Strategic entry in regulated markets

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Abstract

We analyze firms' market entry decisions in the presence of entry regulation. Our empirical context is pharmaceuticals, where we show that firms prioritize larger markets for clinical testing but pursue smaller markets for regulatory approval. This is consistent with a model of strategic entry where pharmaceutical firms prioritize smaller markets to lower regulated entry costs and rely on complementary, non-regulatory pathways—in the form of unapproved, "off-label" drug use—to expand demand. Our findings highlight for managers the benefits of such non-regulatory pathways and for regulators the importance of balancing expedient access to new products with sufficient product quality information.

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

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1 Introduction

Innovating firms have incentives to launch their products in the largest markets possible (Acemoglu and Linn, 2004; Blume-Kohout and Sood, 2013). However, innovative activities often take place in regulated industries, such as transportation and health care, where firms must undergo a series of information-gathering research investments as a precondition for market entry (Malani and Philipson, 2012). Entry regulation ensures a minimum level of quality for novel products, but it may also fundamentally shift firms' market entry decisions on which product markets to prioritize for information-gathering purposes and which to prioritize for regulatory approval (and eventual product launch). For example, an automobile manufacturer may develop various prototypes aimed at different market segments but subsequently launch only the model most likely to meet vehicle emissions standards (Pinkse et al., 2014). Despite the long-standing interest of researchers, managers, and policy makers in understanding firms' market entry strategies, there has been limited empirical research on how these strategies are shaped by entry regulation. Our paper aims to fill this gap.

The idea that entry regulation may shift firms' market entry decisions, while conceptually clear, is difficult to examine empirically. There are two main issues. First, exogenous variation in entry regulation requirements is rare, with regulatory changes typically anticipated and similar across product markets. As a result, traditional empirical methods—which may rely on exogenous changes over time or across product markets—are ill-suited to assess how entry regulation may shift firms' market entry decisions. Second, investigating the impact of entry regulation on firms' entry strategies requires measuring two types of investments: information-gathering (pre-approval) and regulatory (approval) investments. However, firms' information-gathering investments are generally unobserved by the researcher, making it difficult to fully characterize how firms alter their investment decisions in response to market entry regulation.

Our empirical focus is drug development, which allows us to make progress on both of these issues.[1] In the pharmaceutical industry, firms are required to conduct a series of costly, risky, and time-intensive clinical trials to demonstrate the safety and effectiveness of their drugs to the U.S. Food and Drug Administration (FDA) prior to market entry (Adams and Brantner, 2006; Mullard, 2016; Wouters et al., 2020). To address the challenge of identifying exogenous variation in entry regulation, we leverage differences in the regulatory costs and risks of entry across disease markets. In particular, we focus on an important feature of drug regulation—the FDA's allowed use

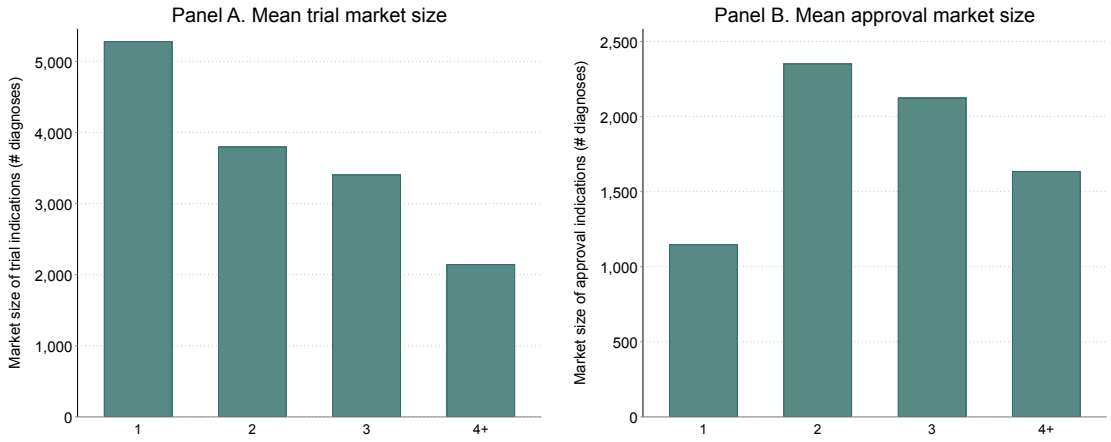
[1]The pharmaceutical industry is projected to exceed $1.1 trillion by 2024, making it a noteworthy sector for analysis (IQVIA Institute, 2020).

of approved drugs for unapproved ("off-label") uses (Adams and Brantner, 2006; Eisenberg, 2005; Mullard, 2016; Wouters et al., 2020)—and exploit variation across markets in their potential for off-label use. For drugs with higher off-label potential, firms have more opportunities to lower their regulated entry costs: Rather than seek formal FDA approval in the largest market possible, they can prioritize approval in disease markets with lower regulatory costs; simultaneously, they can rely on off-label drug use to enter other markets without the significant investment needed for formal regulatory approval. To evaluate firms' market entry strategies, we assemble a dataset of all cancer drug approvals between 1990 and 2006, matched to comprehensive clinical trial information. This dataset allows us to distinguish between the two types of market entry investments. We use clinical trials as a proxy for information-gathering investments and FDA approvals as a proxy for regulatory investments. Using these data, we document evidence that strategic market entry is quantitatively important in the pharmaceutical industry and analyze potential managerial and policy implications.

Theoretically, without strategic entry, we would expect a firm to prioritize a given drug's information-gathering and regulatory investments in its largest possible market (Acemoglu and Linn, 2004). When considering where to seek regulatory approval, firms might expect to earn higher revenues in larger markets and thus be motivated to enter these markets first to gain valuable first-mover advantages. Yet a growing body of evidence suggests that regulatory approval for drugs targeting smaller disease indications may be less costly and risky compared to targeting larger indications, due to the possibility of conducting smaller clinical trials with patients who are more likely to positively respond to treatment (Chandra et al., 2019; Michaeli et al., 2023). And since an estimated 90% of approved drugs have multiple therapeutic uses, significant variation in the costs of regulated entry can meaningfully shift firms' decisions on which indications to prioritize for regulatory approval (Gelijns et al., 1998). To illustrate, the pharmaceutical firm Janssen sought initial U.S. approval for Remicade as a treatment for severe Crohn's disease, opting for a quicker path to approval for this indication, despite earlier success in clinical trials in a larger indication, rheumatoid arthritis (Melsheimer et al., 2019).

To illustrate, Figure 1 explores investments across a drug's lifecycle, plotting mean market size by indication order—defined as the sequence of indications in which a given drug is clinically tested (or approved). There is a notable divergence in firms' information-gathering and regulatory investments: For a given drug, firms prioritize larger indications for information-gathering (Panel A) and smaller indications for regulatory approval (Panel B).

FIGURE 1: MEAN MARKET SIZE BY INDICATION ORDER



NOTES: This figure shows the mean market size by indication order for both information-gathering investments (clinical trials in Panel A) and regulatory 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. Due to data limitations, trial indications are given by cancer sites and approval indications are given by cancer site-stages.

This new fact—the discrepancy between firms' information-gathering and regulatory investments—is consistent with the view that differences in the regulatory costs of entry may meaningfully shape firms' market entry decisions. However, such patterns could also be due to differences in scientific opportunities (Krieger, 2021), market conditions (Acemoglu and Linn, 2004), or intellectual property protection (Budish et al., 2015). To address this, we note that these indication order-market size relationships persist even after controlling for numerous factors, such as disease fixed effects, time fixed effects, competition, regulatory incentives, and intellectual property protection. One factor left unexplained is the potential for strategic entry via off-label drug use; this paper provides empirical evidence of its importance.

One major challenge is that we cannot directly measure the ex-ante potential for a drug's off-label use. Three features of the market for cancer medicines—the largest pharmaceutical market in terms of spending—allow us to address this challenge (IQVIA Institute, 2018). First, among oncology drugs, multiple uses are common and estimates of off-label use range from 50 to 75% (Pfister, 2012).[2] Second, cancer treatment, which is organized around the site (e.g., breast) and stage (e.g., metastatic), provides a tractable way for researchers to measure R&D activity (Budish et al., 2015).

[2]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.

Third, the rise of cancer genome sequencing—which reveals genetic links across diseases—enables us to use genetic data to identify likely off-label disease markets.

