent level. These differences persist when restricting to early-stage trials: Thirty-six percent of early-stage trials conducted for regulatory indications are of high quality, compared to 31 percent of those for off-label indications. This difference is again

statistically significant at the 1-percent level. Consistent with the idea that firms are less likely to conduct lengthy and costly late-stage clinical trials if not intending to pursue regulatory approval, we find no difference in trial quality among late-stage trials.

4.5 Ruling out additional alternative explanations

We consider other possible explanations for the patterns we find. One is that firms may use expected trial length as a factor in their ordering of clinical trial indications. That is, if firms prioritize indications with longer anticipated clinical trials, that could be driving the negative indication order-market size relationship we observe for trials and lack of relationship for approvals. As a robustness check, we consider trial indication order with respect to the trial end dates rather than start dates. In Appendix Figure D1, we see the strong negative relationship between trial indication order and market size persists, reducing concerns that the gap between clinical trials and approvals is due to trial length.

Second, another explanation could be that the non-negative indication order-market size relationship for approvals reflects differences in FDA review timings rather than strategic decision making by firms. If firms submit applications for larger indications first but the FDA requires longer review times for such applications, this would weaken our hypothesis that firms strategically circumvent FDA regulation via initial approvals in small markets. To address this concern, we manually collect application submission dates for each approval from FDA review letters. In Appendix Figure D2, we thus use a robustness check where approval indication order is determined by submission date rather than approval date. We continue to see a non-negative relationship between approval indication order and market size, indicating that FDA review processes are not driving our results.

Finally, the FDA releases information only on successful approvals, and one may be concerned that the non-negative relationship we observe reflects FDA decisions on which indications to approve rather than firms' strategic investments. This is likely not the case as regulators do not time indication approvals according to market size; rather the FDA's objective is to evaluate the safety and efficacy of a drug. Further, pharmaceutical firms will not devote resources towards submitting an NDA if it is unlikely to be approved.

5 Discussion: Managerial and policy implications of regulatory loopholes

The paper's results indicate that pharmaceutical firms circumvent FDA regulation by seeking a drug's initial approval in smaller markets and relying on a non-regulatory pathway, namely off-label use, to expand demand. In this section, we explore the implications of such regulatory loopholes for firm managers, on the speed of entry into new markets and their R&D investment decisions. We also discuss the policy implications for regulators, who must balance the trade-off between expediting consumer access to new products and ensuring sufficient information about their quality.

5.1 Impact on speed of entry into new markets

By prioritizing initial regulatory approval in smaller indications, firms can potentially reach the market quicker due to the ability to conduct smaller clinical trials with the segment of patients more likely to respond to treatment (Chandra et al., 2019). To understand the benefit to firm managers of this strategy, we carry out a back-of-the envelope calculation quantifying its dollar value.

We begin by comparing the speed with which drugs are able to enter the market when pursuing initial approval in small versus large indications. Using our oncology sample, we restrict to each drug's first approval and consider "small" indications to be those within the first quartile of market size and "large" indications to be the rest. Measuring from pivotal trial start date to approval date, drugs with small initial indications reach the market in 43.8 months while those with large initial indications reach the market in 53.1 months, for a difference of 9.3 months. To translate this time savings into dollar savings, we make use of a recent study of clinical trial costs, which finds that each additional month in late-stage clinical trials equals a median of $671,000 spent (Martin et al., 2017). Multiplying this figure by 9.3 months suggests that pharmaceutical firms can save more than $6.2 million alone in clinical trial costs by prioritizing a smaller market for initial regulatory approval.

In addition to costs saved from clinical trials, firms also benefit from earlier revenues obtained. To determine per-drug revenues over this time, we turn to Schuhmacher et al. (2022), who examine new drugs launched and their total sales from 2011–2020. Given we are considering drugs launched in small indications, we take the conservative approach to exclude blockbusters (with mean annual sales of >$1 billion) and high-selling ($0.5–0.999 billion) drugs from our revenue calculations. Looking only at low-selling (<$0.1 billion) and medium-selling ($0.1–0.499 billion) drugs, we determine these

drugs have an average annual revenue of \$143.2 million, equating to \$111 million over 9.3 months.[21] We think of this as an underestimate of total revenues because drugs initially launched in small indications may still generate large, or even blockbuster-level sales, due to both the potential for off-label use and competitive factors allowing monopoly pricing to be high. Summing the costs saved from clinical trials and the revenues obtained via earlier market entry, we obtain a total value to firms of \$6.2 million + \$111 million = \$117.2 million per drug from exploiting regulatory loopholes and prioritizing small markets for initial approval.

5.2 Impact on R&D investments

Next, we consider how these regulatory loopholes influence managerial decisions on R&D investments. For each drug in our oncology sample, we look at all indications tested in clinical trials and consider the level of R&D, as measured by number of indications, resulting from regulatory loopholes. We distinguish between those indications receiving regulatory approval versus those that do not. In contrast to the analysis of Section 4.4, which considered all non-regulatory indications as "off-label" and examined corresponding differences in trial quality, here we make some additional assumptions based on trial quality and terminations to explicitly separate non-regulatory indications into two distinct categories: off-label indications and "dropped" indications, i.e., those that are discontinued due to scientific rationales.

To do this, we first incorporate data on trial terminations and classify drug-indication pairs without regulatory approval and with an above-median share of early terminations as dropped indications. That is, if firms terminate trials early for certain indications, it means they do not plan to publicize trial results for off-label purposes, and we assume that the lack of regulatory approval must be due to scientific reasons. For indications that are not terminated early, we categorize them by also exploiting data on trial quality. We assume that those with an above-median share of high-quality (randomized and controlled) trials but not receiving approval must also be dropped due to scientific rationales. This assumption is based on the idea that if pharmaceutical firms conduct high-quality trials for these indications but then do not pursue regulatory approval, it is likely that the trial results suggested a lack of efficacy. In contrast, we classify non-regulatory indications with trials *not* terminated early but of lower quality as off-label indications. In this case, pharmaceutical firms do not seek regulatory approval for the indications but conduct and complete lower-quality trials, the

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[21]We calculate annual revenues from Figure 1 of Schuhmacher et al. (2022) as follows: \$82.1 billion total revenues for medium-selling drugs + \$4.7 billion for low-selling drugs)/(51 medium-selling drugs + 50 low-selling drugs)/6 years average commercialization period over 2011–2020 = \$143.2 million annual per-drug revenues.