Relying on these institutional features, we present evidence from two empirical tests supporting the role of regulatory costs and off-label drug use in shaping firms' market entry decisions. 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 cancer genomic sequencing data. Using this index, we can approximate an indication's total market size, including off-label drug use. Accounting for the size of expected off-label markets, we recover a strictly negative and significant relationship between the order of regulatory approval for an indication and its market size. These findings are consistent with a strategy of prioritizing smaller markets to reduce regulatory costs and relying on off-label use to enter new markets without formal approval.

Second, we expand our analyses to diseases beyond oncology and exploit variation across diseases in their propensity for off-label use. Using estimates from the medical literature, we categorize diseases into those with high and low levels of off-label drug use.[3] We confirm that for disease markets where off-label drug use is prevalent, firms are significantly less likely to prioritize large indications for regulatory approval. The results of these two empirical tests are consistent with a model of strategic market entry: In settings where off-label use is less likely to occur, firms are more likely 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.[4]

Finally, we consider the managerial and policy implications of our findings. First, our findings clarify how firms can minimize the costs associated with entry regulation by relying on complementary, non-regulatory entry strategies. 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.

[3]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.

[4]We discuss the underlying assumptions for a model of strategic entry and provide proofs in Appendix A.

Additionally, our results should prompt regulators to consider whether firms are actively avoiding engaging in regulatory processes and the implications for consumers.[5] Across a variety of industries, the belief that entry regulation may shape firms' market entry decisions 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). Regulators must strike a balance between expediting consumer access to new products or services and ensuring their quality via rigorous standards and examination.

In the pharmaceutical sector, 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).[6] These papers—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

[5] A *New England Journal of Medicine* perspective piece highlights potential concerns associated with strategic market entry among pharmaceutical firms: "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).

[6] 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 market entry decisions focuses on a drug's introduction into different therapeutic markets.

introduced to the market. Our data allow us to extend this literature by documenting a discrepancy between firms' information-gathering and regulatory investments for a single product. Though we caution that we unable to make causal conclusions, we provide a series of empirical evidence that suggests this discrepancy may, in part, be related to entry regulation.

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 opportunities for market learning and technology development, we highlight an additional rationale for pursuing a smaller, selective market: to lower the regulatory costs of entry.

Third, we contribute to a growing set of papers on off-label drug use measurement (Radley et al., 2006; Stafford, 2008), drivers (Dubois et al., 2023; Larkin et al., 2014; McKibbin, 2023; Shapiro, 2018) and consequences (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 information-gathering and regulatory investments.

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, in response to the high costs of regulated entry, firms may turn to complementary, non-regulatory pathways to enter new product markets.

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 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 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% of drugs that initiate clinical testing receive regulatory approval) (Adams and Brantner, 2006; CSDD, 2014; Danzon and Keuffel, 2014; DiMasi, 2001; DiMasi et al., 2003; Wouters et al., 2020).

The development and review process is indication-specific—i.e., a drug receives regulatory approval for a specific use. 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.[7]

The costs of drug development also vary across indications. To the best of our knowledge, there are no publicly available data estimates of drug development costs by indication size. However, some

[7] Examples include a new stage of the same disease or the same disease in a new population.

quantitative evidence suggests that drug development may be less costly for smaller indications relative to larger indications: Participant recruitment and enrollment costs constitute a major portion of clinical trial costs (Sertkaya et al., 2016), and trials for smaller indications often require fewer participants than those for larger indications (Hee et al., 2017). While identifying suitable trial participants for trials in smaller indications may be challenging, firms have increasingly utilized genetic sequencing and biomarkers to target specific patient subgroups that are most responsive to treatment, which may reduce costs and risks (Chandra et al., 2019; Michaeli et al., 2023). Consistent with this, since the beginning of the Orphan Drug Act of 1983 (ODA), a law enacted to incentivize the development of drugs to treat orphan diseases (defined as those affecting less than 200,000 people in the U.S.), there has been a significant increase in the number of approved drugs targeting small indications (from 10 in 1990 to 77 in 2017) (Miller and Lanthier, 2018). 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).

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]

The FDA recognizes that off-label use can be clinically appropriate under some circumstances, but is concerned that widespread off-label drug use may lead to public health risks due to the lack of

[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.

rigorous research supporting it (FDA, 2014). As a result, the FDA prohibits the direct promotion of off-label uses. Despite this, evidence suggests that manufacturers still utilize clinical evidence as a means to promote off-label uses.[10] Additionally, the agency's policy towards off-label advertising has gradually loosened and been challenged over time (FDA, 2014). Manufacturers are currently permitted to respond to unsolicited questions about off-label 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).

3 Data and summary statistics

To empirically investigate pharmaceutical firms' strategic entry decisions, we evaluate market entry investments associated with drugs initially approved for oncology. Our sample consists of the set of 129 cancer drugs first approved by the FDA between 1990 and 2016.

3.1 Market entry investments

For these 129 cancer drugs, we obtain detailed market entry investment data on clinical trials and drug approvals. With these data, we can thus distinguish between two types of market entry investments: information-gathering investments (measured via clinical trials) and regulatory investments (measured via FDA approvals).

To proxy for information-gathering investments, we obtain clinical trial data from the Clarivate Analytics Cortellis Clinical Trials Intelligence Global database. Data limitations prevent us from categorizing clinical trial indications to the cancer stage level. As a result, our information-gathering investment analyses are conducted at the drug-cancer site level.

To measure regulatory investments, we identify each drug's set of approvals (NDA and any sNDAs) from the Clarivate Analytics Cortellis Competitive Intelligence Global database and the FDA's Drugs@FDA database. Approval indications are categorized at the cancer site-stage level.[11] As a result, our regulatory investment analyses are conducted at the drug-cancer site-stage level.

[10] The U.S. Department of Justice has charged and fined several 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).

[11] Note 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

3.2.1 Size of approved indication

As a proxy for the market size of approved indications, 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 calculate these lags relative to either the trial start year (for information-gathering analyses) or the indication approval year (for regulatory investment analyses). Due to data limitations previously described, market size for trial indications is measured at the cancer site level, while market size for approval indications is measured at the level of the cancer site-stage level.

3.2.2 Size of potential off-label market

Cancer genome mapping data.– To construct a proxy for the potential off-label market size for each indication, 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 the 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).[12] The COSMIC team curates cancer genome data from hundreds of genetic 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

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

(e.g., breast cancer, ovarian cancer) where mutations in that gene are likely contributors to the disease's development.[13]

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 80 potential cancer sites. 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.

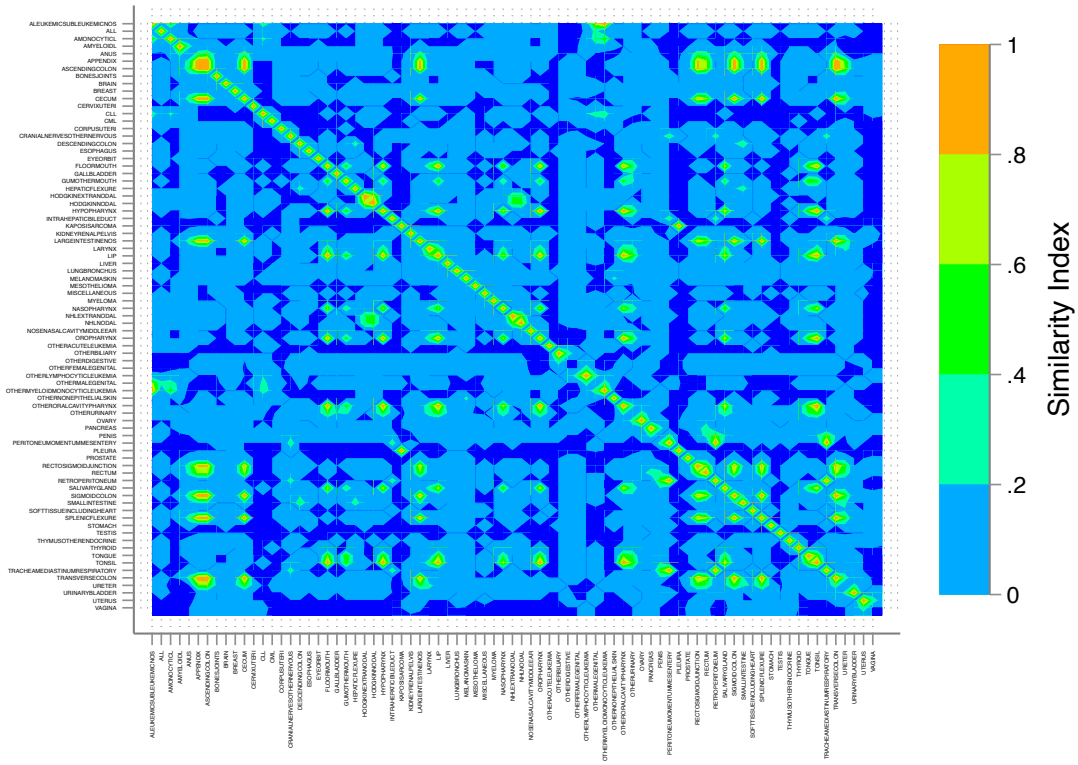
Calculating off-label market sizes.– We use the similarity index to determine the expected off-label market size for each indication. This calculation is based on the market size for cancer sites related to indication i, weighed by the similarity index:

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

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 a similarity with cancer site C ($s_{B,C} = 0.01$). Suppose that at time t, the market size for cancer site A is 100 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 $(0.09 \times 100) + (0.01 \times 20) = 9.2$.

[13]We focus specifically on somatic mutations, meaning mutations that occur in any cell type other than germ cells.

FIGURE 2: SIMILARITY INDEX HEAT MAP



NOTES: This figure shows a heat map of our similarity index across all 80 potential cancer sites.

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.[14]

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

[14]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/`.

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).

3.3 Drug characteristics

Competition.– As a proxy for the level of competition faced by each drug in a given indication, we count the number of drug approvals in the same indication in the five years prior to the trial start year (for information-gathering investment analyses) or the indication approval year (for regulatory investment analyses) .

Regulatory incentives.– To capture regulatory incentives associated with subsequent market entry investments, we compile data on whether the drug ever received an orphan drug designation. Established in 1983, the Orphan Drug Act (ODA) act offers incentives (e.g., tax benefits and regulatory exclusivities) to firms developing drugs for "orphan" diseases (i.e., rare diseases affecting less than 200,000 individuals).[15]

Intellectual property protection.– We incorporate information on intellectual property (IP) protection using data from the FDA's Orange Book and the United States Patent and Trademark Office (USPTO).[16] We create two controls for IP protection: primary and potential IP protection. Primary IP protection measures the months from each trial start (or indication 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.[17] Potential IP protection measures from each trial start (or indication approval) to when the final IP on the drug expires.[18]

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

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

[17]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.

[18]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.

3.4 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 47 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 (6,369 diagnoses) is nearly 4 times the mean market size of trial indications (1,616 diagnoses) and almost 6.5 times that of approval indications (985 diagnoses).

Table 1: Summary Statistics

	Mean	SD	Min	Max	N
Drug level					
Number of Unique Trial Indications (Cancer Site Level)	46.7	23.6	1	78	127
Number of Unique Approval Indications (Cancer Site-Stage Level)	4.0	6.0	1	35	129
Share with Orphan Disease Drug Designation	0.64	0.48	0	1	113
Drug-trial indication level					
Mkt Size: Trial Indications (Diag., Cancer Site Level)	1,615.7	3,217.9	4.6	17,915	5,933
Drug-approval indication level					
Mkt Size: Approval Indications (Diag., Cancer Site-Stage Level)	984.6	1,749.0	2.4	9,104	428
Mkt Size: Potential Off-Label (Diag., Cancer Site-Stage Level)	6,369.3	7,973.6	0	24,891	518
IP Protection: Primary (Months)	123.5	55.3	0	277	513
IP Protection: Potential (Months)	173.9	50.6	44	346	513

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.

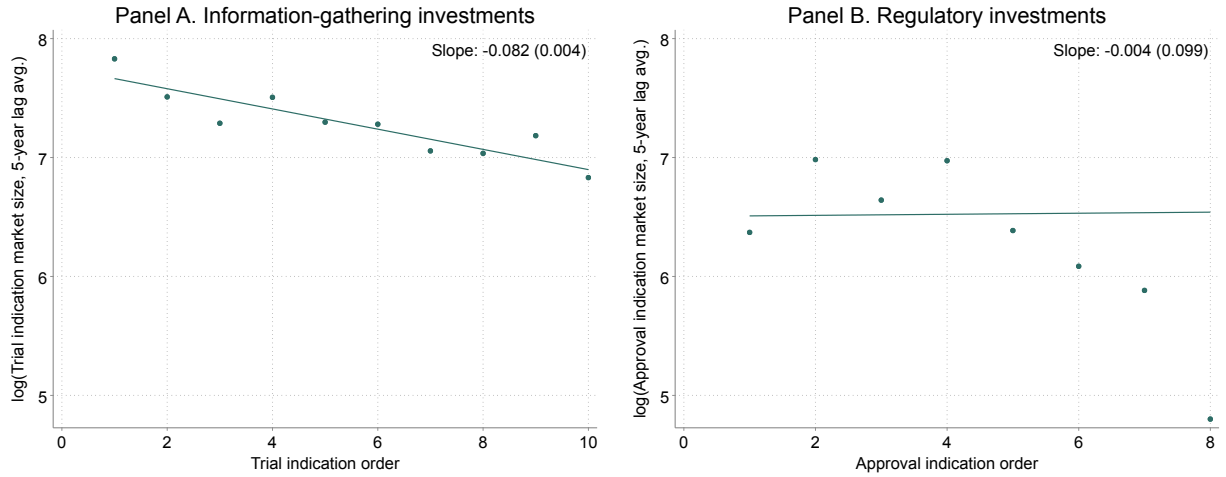
4 Empirical results

4.1 Entry investments and market size

We aggregate the market entry, market size, and drug characteristics data into drug-indication order (e.g., Letrozole - first indication) observations, where indication order is defined as the sequence of indications in which a given drug is clinically tested (or approved).[19] Figure 3 plots the relationship between market entry investments and market size for our oncology sample. Consistent with

[19]When a single indication order corresponds to multiple indications (e.g., a drug is initially clinical tested in both breast and ovarian cancers in trials starting on the same date), we take the average of their market sizes.

FIGURE 3: ENTRY INVESTMENTS AND MARKET SIZE



NOTES: This figure shows the relationship between entry 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 1,980. 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.

Figure 1, Panels A and B illustrate key differences between the timing of information-gathering and regulatory investments. Panel A documents that trial indication order is strongly negatively correlated with market size. Contrasting this, Panel B documents that approval indication order has a non-negative relationship with market size; firms do not prioritize approvals in larger markets. This pattern is consistent with the view that given the relatively lower costs of obtaining regulatory approval for conditions with smaller market sizes and the potential to rely on off-label markets, firms strategically seek first approval for indications with smaller markets.

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

TABLE 2: ENTRY INVESTMENTS AND MARKET SIZE

	Information-gathering investments		Regulatory investments	
	(1)	(2)	(3)	(4)
Indication order	-0.0823***	-0.0786***	0.00448	-0.0442
	(0.00371)	(0.00518)	(0.0995)	(0.141)
Mean of Dep. Var.	6.829	6.794	6.513	6.522
Observations	1,980	1,783	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 information-gathering investments (clinical trials), and the second two columns look at regulatory 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.

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 an 8-percent ($\approx (exp(-0.0823)-1)\times 100$) 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. 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 gap between the timing of information-gathering versus regulatory investments and their relationship to market size.[20]

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 3.2.2, 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. The relationship between indication order and market size remains negative, with an increase in indication order associated with a 9-percent ($\approx (exp(-0.0944) - 1) \times 100$) 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. An increase in indication order is associated with a 16-percent ($\approx (exp(-0.179) - 1) \times 100$) decline in total market size.[21]

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 (off-label drug use) that allows them to expand into other indications without formal approval.

[20] 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.

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

Table 3: Entry Investments and Market Size, Incorporating Off-Label Potential

	Information-gathering investments		Regulatory investments	
	Focal market size (1)	Total market size (2)	Focal market size (3)	Total market size (4)
Indication order	-0.0786***	-0.0944***	-0.0442	-0.179*
	(0.00518)	(0.00548)	(0.141)	(0.107)
Mean of dep. var	6.794	7.657	6.522	8.568
Observations	1,783	1,783	182	182
Controls:				
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 information-gathering investments (clinical trials), and the second two columns look at regulatory 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.

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.

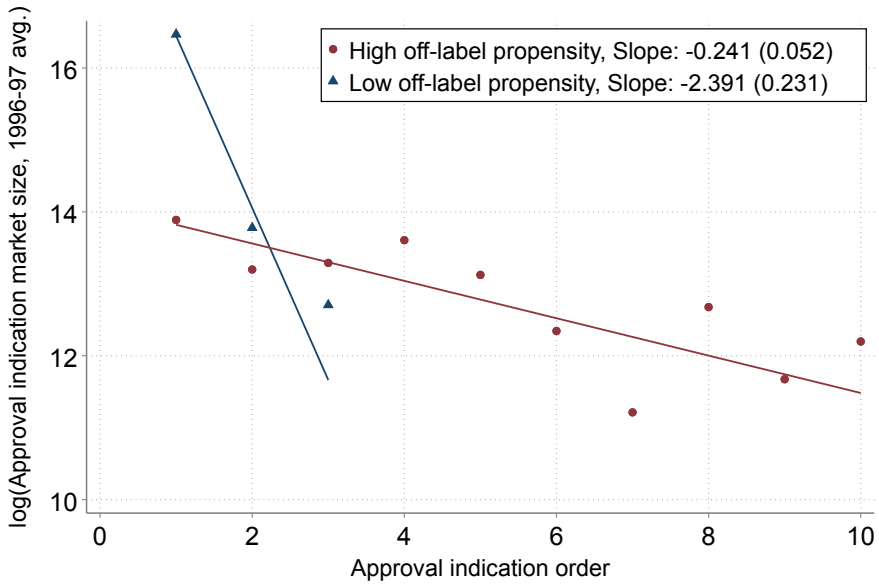
For this analysis, we categorize diseases using ICD-9 (International Classification of Disease) codes. We then use diagnosis data from the Medical Expenditure Panel Survey (MEPS) from 1996 to 1997 to generate ICD-9 level measures of market size. Drug approval data for all drugs first approved between 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.[22] On average, among drugs first approved in diseases with a high off-label propensity, an increase in indication order is associated with a 21-percent ($\approx (exp(-0.241)-1)\times 100$) decrease in market size. In contrast, an increase in indication order is associated with a 91-percent ($\approx (exp(-2.391)-1)\times 100$) smaller market size among drugs first approved in diseases with a low off-label propensity. This is consistent with the view that manufacturers of drugs in therapeutic areas with a low off-label propensity 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.

[22] Figure 4 also indicates that drugs first approved for diseases with a high off-label propensity have more approvals, on average, than those approved in diseases with a low off-label propensity. This is consistent with the idea that firms able to rely on off-label drug use may invest in seeking approval for a greater number of indications with relatively small market sizes.

FIGURE 4: REGULATORY INVESTMENTS AND MARKET SIZE ACROSS DISEASES, BY PROPENSITY FOR OFF-LABEL DRUG USE



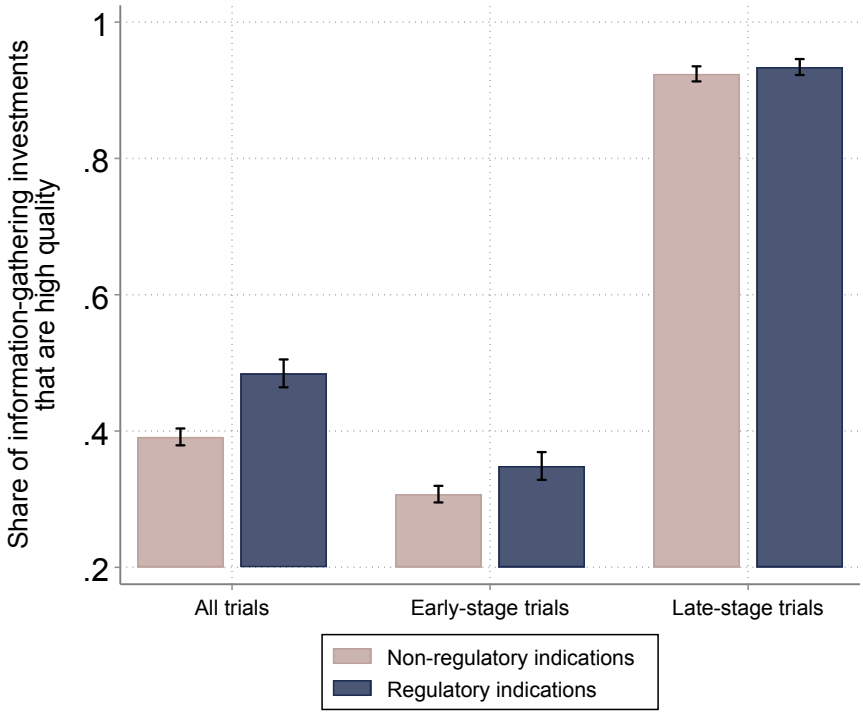
NOTES: This figure shows the relationship between regulatory investments (FDA approvals) and market size for approved drugs across several disease categories from 1998-2021, by propensity for off-label drug use. The level of observation is the drug-indication order, where an indication corresponds to 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 enter larger disease markets via off-label drug use. A possible concern with this interpretation would be if the gap between information-gathering and regulatory investments were primarily due to scientific rationales rather than strategic ones. However, if this holds, then we would expect to see little difference in trial quality between indications with regulatory approval and those without. As a result, we compare the quality of trials likely conducted for non-regulatory purposes to those likely conducted for regulatory purposes.

For each drug in our oncology sample, we classify indications associated with information-gathering investments as either "non-regulatory" or "regulatory." A "non-regulatory indication" is one that is tested in clinical trials but for which the firm does not seek regulatory approval. This includes

Figure 5: Quality of Information-Gathering Investments: Non-Regulatory vs. Regulatory Indications



Notes: This figure shows differences in the quality of information-gathering investments (clinical trials) for non-regulatory versus regulatory indications for cancer drugs approved from 1990-2016. High quality information-gathering investments refer to trials that are randomized and controlled. Bars give shares, while capped ranges provide 95-percent confidence intervals.

indications in which firms conduct trials with the aim of expanding off-label drug use but not to support a future sNDA. A "regulatory indication" is an indication that receives FDA approval.

Figure 5 compares the average trial quality for non-regulatory and regulatory 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 (48 percent), relative to trials for non-regulatory indications (39 percent, $p < 0.01$). We then explore differences across early-stage and late-stage trials, which vary in length and cost. We find that these differences persist when restricting to early-stage trials: 35 percent of early-stage trials conducted for regulatory indications are of high quality, compared to 31 percent of those for non-regulatory indications ($p < 0.01$). 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 little difference in trial quality among late-stage trials.

One caveat to these results is that the set of non-regulatory indications includes those that are primarily used for off-label purposes, as well as those discontinued by the firm due to scientific reasons—for example, an sNDA is not sought since the drug is found to be ineffective in treating a particular indication. However, as discussed earlier, if the difference in the pattern of information-gathering and regulatory investments were primarily due to scientific, rather than economic rationales, we would expect to see little difference in trial quality between indications with and without regulatory approval. Contrary to this expectation, we notice a statistically significant difference. As a supplement to this analysis, in a subsequent exercise, we account for non-regulatory indications that are discontinued due to scientific reasons by incorporating data on trial quality.

4.5 Ruling out additional alternative explanations

We consider other possible explanations for the patterns we document. 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 information-gathering and regulatory investments is due to trial length.

Second, another explanation could be that the non-negative indication order-market size relationship for regulatory investments 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 for regulatory investments we observe reflects FDA decisions on which indications to approve rather than firms' strategic choices. 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 are unlikely to devote resources towards submitting an NDA if it is unlikely to be approved.

5 Discussion: Managerial and policy implications of strategic entry

The paper's results indicate that opportunities to lower the regulatory costs of market entry cause pharmaceutical firms to seek a drug's initial approval in smaller markets and rely on a complementary, non-regulatory pathway—namely off-label use—to enter additional markets. In this section, we explore the implications of such strategic market entry for firm managers on the speed of entry into new markets and their market entry 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

Long drug development timelines are a major driver of high drug development costs (Wong et al., 2014). By prioritizing initial regulatory approval in smaller indications, firms can potentially introduce a drug to the market more quickly due to the ability to conduct smaller clinical trials with the segment of participants 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.[23] We consider this to be a conservative estimate 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 relying on non-regulatory pathways and prioritizing small markets for initial approval.