FIGURE 6: R&D FOR REGULATORY AND OFF-LABEL INDICATIONS
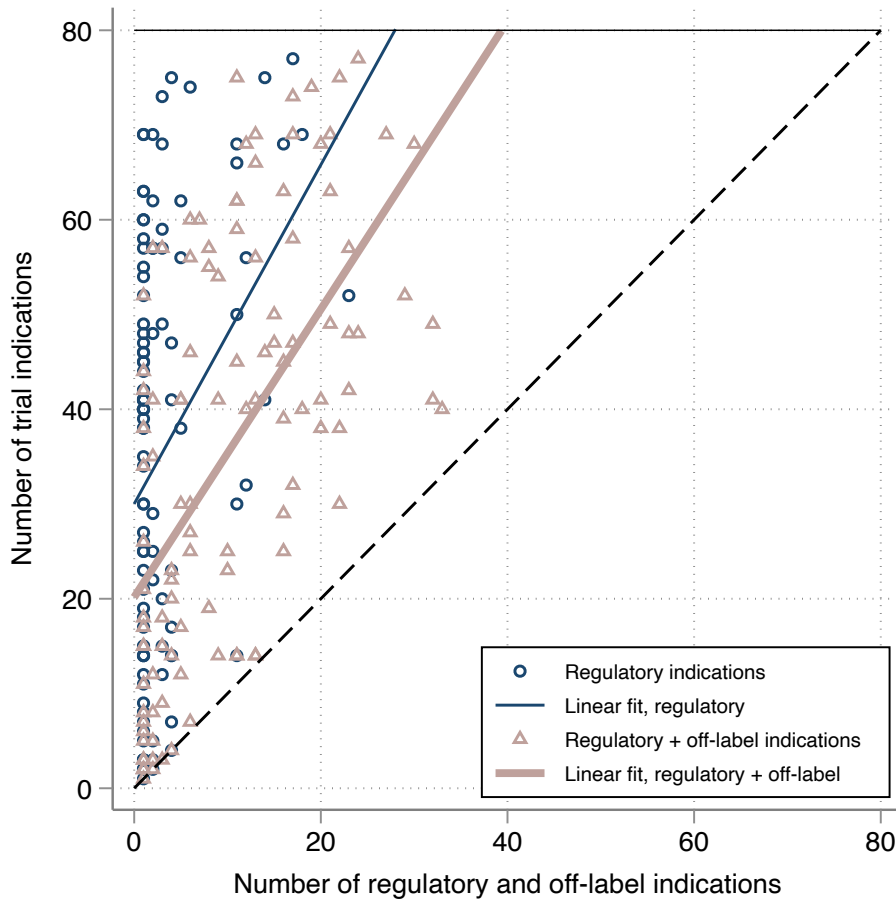
NOTES: This figure plots the number of trial indications against the number of regulatory (approved) and off-label indications for cancer drugs approved from 1990-2016. Circles depict regulatory indications and triangles depict total regulatory plus off-label indications for each drug. Number of drugs is 111.

results of which can be shared with doctors who may prescribe the drug off-label. To summarize, by matching a drug's trials and approvals and incorporating data on trial quality and terminations, we can classify each of a drug's indications into one of three types: regulatory, off-label, and dropped.

Figure 6 depicts for each drug, its number of trial indications against its number of regulatory and off-label indications. The 45-degree line in this figure would correspond to the scenario where all of a drug's indications tested in clinical trials either receive regulatory approval or are used off-label. We first plot for each drug its trial and corresponding regulatory indications in blue circles, with a blue (thinner) line depicting the linear fit. This line thus gives for each number of trial indications per drug, the expected number of approved indications. On average, the drugs in our sample are

tested in 35.7 different trial indications, and of these, 3.2 receive regulatory approval.[22] We next plot each drug's trial indications against its regulatory *and* off-label indications in pink triangles, with a pink (thicker) line depicting the linear fit. We see this pink line is shifted to the right of the blue one, and for any given number of trial indications, we can consider the distance between these two lines as the number of trial indications pursued for off-label purposes. On average, an additional 7 indications are pursued for off-label purposes. That is, with the potential for strategic expansion via off-label drug use, firms devote R&D investments to both regulatory and off-label uses, with the number of off-label indications more than double the number of regulatory indications.

5.3 Impact for off-label policy

Opinions on the regulation of off-label use differ across stakeholders, including pharmaceutical firms, payers, physicians, and consumers. Many off-label uses are not supported by high-quality scientific evidence; yet at the same time, off-label use represents an important source of medical innovation, offering earlier access to potential treatments for patients who may not respond to on-label indications (Radley et al., 2006; Stafford, 2008). Although FDA guidance on off-label promotion has gradually loosened over time (FDA, 2014), policy makers and regulators have recently proposed legal provisions that would ban certain off-label uses (Zinberg, 2023).

While we leave a full welfare analysis of the costs and benefits to banning off-label use to future research, we consider its implications from a conceptual standpoint. Our calculations above on the impact of regulatory loopholes on firms' R&D investments suggest a sizeable portion of R&D goes towards indications used off-label. If off-label use were banned, we might expect firms to pursue regulatory approval for a portion of these indications, provided the benefits from approval in terms of market expansion exceed the costs of obtaining sufficient scientific evidence necessary for regulatory processes. For the remaining indications, for which the benefts do not exceed the costs, these drug-indication pairs would become "missing" in the sense that firms would no longer pursue them and consumers would not have access to them. Thus, any gains in information quality for indications that would have been used off-label but now go through regulatory approval processes must be balanced against the loss in potential therapeutic options due to missing indications.

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[22]Our main analyses consider trial indications at the site level and approval indications, for which we have more granular data, at the site-stage level. For this analysis of R&D investment impacts, because we explicitly match trial to approval indications, all indications are at the site level. As such, we have a mean of 3.2 approval indications per drug at the site level versus, as indicated in Table 1, 4 approval indications per drug at the site-stage level.

6   Conclusion

Understanding the factors that shape firms' market entry decisions has been of long-standing interest to researchers, managers, and policymakers. However, there has been little work on understanding the role of regulatory loopholes in shaping these decisions. The possibility that firms can exploit a regulatory loophole may shift the predicted relationship between entry order and market size. Using detailed data on cancer markets, our paper confirms that while pharmaceutical firms undergo research investments in a drug's largest potential markets first, they seek initial approval in smaller markets. These results are consistent with the view that pharmaceutical firms circumvent regulation by relying on off-label drug use as a non-regulatory pathway to market entry.