5.2 Impact on number of markets

Next, we consider how the opportunity to lower regulated entry costs by targeting smaller disease markets and leveraging off-label drug use impacts firm decisions on the number of markets to enter for a single drug. The high costs associated with regulatory approval for larger markets suggests that, 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 benefits do not exceed the costs, these drug-indication pairs would become "missing" in the sense that firms would no longer pursue them. In light of this, a natural next question is: How many "additional" indications do firms explore because of the potential to enter new markets through off-label drug use? Stated differently, how many off-label indications are associated with a drug?[24]

[23] 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.

[24] For simplicity, this exercise does not consider the "size" of the associated indications.

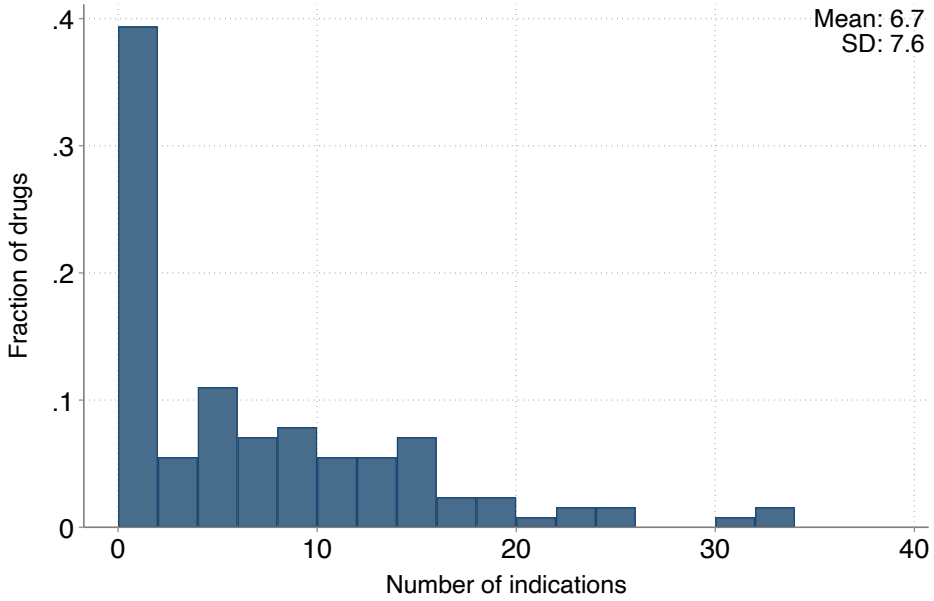
To investigate this, we examine the indications associated with information-gathering investments. We focus on (1) the subset of indications likely pursued for regulatory purposes, i.e., "regulatory indications," and (2) the subset of "non-regulatory indications" likely pursued for off-label use. Recall from the discussion in Section 4.4, we noted that the set of non-regulatory indications included both those that were likely used for off-label drug use and those that were likely discontinued due to scientific rationales.

To isolate the set of "off-label" indications, we remove indications that are dropped due to scientific reasons using two methods. Our first method is based on the idea that firms are likely to terminate trials when they encounter safety or efficacy issues, making it unlikely that they'll seek regulatory approval for the indication or disclose trial outcomes to facilitate off-label drug use (Cook et al., 2014). Using data on early trial terminations, we classify an indication as "dropped" if it is ultimately unapproved and associated with a high (above-median) share of trial terminations. Our second method is motivated by the idea that firms conducting high-quality (i.e., randomized and controlled) trials without seeking regulatory approval likely do so due to inadequate safety and efficacy findings. As a result, for indications that are not terminated early, we assume that being associated with a high (above-median) percentage of such trials indicates it was likely also dropped for scientific reasons. "Off-label" indications encompass all non-regulatory indications that are not discontinued due to scientific reasons. For such off-label indications, firms may complete lower-quality trials and share trial results with doctors to increase off-label drug use without seeking formal approval.

Using these data, we document the total number of regulatory and off-label indications associated with a drug. The average drug is associated with 9.7 total indications, of which only 3 are for regulatory purposes. In contrast, a mean of 6.7 indications are for off-label uses; Figure 6 gives the full distribution of off-label indications across drugs.[25] Our findings support the idea that the opportunity for market entry via smaller markets and off-label drug use likely increases the overall number of indications that firms focus on in their information-gathering efforts. However, a key caveat to interpreting these results is that we are examining equilibrium outcomes. If off-label use were banned, the total number of indications associated with information gathering may decline. However, it is not clear that the average number of indications for a given drug would fall to 3; firms might pursue regulatory approval for some indications initially intended for off-label use. Therefore,

[25] 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 number of markets, because we explicitly match trial to approval indications, all indications are at the site level. As such, we have a mean of 3 approval indications per drug at the site level versus, as indicated in Table 1, 4 approval indications per drug at the site-stage level.

FIGURE 6: NUMBER OF OFF-LABEL INDICATIONS



NOTES: This figure plots the number of off-label indications for cancer drugs approved from 1990-2016. Number of drugs is 127.

we consider the mean number of off-label indications (6.7) as an upper bound on the number of indications that firms might not pursue, for a given drug, if off-label use were prohibited.

5.3 Impact for off-label policy

Overall, firms appear to respond to the regulatory costs of entry by relying on off-label drug use. 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.[26] Our calculations above on the impact of entry regulation on firms' market entry investments suggest a sizeable portion of investment goes towards indications used off-label. Hence, regulators considering whether to limit

[26] For recent work on this, see Tuncel (forthcoming).

off-label use must weigh any gains in information quality for indications that would have been used off-label but now go through regulatory approval processes against the loss in potential therapeutic options due to missing indications.

6 Conclusion

The high costs of new product development necessitate an understanding of how regulation shapes firms' market entry decisions. In industries with regulation, entry regulation can play an important role in shaping the markets and timing in which firms choose to introduce new products. This study suggests that entry regulation plays an important role in shaping firms' decisions on which markets to prioritize for information gathering and regulatory approval. Using data on cancer drug approvals from 1990 to 2016, we show that a firm's regulatory environment plays a critical role in its market entry decisions. We find that pharmaceutical firms, deciding which disease markets to enter, focus their information-gathering investments in larger markets, while allocating their regulatory investments in smaller ones. Using detailed genetic sequencing data, we provide evidence supporting the view that pharmaceutical firms seek to lower the regulatory costs of entry by prioritizing approvals in smaller markets and relying on non-regulatory methods (i.e., off-label drug use) to increase demand for their drugs. Additional evidence that exploits differences in the likelihood of off-label use across different disease types provides further support of this view.

These findings have important implications. From a managerial perspective, such strategic investments might be particularly important for firms facing financial constraints or operating in markets where the first-mover advantage is large. Our results suggest that pharmaceutical firms can lower the cost of market entry by initially targeting smaller indications, which are associated with shorter development times, rather than pursuing longer and costlier approvals in larger markets.[27] We calculate that by focusing on obtaining regulatory approval in smaller markets for a drug's initial indication, pharmaceutical firms may be able to reduce their development timelines by an average of 9.3 months. This reduction in development time corresponds to a value of $6.2 million, plus an additional $111 million in revenues from earlier market entry.

In addition, the potential for off-label drug use may shift the allocation and level of firms' R&D investments. Without the possibility of off-label drug use, firms seeking to expand demand for

[27] 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.

approved drugs (e.g., in additional indications) would allocate their research efforts towards regulatory investments. Due to the high costs of regulatory approval, this scenario could result in firms' reduced investment in pursuing additional indications. Our calculations suggest that the opportunity to lower the regulatory costs of entry by targeting smaller indications and utilizing off-label drug use encourages firms to increase investment in additional indications for their drugs.