For firms in regulated markets, there is a trade-off inherent in obtaining regulatory approval. Although seeking formal regulatory approval for a product is time-intensive and costly, it offers the advantage of obtaining quality certification and ultimately increasing demand (Berger et al., 2021). Our results suggest that pharmaceutical firms can financially benefit by seeking smaller indications first rather than initially seeking potentially longer and costlier regulatory approvals in larger market sizes. From a managerial perspective, such strategic investments might be particularly important for firms facing financial constraints or in markets where the first-mover advantage is large. This may be the case, for example, with targeted therapies for specific genes. In these situations, firms may benefit by getting a drug into the hands of physicians and patients as quickly as possible via one indication approval and then relying on off-label use or later regulatory approvals for broader indications.

From a policy perspective, our results raise important considerations for regulators such as the FDA, which must consider the trade-off between expedient access to drugs versus the need for sufficient quality information on potential therapies. At one extreme, regulatory processes may slow entry of valuable products that would benefit consumers if available earlier. At the other, firms may choose to avoid regulatory approval entirely, leading to a dearth of valuable new products and/or limited information about the quality of products on the market that may have bypassed formal regulatory approval. While we cannot speak to overall welfare effects, our findings suggest the need to think more deeply about the costs of regulatory approval and policies like the Orphan Drug Act meant to expedite drug development, both of which may encourage the use of non-regulatory entry pathways. Further, proposed reforms to ban off-label use may have unintended consequences, such as reducing R&D investment levels and consumer access to important drug innovations.

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Appendices

A   A model of strategic entry

In this section, we develop a simple model to show why firms may prioritize smaller indications in their commercialization investments. Our model points to the potential for off-label drug use as a profitable non-regulatory strategy to expand markets. Given our empirical setting, the model naturally focuses on the pharmaceutical industry; however, such product line decisions are applicable across industries to any firm bringing new products to market.

A.1   Model framework

The model is a single-agent, two-period model where a representative firm must choose in each period which product line version, if any, to bring to market. In our setting, this corresponds to a pharmaceutical firm deciding whether or not to seek FDA regulatory approval for a given drug, and if so, for which indication. We outline the model framework and parameters below:

Model timing. The model consists of two periods. In the first period, the pharmaceutical firm chooses whether to enter the market with its drug. This means deciding whether to seek FDA regulatory approval for its drug and the drug's initial indication for approval. In the second period, the firm decides whether to obtain regulatory approval for a supplemental indication, and if so, the choice of indication. For simplicity, the model runs for two periods, although it could be extended to additional periods (in which additional supplemental indications may be chosen). The drug has an on-patent life of two periods, although this could also be extended to additional periods. We assume no discounting between periods.

Indication choice set. We assume that the choice set of potential indications for approval is known and fixed prior to the time of the drug's initial approval; i.e., we abstract away from the situation where learning about additional indications may occur after the drug's initial approval. This is consistent with the growth of large-scale screening methods to identify new indications early in a drug candidate's life, such as in silico screens (Cha et al., 2018). We can consider the choice set for a given drug as the finite set of indications $\mathcal{I}$ in which the firm tested the drug in early-stage clinical trials. If an indication i is chosen for initial approval, it is no longer available as a choice for supplemental

approval. For simplicity, we assume the choice set contains two indications: $i \in \mathcal{I} = \{A, B\}$, where indication A has a large potential market and B has a small one.

Cost of regulatory approval. If the firm seeks regulatory approval for an indication, it incurs associated costs, for example, the costs of high-quality, later-stage clinical trials necessary for FDA approval. For simplicity, we consider this a fixed cost K_i incurred at the time of the indication's regulatory approval. Consistent with existing evidence on the costs of clinical trials, we consider the costs of regulatory approval to be greater for indications of larger market size, i.e., $K_A > K_B$.

Probability of regulatory approval. Each indication has a probability p_i of receiving regulatory approval. We can consider this as the likelihood clinical trials for that indication are successful in demonstrating safety and efficacy. We assume that the probability of approval is greater for smaller indications, i.e., $p_A < p_B$. This is plausible due to selective patient enrollment for smaller indications.

Off-label markets. Each indication has a corresponding set of potential off-label indications, denoted by $\mathcal{O}_i$. If a drug receives regulatory approval for indication i, then $\mathcal{O}_i$ is the set of all indications for which doctors may choose to prescribe the drug off-label (i.e., indications in $\mathcal{O}_i$ exceed some threshold of known relatedness to indication i). We assume that $\mathcal{O}_A = \{B, C\}$ and $\mathcal{O}_B = \{A, C\}$, where C is a separate indication that was never tested in early-stage trials. That is, if a drug is approved for A, doctors may prescribe it off-label for B and C. Similarly, if a drug is approved for B, doctors may prescribe it off-label for A and C.

Off-label diffusion rate. A drug's rate of off-label diffusion is $d \in [0, 1]$. The firm has an ex-ante prior of this rate, which gives the proportion of potential off-label markets that will actually use the drug off-label following regulatory approval. For example, a diffusion rate of 0 would imply that, following initial regulatory approval, the drug is not used at all off-label, and a diffusion rate of 1 would imply that it is used by the entire expected off-label market associated with the initial indication.

Market size. Each indication has a corresponding focal market size M_i. Total market size T_i for a given indication is the sum of its focal market size plus its potential off-label market size O_i multiplied by the drug's off-label diffusion rate, i.e., $T_i = M_i + dO_i$. Given the assumptions above

on the relative sizes of A and B and each indication's off-label markets, we have that $M_A > M_B$ and that $O_A = M_B + M_C < M_A + M_C = O_B$. Whether T_A is greater than T_B or vice versa will depend on the rate of off-label diffusion. We hold market sizes as fixed over the model periods.

Per-period profits. Holding price fixed across indications and normalizing it to equal 1, per-period expected profits π for each indication are simply the probability of approval multiplied by total market size, including off-label markets.[1] That is, $\pi_i = p_i T_i = p_i(M_i + dO_i)$.

The profit-maximizing pharmaceutical firm will seek to enter the market with its drug in period 1 if and only if the expected return from the initial indication exceeds its fixed cost of regulatory approval. Similarly, the firm will seek a supplemental regulatory approval if and only if the expected return from the supplemental indication exceeds its fixed cost. Conditional on entry, the firm chooses an order of indications for its drug that maximizes the expected stream of total profits over the model's two periods (i.e., the drug's on-patent life). The firm's decision tree is given in Figure A1.