Our analysis contains several limitations and suggests opportunities for future research. First, while our main analysis offers a comprehensive and detailed examination into an important class of drugs—cancer treatments—our dataset is relatively small. This data limitation prevents a direct exploration into important sources of heterogeneity and other important outcomes. For example, our analysis has primarily focused on how regulatory costs may shift firms' decisions to prioritize approval in small indications. However, drug prices may also play an important role in these decisions. In particular, drug pricing is not indication-specific. Firms might prioritize seeking approval for rare diseases, where patients may be willing to pay high prices for effective treatments (Chandra and Garthwaite, 2017). Similarly, it would be interesting to investigate the types of firms that are driving our results. On the one hand, small, financially constrained firms might view regulatory investments in small disease markets as a cost-effective strategy for launching a new product. On the other hand, our effects may be driven by larger firms that have the marketing resources to encourage off-label drug use among physicians and patients. We hope that our findings serve as a foundation for further investigation into the role of entry regulation on firms' information-gathering and regulatory investments that incorporates data on key factors, such as drug prices and firm types. Second, because we cannot directly observe firms' regulatory investments that do not lead to success (i.e., sNDAs that are not approved), our research may reflect an underestimate of firms' regulatory efforts. Nonetheless, this concern is mitigated by the fact that firms generally do not submit applications to the FDA that they anticipate will be rejected.

A full welfare analysis of the role of entry regulation on firms' market entry decisions is beyond the scope of this study. However, our findings suggest the need to think more deeply about the costs of regulatory approval and corresponding policies. For example, anecdotal accounts of pharmaceutical firms prioritizing smaller indications and depending on off-label markets has raised concerns among regulators and health policy researchers, prompting a reevaluation of existing regulatory policies (Tribble and Lupkin, 2017). For example, there is growing concern that the ODA might be encouraging firms to strategically narrow the indicated uses of their non-rare disease drugs (a practice referred to as "salami slicing") in order to qualify for orphan drug designations.

Further, proposed reforms to ban off-label use may have unintended consequences, such as reducing R&D investment levels and restricting consumer access to important drug innovations.

Viewed from a public policy perspective, our analysis highlights the critical trade-offs that regulators must navigate between encouraging expedient access to drugs and the need for sufficient quality information on new therapies. At one extreme, stringent regulatory processes may slow entry of valuable products. At the other, firms may choose to avoid regulatory approval entirely, leading to a dearth of valuable new products and insufficient information regarding the quality of products on the market that may have bypassed formal regulatory approval. Our findings suggest that policy makers should consider the impact to firms' strategic market entry decisions when designing regulatory processes.

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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 regulatory 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. 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 (Sertkaya et al., 2016), 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., $p_B > p_A$. This is plausible due to selective participant enrollment for smaller indications (Chandra et al., 2019; Michaeli et al., 2023).

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 $\mathcal{O}_\mathcal{B} = \{A, C\}$, 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.

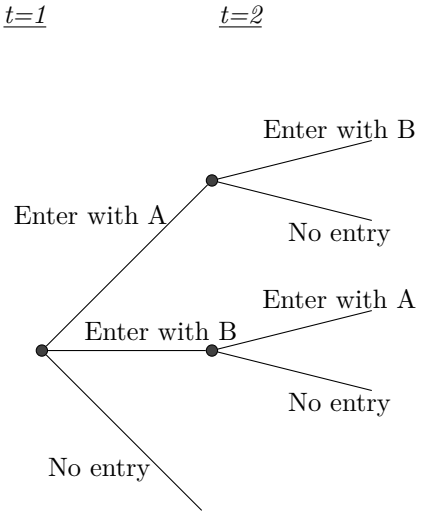
Off-label diffusion rate. A drug's rate of off-label diffusion is $d \in [0, 1]$, which gives the proportion of potential off-label markets that will actually use the drug off-label following regulatory approval. For example, a diffusion rate of 0 would imply that, following initial regulatory approval, 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. We make the simplifications that this rate is fixed at the drug level and known to the firm prior to market entry; we thus abstract away from scenarios where the rate is learned over time or where it varies across indications.

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



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.

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.

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

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 Main 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. To do this, we evaluate three alternative scenarios, where there is no off-label use ($d = 0$), complete off-label diffusion ($d = 1$), or some off-label use ($d \in (0, 1)$).

A.3.1 Scenario: No off-label use

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:

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

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

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

A.3.2 Scenario: Complete off-label diffusion

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.

A.3.3 Scenario: Some off-label use

Finaly, we consider the intermediate scenario where $d \in (0, 1)$ and some degree of off-label use occurs. Conditional on $2p_B[M_B + d(M_A + M_C)] - K_B > 0$ and $p_A[(1 - d)(M_A + dM_C)] - K_A > 0$, the firm will select indication B for regulatory approval in period 1 and indication A for approval in period 2 if and only if:

$$\begin{aligned} EV_{B,A} = 2p_B[M_B + d(M_A + M_C)] + p_A[(1 - d)(M_A + dM_C)] - K_B - K_A > \\ 2p_A[M_A + d(M_B + M_C)] + p_B[(1 - d)(M_B + dM_C)] - K_A - K_B = EV_{A,B} \end{aligned} \tag{10}$$

Simplifying gives the following condition:

$$\begin{aligned} p_B M_B + 2dp_B M_A + dp_B M_C - dp_A M_A - d^2 p_A M_C > \\ p_A M_A + 2dp_A M_B + dp_A M_C - dp_B M_B - d^2 p_B M_C \end{aligned} \tag{11}$$

And rearranging terms gives:

$$\frac{p_B}{p_A} > \frac{2dM_B + (1+d)\frac{M_A}{M_B} + (1+d)d\frac{M_C}{M_B}}{2d\frac{M_A}{M_B} + (1+d) + (1+d)d\frac{M_C}{M_B}} \tag{12}$$

Based on our initial assumption that $M_A > M_B$, we have that $\frac{M_A}{M_B} > 1$. To understand how firms make their product line decisions in the presence of some off-label diffusion, we fix $\frac{P_B}{P_A}$ and consider the scenarios where $\frac{M_A}{M_B}$ approaches $\frac{P_B}{P_A}$, 1, and ∞, respectively.

When $\frac{M_A}{M_B} \to \frac{P_B}{P_A}$, the inequality in (12) becomes:

$$\frac{p_B}{p_A} > \frac{2dM_B + (1+d)\frac{P_B}{P_A} + (1+d)d\frac{M_C}{M_B}}{2d\frac{P_B}{P_A} + (1+d) + (1+d)d\frac{M_C}{M_B}} \tag{13}$$

Rearranging terms and simplifying gives::

$$2d\left(\frac{P_B}{P_A}\right)^2 + \left(\frac{P_B}{P_A}\right)(1+d)d\frac{M_C}{M_B} > 2dM_B + (1+d)d\frac{M_C}{M_B} \tag{14}$$

Given our initial assumption that $P_B > P_A$, then $\frac{P_B}{P_A} > 1$ and the inequality in (12) holds irrespective of the off-label diffusion rate. That is, if $\frac{P_B}{P_A} = \frac{M_A}{M_B}$, then the firm will choose indication B for regulatory approval in period 1 and indication A for regulatory approval in period 2. That is, in the presence of some off-label use, and when the ratio of the probabilities of regulatory approval for potential indications equals the inverse of the ratio of their market sizes, we would expect firms to prioritize the smaller indication for approval.

When $\frac{M_A}{M_B} \to 1$, the inequality in (12) becomes:

$$\frac{P_B}{P_A} > \frac{2d + (1+d) + (1+d)d\frac{M_C}{M_B}}{2d + (1+d) + (1+d)d\frac{M_C}{M_B}} = 1 \tag{15}$$

Again, given the initial assumption that $P_B > P_A$, we have that $\frac{P_B}{P_A} > 1$ holds irrespective of the diffusion rate and the firm chooses indication B for regulatory approval in period 1 and indication

A in period 2. That is, in the presence of some off-label use, and when the market sizes of potential indications become more similar, we would expect firms to prioritize the smaller indication given its higher probability of approval.