FIGURE A1: TWO-PERIOD MODEL OF STRATEGIC ENTRY

t=1   *t=2*
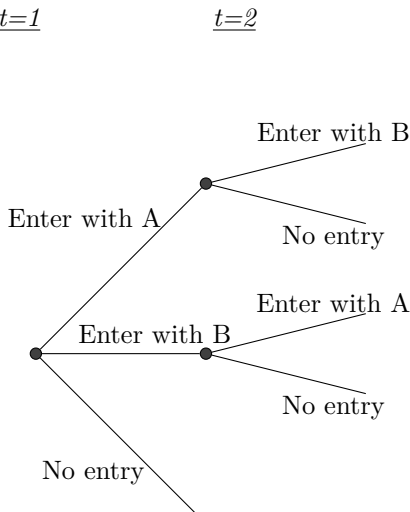
NOTES: This figure shows the firm's decision tree. The firm chooses in each period whether to seek regulatory approval (enter) or not and if so, for which indication $i \in I = \{A, B\}$, where indication A has a large potential market and B, a small one.

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[1] We set per-period variable costs to be zero.

A.2   Firm incentives to seek regulatory approval

This model produces five potential strategies for the firm: (1) enter with A in period 1, enter with B in period 2; (2) enter with A, no entry; (3) enter with B, enter with A; (4) enter with B, no entry; and (5) no entry at all. We consider the expected value from each strategy in turn.

The expected value of seeking regulatory approval for indication A in period 1 and for indication B in period 2 is:

$$EV_{A,B} = 2p_A[M_A + d(M_B + M_C)] + p_B[(1-d)(M_B + dM_C)] - K_A - K_B \tag{4}$$

Note that with regulatory approval for A in period 1, the firm penetrates a portion d of the markets for B and C via off-label use. This leaves $(1-d)$ of the markets for B and C that can be gained via regulatory approval for B in period 2. Note also that while $\mathcal{O}_B = \{A, C\}$ initially, since the drug receives regulatory approval for A in period 1, it is no longer included among B's potential off-label markets at period 2; i.e., in period 2, $\mathcal{O}_B = \{C\}$.

The expected value of seeking regulatory approval for indication A in the first period and not entering in the second is:

$$EV_{A,no\ entry} = 2p_A[M_A + d(M_B + M_C)] - K_A \tag{5}$$

Similarly, the expected value of seeking regulatory approval first for B and second for A is:

$$EV_{B,A} = 2p_B[M_B + d(M_A + M_C)] + p_A[(1-d)(M_A + dM_C)] - K_B - K_A \tag{6}$$

And the expected value of seeking regulatory approval for B in the first period and not entering in the second is:

$$EV_{B,no\ entry} = 2p_B[M_B + d(M_A + M_C)] - K_B \tag{7}$$

Seeking no regulatory approval at all yields a reservation value $\bar{V} = 0$.

The firm chooses the strategy (whether to seek regulatory approval and choice of indications in each period) that maximizes its expected value. If the expected values in equations (4)–(7) are less than

reservation value $\bar{V}$, the firm does not obtain regulatory approval and does not enter the market with its drug.

A.3   Model prediction

We aim to understand how market size relates to regulatory approval decisions in settings where off-label use is more or less common. First, we consider the scenario where $d = 0$ and no off-label use occurs. In that case, the expected value in equation (4) simplifies to $2p_A M_A + p_B M_B - K_A - K_B$ and the expected value in equation (5) simplifies to $2p_A M_A - K_A$. Equations (6) and (7) simplify similarly. Conditional on $2pM_A - K_A > 0$ and $pM_B - K_B > 0$, and given our initial assumption on market size $M_A > M_B$, the firm will select indication A for regulatory approval in period 1 and indication B for approval in period 2 if and only if:

$$2p_A M_A + p_B M_B - K_A - K_B > 2p_B M_B + p_A M_A - K_B - K_A, \text{ or} \tag{8}$$

$$M_A > \frac{p_B}{p_A} M_B \tag{9}$$

Equation (9) shows that if p_A is sufficiently large, then the firm prioritizes larger indications for its regulatory approvals in settings where off-label use is uncommon.

Second, we consider the scenario where $d = 1$ and regulatory approval for an indication leads to complete off-label diffusion, i.e., the total off-label population for that indication also uses the drug. Here, the expected value in equation (4) simplifies to $2p_A[M_A + M_B + M_C] - K_A - K_B$ and the expected value in equation (5) simplifies to $2p_A[M_A + M_B + M_C] - K_A$. That is, under complete diffusion, the firm has no incentive to seek regulatory approval in the second period because it is already reaching all potential markets, including off-label ones, with regulatory approval in the first period. Again, equations (6) and (7) simplify similarly. Conditional on $2p_B[M_A + M_B + M_C] - K_B > 0$ and given our initial assumptions on the probability of regulatory approval $p_A < p_B$ and fixed costs of approval $K_A > K_B$, the firm will select indication B for regulatory approval in period 1 and seek no approval in period 2.

Thus we can summarize the main prediction of our model as follows:

In settings where off-label use is less likely to occur, we would expect firms to prioritize larger indications for their regulatory approvals. Conversely, in settings where off-label use is more likely, firms may prioritize smaller indications for approval.

B Similarity index example: Breast and ovarian cancers

Table B1 provides the genetic mutations associated with breast and ovarian cancers from the CGC database. We calculate their similarity index as follows: $s_{Breast,Ovarian} = \frac{|B \cap O|}{|B \cup O|} = 7/75 = 0.093$.

TABLE B1: GENETIC MUTATIONS FOR BREAST AND OVARIAN CANCERS

Breast gene mutations	Ovarian gene mutations	Breast & ovarian gene mutations
ALK	AKT2	AKT1
ASPM	ATR	ARID1A
BAP1	BRAF	ARID1B
BARD1	BRCA1	BRCA2
CASP8	CASP3	ERBB2
CCND1	CCNE1	GOLPH3
CDH1	CDK12	PPM1D
CDKN1B	COL3A1	
CTCF	CREB1	
DCTN1	CSMD3	
EP300	CTNNB1	
ESR1	EIF1AX	
ETV6	EWSR1	
FADD	FES	
FBLN2	FOXL2	
FLNA	GOPC	
FOXA1	LRP1B	
GATA3	MAPK1	
HGF	MLH1	
IKZF3	MSH2	
IRS4	PIK3R1	
KEAP1	PLAG1	
MAP2K4	PPP2R1A	
MAP3K1	PRDM2	
MAP3K13	PTK6	
MED12	RNF43	
NCOR1	ROS1	
NOTCH1		
NTRK3		
PBRM1		
PIK3CA		
PPFIBP1		
RAD50		
RANBP2		
RB1		
SALL4		
SMARCD1		
TBX3		
TP53		
VHL		
ZMYM3		

NOTES: This table lists gene mutations for breast and ovarian cancers from the CGC database.

C Variation in approval and trial indications

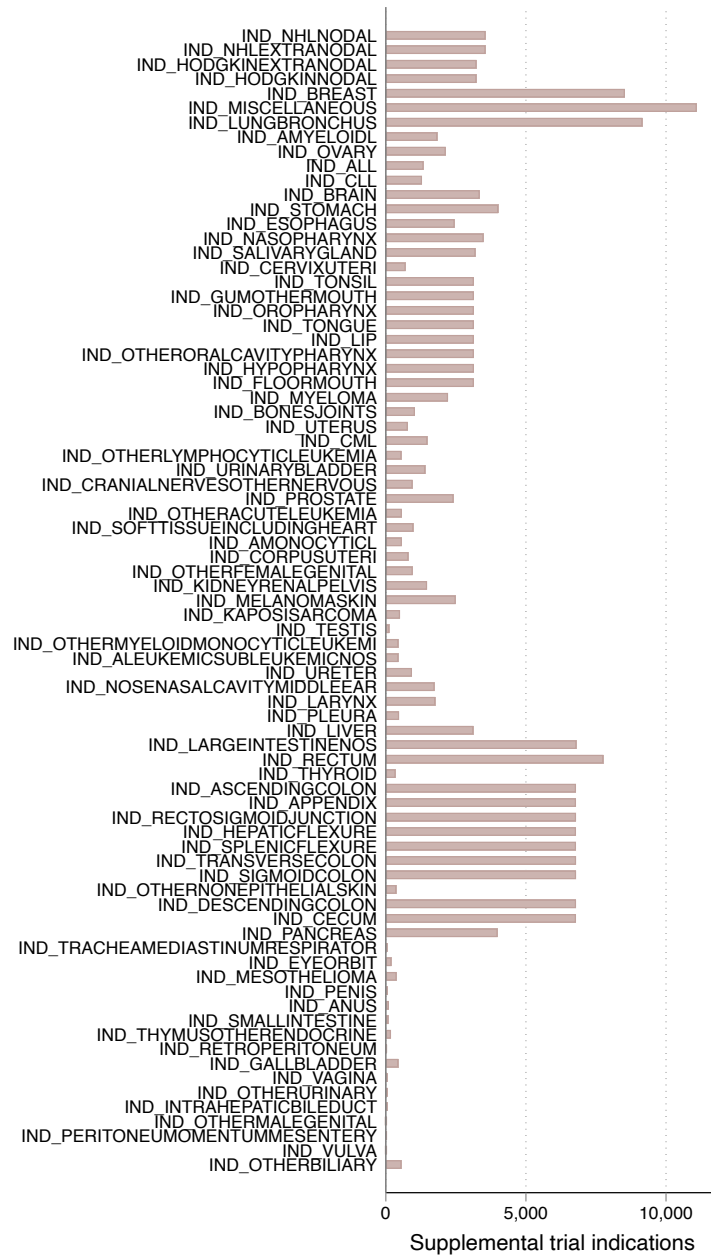FIGURE C1: PER-DRUG DISTRIBUTION OF PRODUCT LINE INVESTMENTS
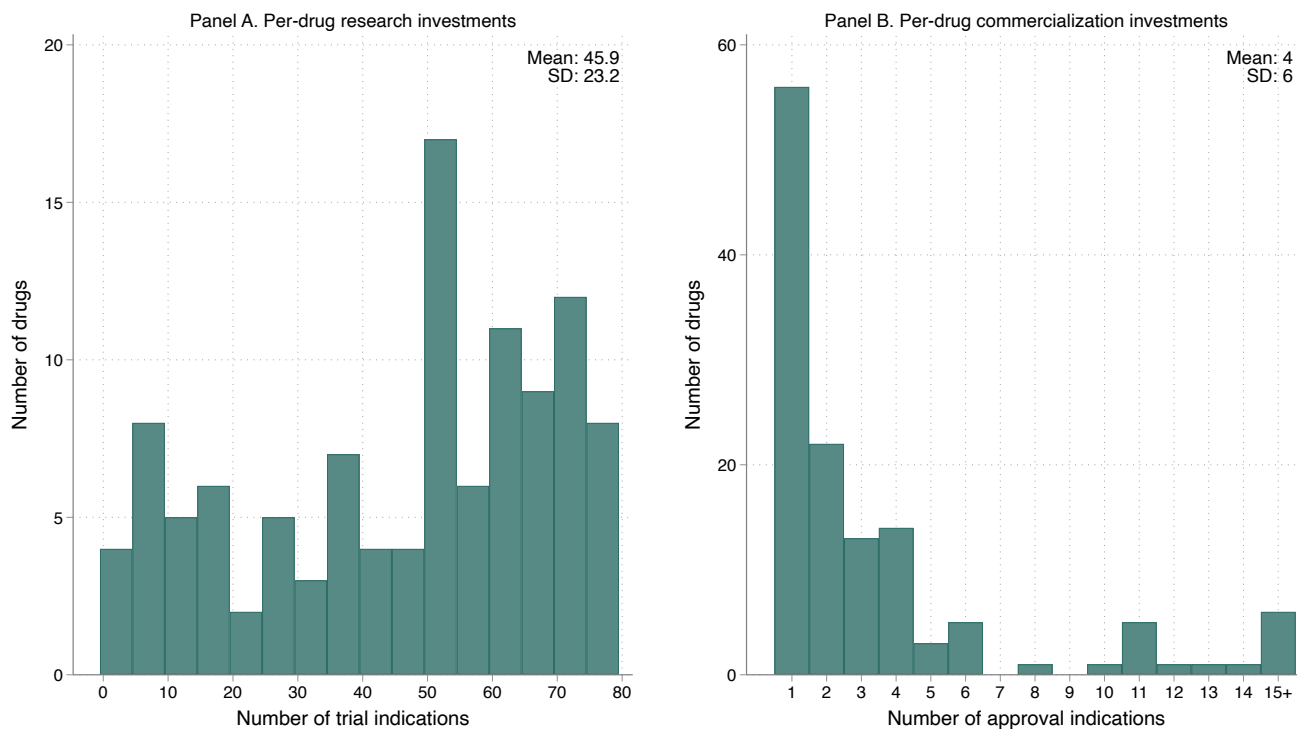
NOTES: This figure shows the distribution of product line investments for cancer drugs approved from 1990-2016. Panel A gives the per-drug distribution of trial indications; number of drugs is 111. Panel B gives the per-drug distribution of approval indications; number of drugs is 129.