Lastly, in order to evaluate the scenario when $\frac{M_A}{M_B} \to \infty$, we divide the numerator and denominator of the right-hand side of the inequality in (12) by $\frac{M_A}{M_B}$:

$$\frac{p_B}{p_A} > \frac{\frac{2dM_B}{\frac{M_A}{M_B}} + (1+d) + \frac{(1+d)d\frac{M_C}{M_B}}{\frac{M_A}{M_B}}}{2d + \frac{(1+d)}{\frac{M_A}{M_B}} + \frac{(1+d)d\frac{M_C}{M_B}}{\frac{M_A}{M_B}}} \tag{16}$$

Taking the limit as $\frac{M_A}{M_B} \to \infty$ gives:

$$\frac{P_B}{P_A} > \frac{1+d}{2d} \tag{17}$$

We now consider the firm's decision as $d \to 1$ and $d \to 0$. As $d \to 1$, we have that $\frac{P_B}{P_A} > 1$ which holds given our initial assumptions on the probabilities of approval. As $d \to 0$, we have that $\frac{P_B}{P_A} \to \infty$, i.e., $\frac{P_B}{P_A}$ must become increasingly large in order for the firm to prioritize the smaller indication. That is, as the difference in market sizes between potential indications becomes large, we would expect firms to prioritize the smaller indication only when there is either a sufficiently high off-label diffusion rate and/or the smaller indication has a sufficiently high probability of approval.

Combining the above scenarios, we can summarize our **main model prediction** 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.*

Sections 4.2 and 4.3 test this main model prediction empirically.

B Similarity index example: Breast and ovarian cancers

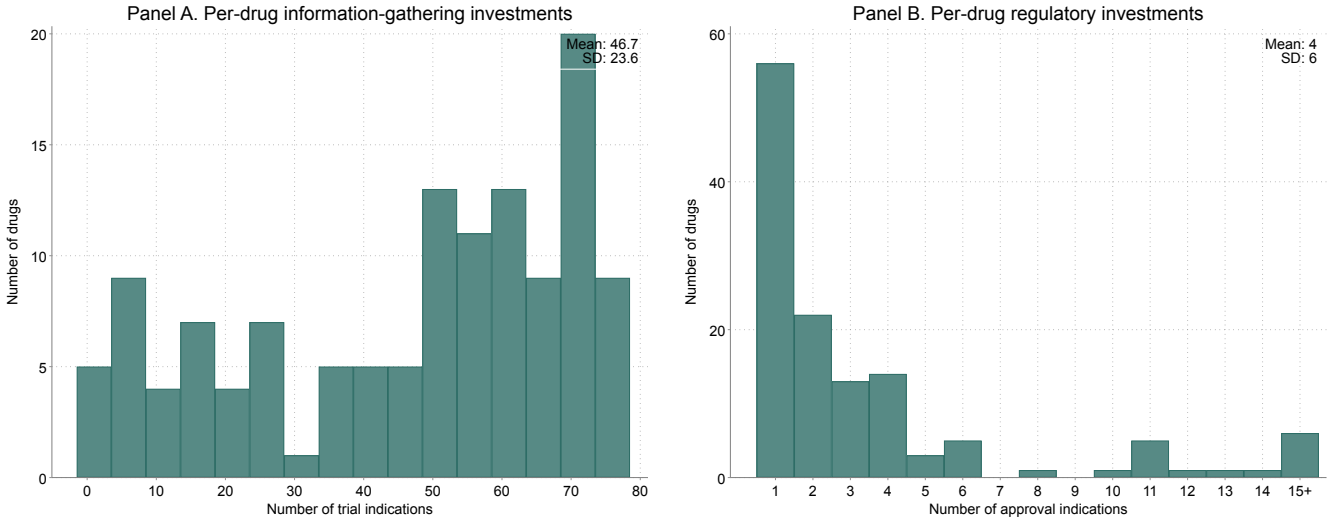
Table B1 provides the genetic mutations associated with breast and ovarian cancers from the CGC database. We calculate their similarity index as follows: $s_{Breast,Ovarian} = \frac{|B \cap O|}{|B \cup O|} = 7/75 = 0.093$.

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	
MAP2K4	PLAG1	
MAP3K1	PPP2R1A	
MAP3K13	PRDM2	
MED12	PTK6	
NCOR1	RNF43	
NOTCH1	ROS1	
NTRK3		
PBRM1		
PIK3CA		
PPFIBP1		
RAD50		
RANBP2		
RB1		
SALL4		
SMARCD1		
TBX3		
TP53		
VHL		
ZMYM3		

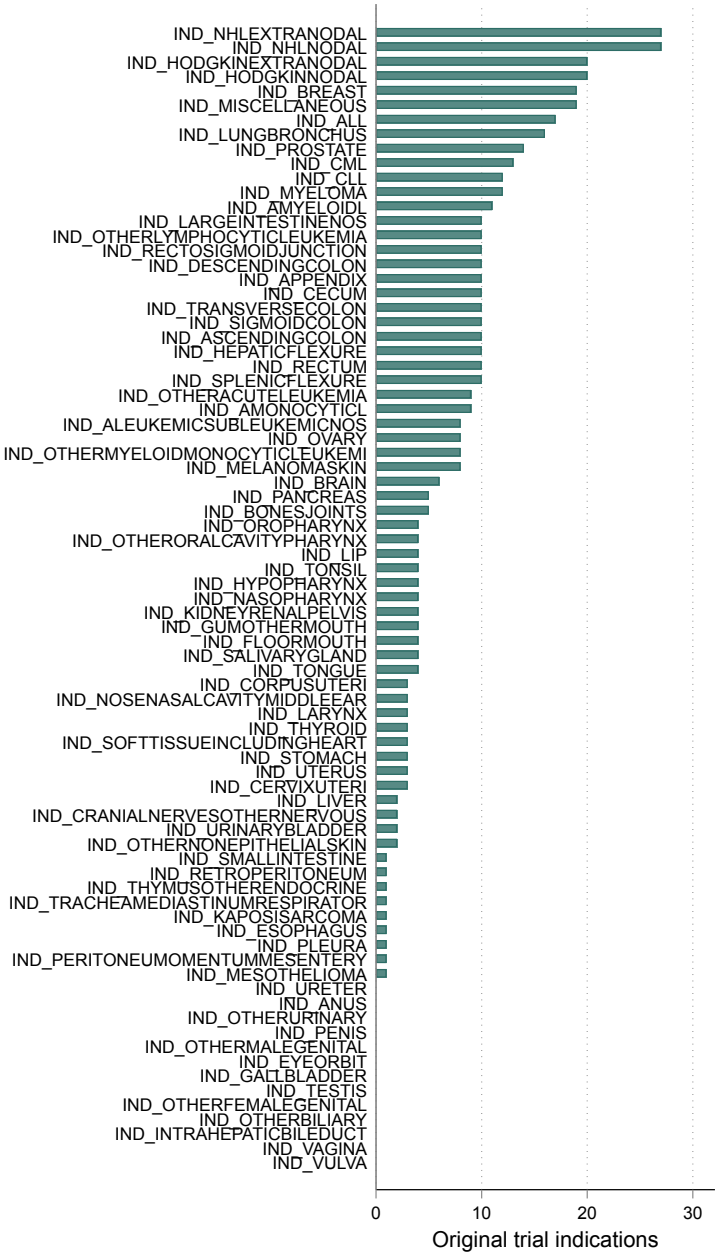
C Variation in approval and trial indications