FIGURE C2: DISTRIBUTION OF ORIGINAL TRIAL INDICATIONS ACROSS CANCER SITES
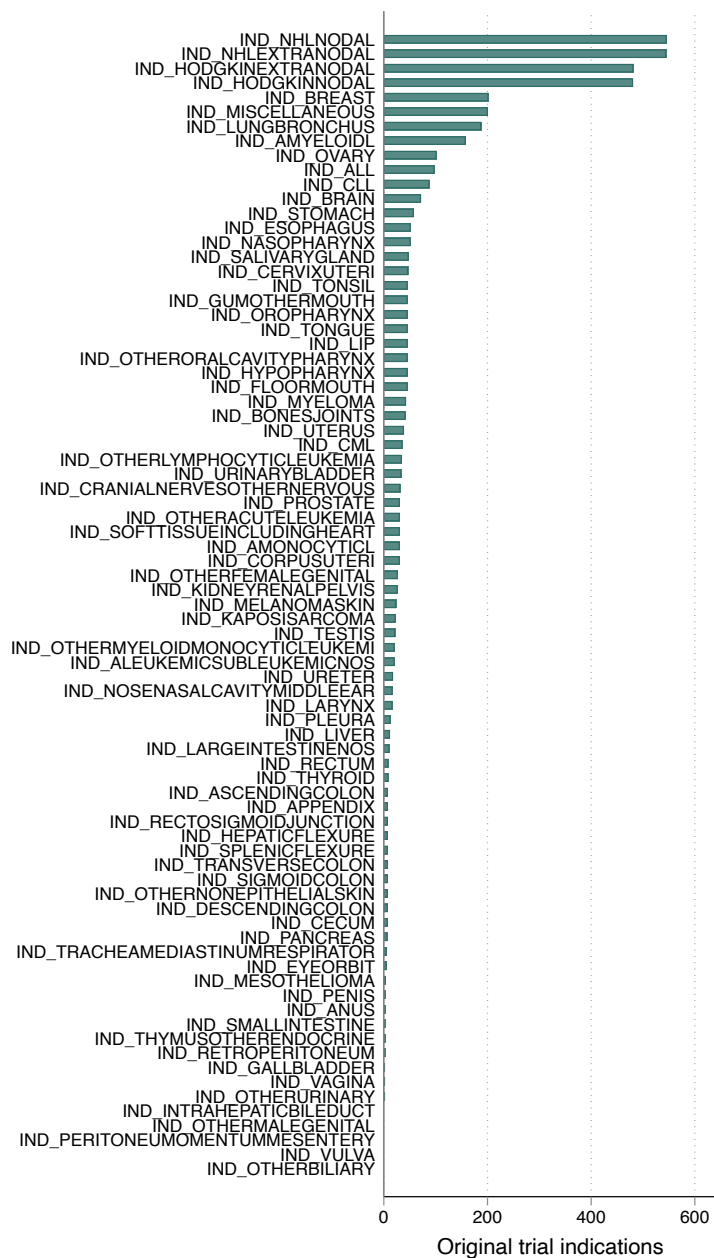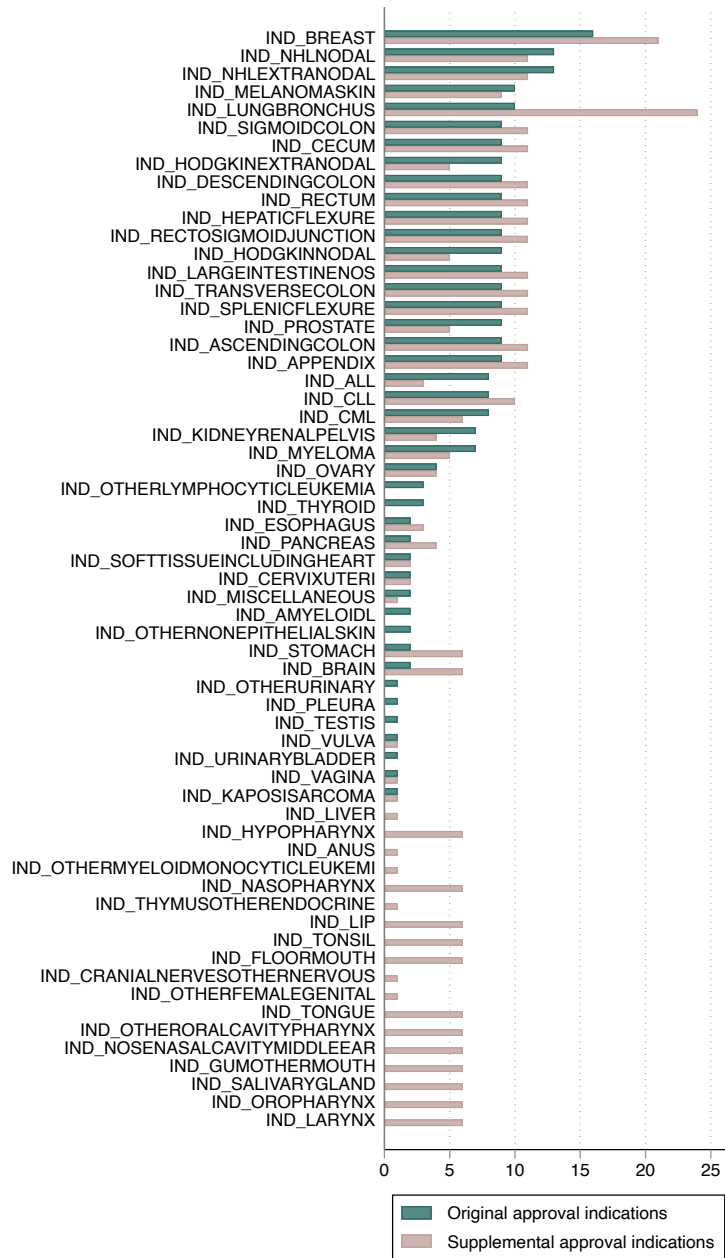
NOTES: This figure shows the distribution of the original trial indications across cancer sites for cancer drugs approved from 1990-2016.
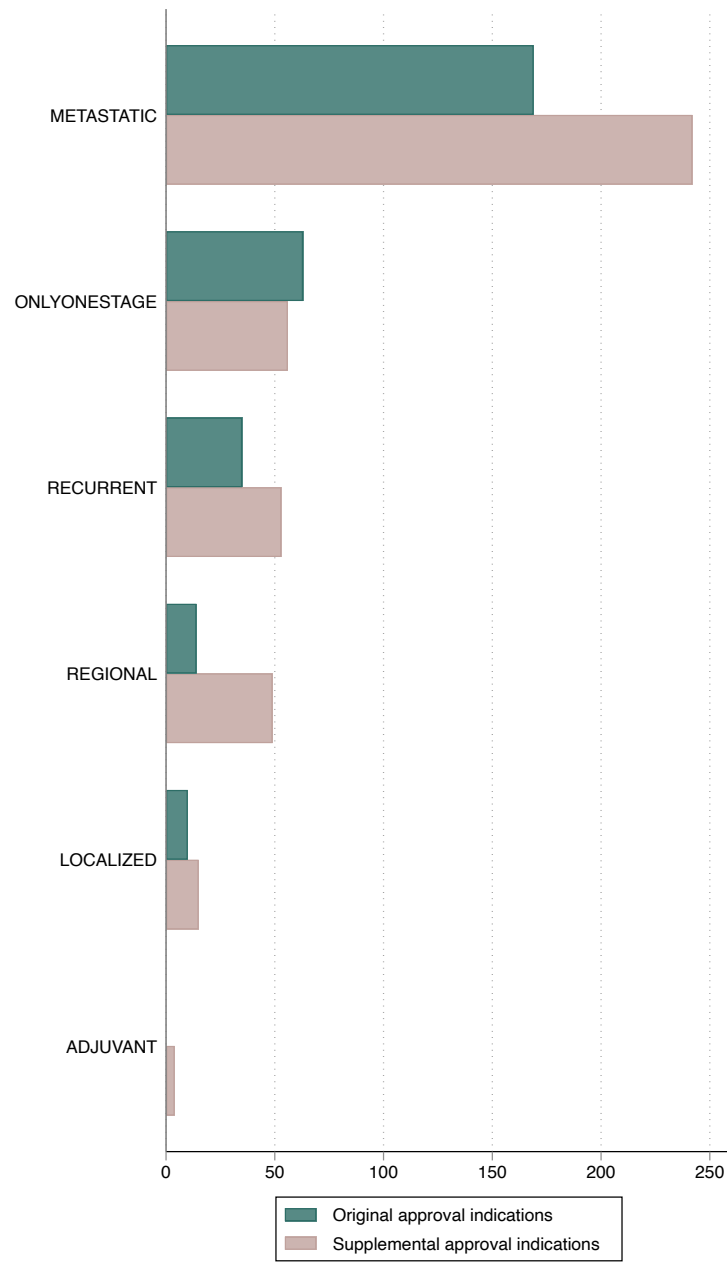
NOTES: This figure shows the distribution of the supplemental trial indications across cancer sites for cancer drugs approved from 1990-2016.

FIGURE C4: DISTRIBUTION OF APPROVAL INDICATIONS ACROSS CANCER SITES

NOTES: This figure shows the distribution of original and supplemental approval indications across cancer sites for cancer drugs approved from 1990-2016.

FIGURE C5: DISTRIBUTION OF APPROVAL INDICATIONS ACROSS CANCER STAGES

NOTES: This figure shows the distribution of approval indications across cancer stages for cancer drugs approved from 1990-2016.

D Robustness checks

D.1 Difference between first and subsequent indications

TABLE D1: PRODUCT LINE INVESTMENTS AND MARKET SIZE

	Research investments		Commercialization investments	
	(1)	(2)	(3)	(4)
$\mathbb{1}_{First\ indication}$	1.152***	0.626***	-0.386*	-0.591**
	(0.125)	(0.147)	(0.220)	(0.272)
Mean of dep. var.	6.842	6.820	6.513	6.522
Observations	1,656	1,570	187	182
Initial approval year	no	yes	no	yes
Indication group	no	yes	no	yes
Competition	no	yes	no	yes
Regulatory incentives	no	yes	no	yes
Intellectual property	no	yes	no	yes

NOTES: This table shows the difference in market size between the first and subsequent indications for cancer drugs approved from 1990-2016. The level of observation is the drug-indication order. The first two columns look at research investments (clinical trials), and the second two columns look at commercialization investments (FDA approvals). Market size is measured by new diagnoses for an indication in the SEER data. The outcome variable is the log of the 5-year average market size associated with indication order. Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1.

	Research investments		Commercialization investments	
	Focal market size (1)	Total market size (2)	Focal market size (3)	Total market size (4)
$\mathbb{1}_{First\ indication}$	0.626***	0.634***	-0.591**	-0.0462
	(0.147)	(0.164)	(0.272)	(0.238)
Mean of dep. var.	6.820	7.738	6.522	8.649
Observations	1,570	1,570	182	182
Initial approval year	yes	yes	yes	yes
Indication group	yes	yes	yes	yes
Competition	yes	yes	yes	yes
Regulatory incentives	yes	yes	yes	yes
Intellectual property	yes	yes	yes	yes

NOTES: This table shows the difference in market size between the first and subsequent indications for cancer drugs approved from 1990-2016. The level of observation is the drug-indication order. The first two columns look at research investments (clinical trials), and the second two columns look at commercialization investments (FDA approvals). The outcome variable in Columns (1) and (3) is focal market size while the outcome variable in Columns (2) and (4) is total market size, including potential off-label markets; for both variables, we consider the log of the 5-year average market size associated with indication order. Focal market size is measured by new diagnoses for an indication in the SEER data, while total market size is measured by new diagnoses for the focal indication plus a proportion of new diagnoses for any potential off-label indications, with the proportions given by our disease similarity index. Robust standard errors in parentheses. *** $p<0.01$, ** $p<0.05$, * $p<0.1$.

D.2 Alternative similarity measures

Table D3: Commercialization Investments and Total Market Size, Using Alternative Similarity Measures

	All genes			Cancer Gene Census		
	Top 10% (1)	Top 20% (2)	Top 30% (3)	Top 10% (4)	Top 20% (5)	Top 30% (6)
Indication order	-0.193*	-0.209*	-0.227*	-0.199*	-0.217*	-0.243*
	(0.111)	(0.115)	(0.120)	(0.117)	(0.120)	(0.125)
Mean of dep. var.	9.432	9.636	9.788	9.586	9.880	10.06
Observations	182	182	182	182	182	182
Initial approval year	yes	yes	yes	yes	yes	yes
Indication group	yes	yes	yes	yes	yes	yes
Competition	yes	yes	yes	yes	yes	yes
Regulatory incentives	yes	yes	yes	yes	yes	yes
Intellectual property	yes	yes	yes	yes	yes	yes

NOTES: This table shows the relationship between indication order for commercialization investments (FDA approvals) and total market size for cancer drugs approved from 1990-2016, using alternative similarity measures. Alternative measures are generated by directly using cancer genome sequencing data from 168 large-scale mapping studies. Genetic mutations are restricted to those that occur at a high frequency within each mapping study, where a genetic mutation as "high frequency" within a cancer if it occurs in the top 10 percent (Columns 1 and 4), top 20 percent (Columns 2 and 5), or top 30 percent (Columns 3 and 6) of most frequency occurring mutations. Columns 1 to 3 focus on genetic mutations occurring among all genes. Columns 4 to 6 focus on the set of genetic mutations occurring among genes found in the Cancer Gene Census. The level of observation is the drug-indication order. The outcome variable is total market size, including potential off-label markets, where we consider the log of the 5-year average market size associated with indication order. Total market size is measured by new diagnoses for the focal indication plus a proportion of new diagnoses for any potential off-label indications, with the proportions given by our disease similarity index. Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1.

D.3 Trial end dates

FIGURE D1: RESEARCH INVESTMENTS AND MARKET SIZE,
WITH INDICATION ORDER DETERMINED BY TRIAL END DATES
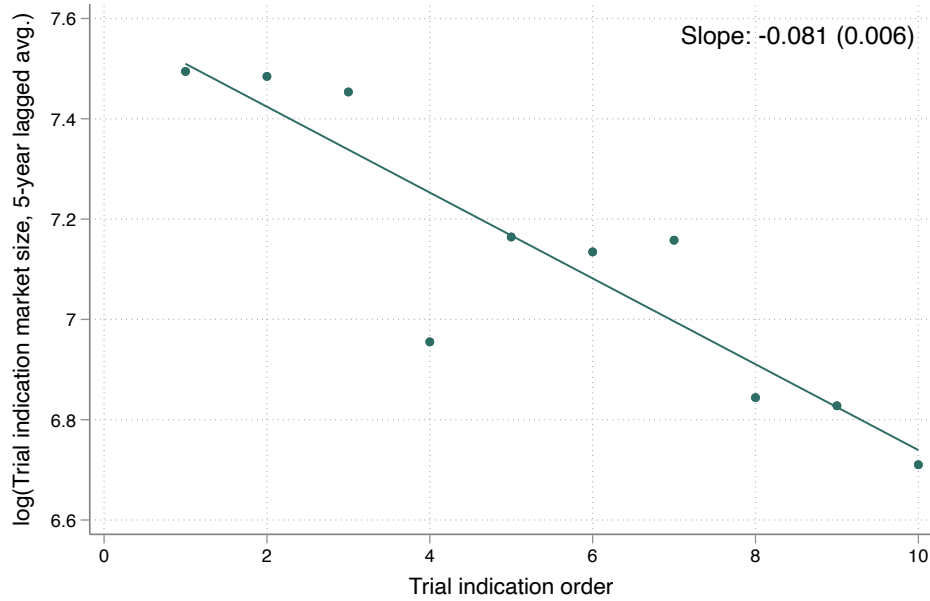
NOTES: This figure shows the relationship between research investments (clinical trials) and market size for cancer drugs approved from 1990-2016, with indication order determined by trial end dates. The level of observation is the drug-indication order. Market size is measured by new diagnoses for an indication in the SEER data; we consider the log of the 5-year average market size. Each marker represents binned averages for a given indication order.

D.4   Submission dates

FIGURE D2: COMMERCIALIZATION INVESTMENTS AND MARKET SIZE, WITH INDICATION ORDER DETERMINED BY SUBMISSION DATES
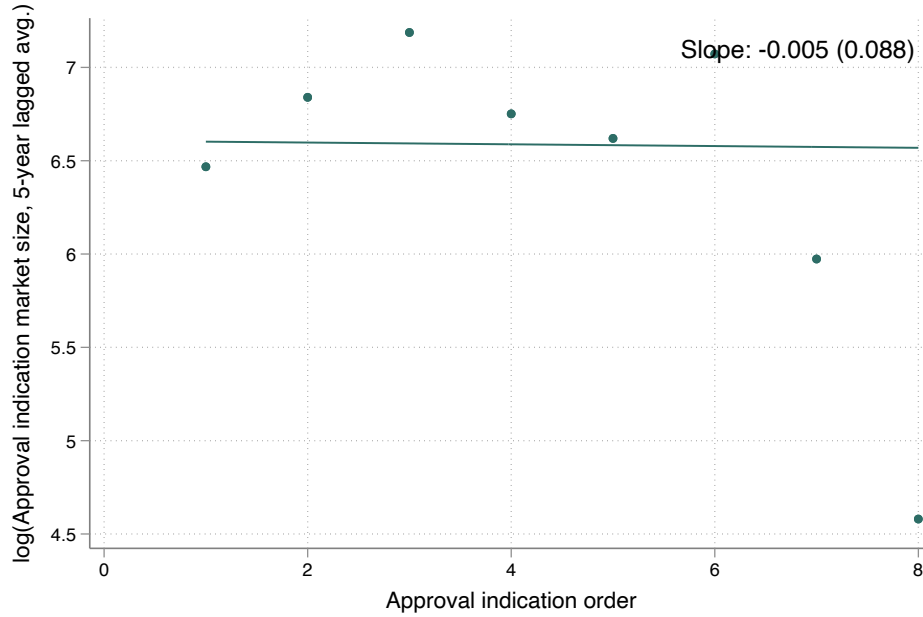
NOTES: This figure shows the relationship between commercialization investments (FDA approvals) and market size for cancer drugs approved from 1990-2016, with indication order determined by FDA submission dates. The level of observation is the drug-indication order. Market size is measured by new diagnoses for an indication in the SEER data; we consider the log of the 5-year average market size. Each marker represents binned averages for a given indication order.