FIGURE C1: PER-DRUG DISTRIBUTION OF ENTRY INVESTMENTS



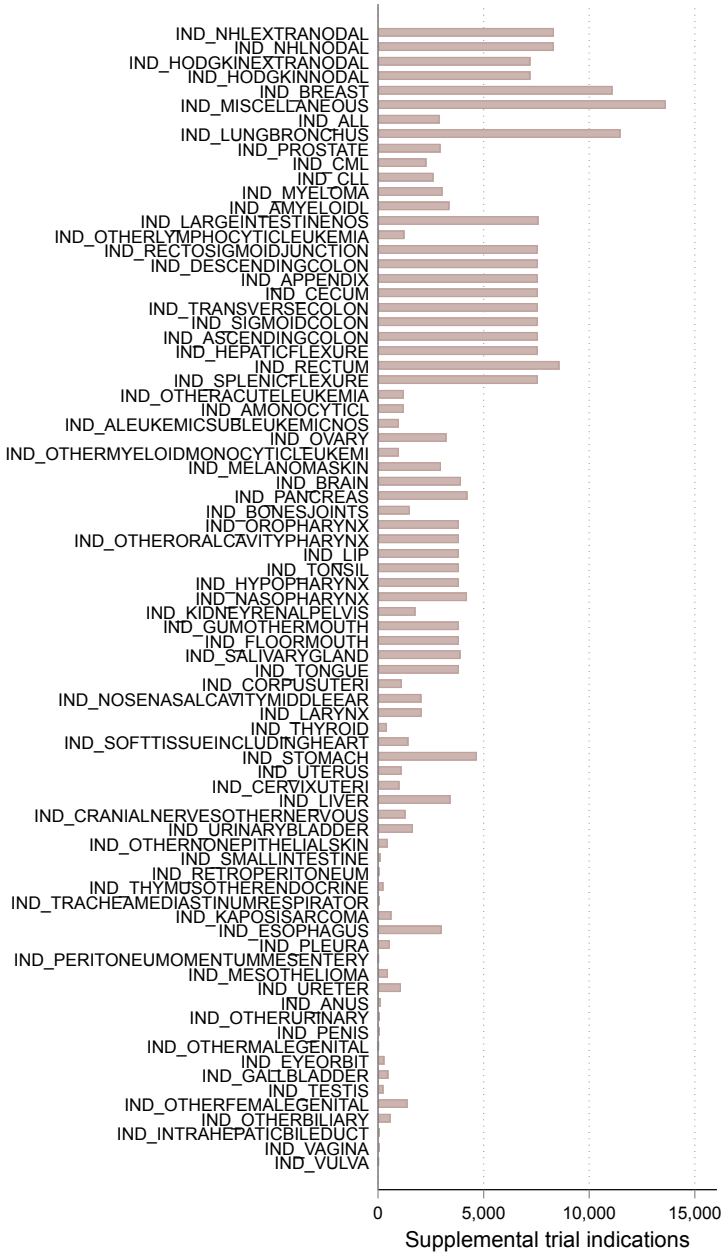
NOTES: This figure shows the distribution of entry investments for cancer drugs approved from 1990-2016. Panel A gives the per-drug distribution of trial indications; number of drugs is 127. Panel B gives the per-drug distribution of approval indications; number of drugs is 129.

FIGURE C2: DISTRIBUTION OF ORIGINAL TRIAL INDICATIONS ACROSS CANCER SITES



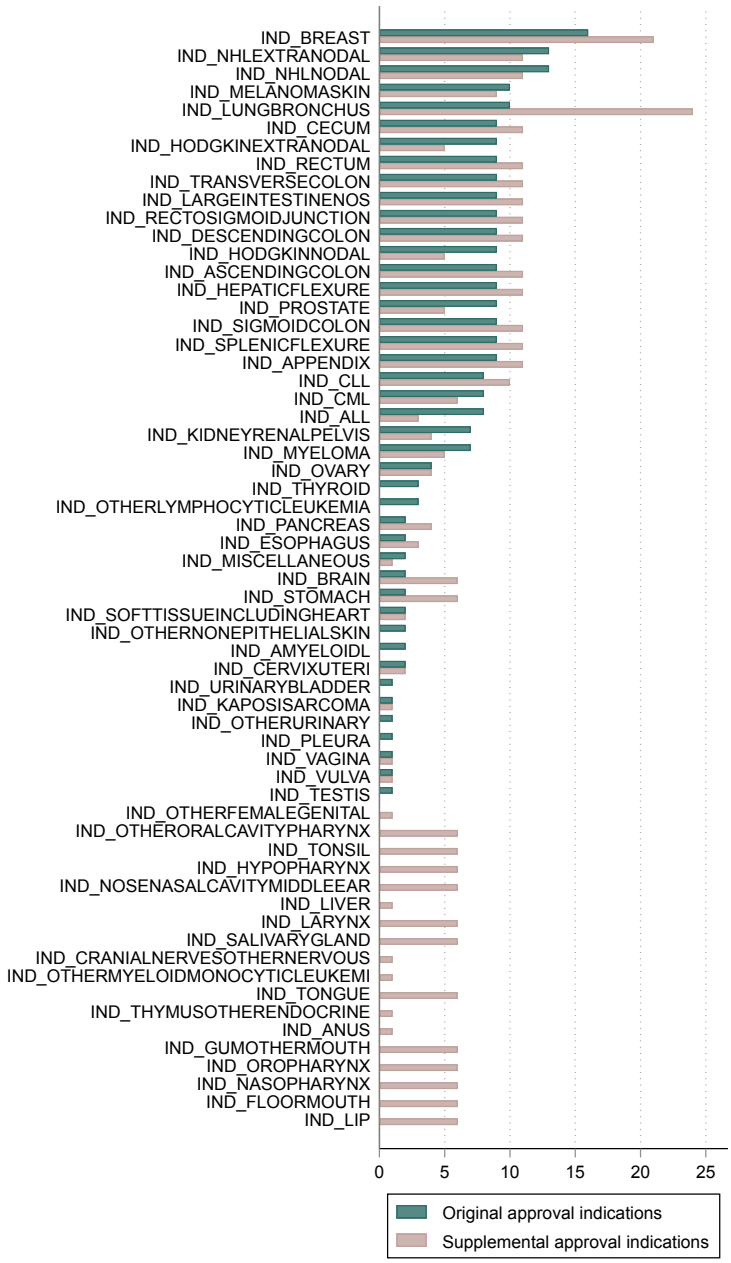
NOTES: This figure shows the distribution of original trial indications across cancer sites for cancer drugs approved from 1990-2016.

FIGURE C3: DISTRIBUTION OF TRIAL INDICATIONS ACROSS CANCER SITES



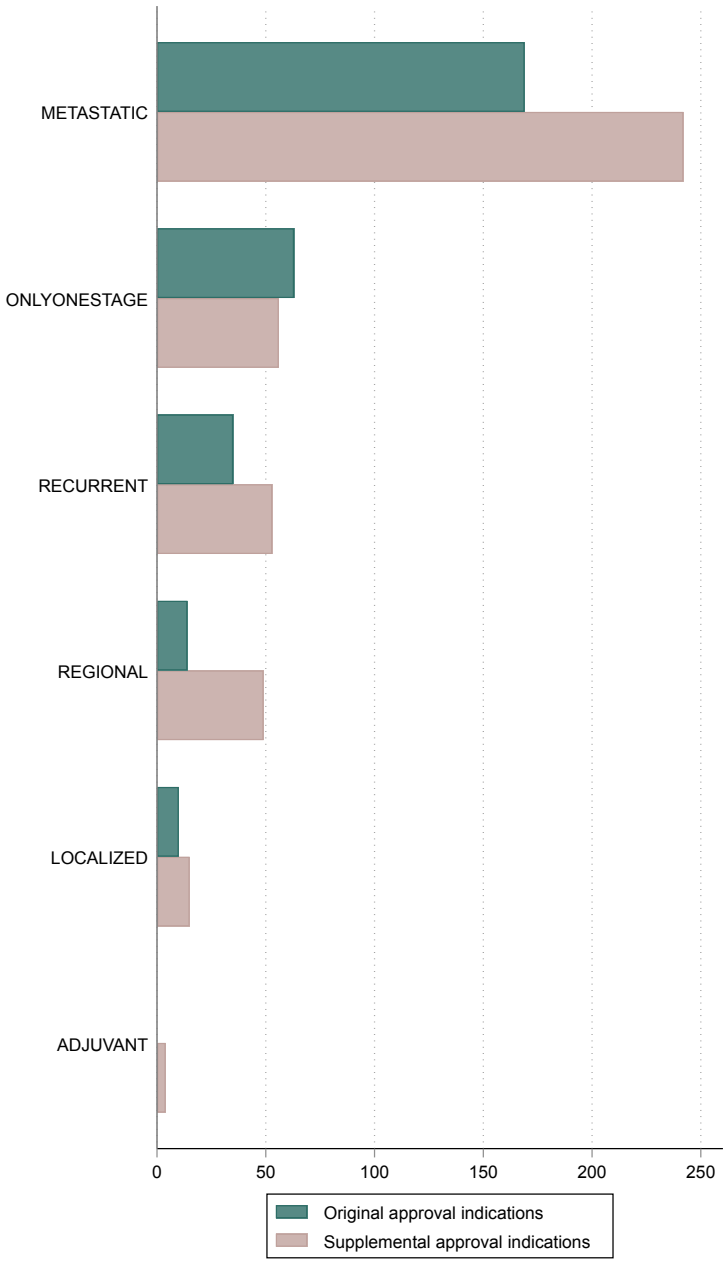
NOTES: This figure shows the distribution of trial indications across cancer sites for cancer drugs approved from 1990-2016.

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: ENTRY INVESTMENTS AND MARKET SIZE

	Information-gathering investments		Regulatory investments	
	(1)	(2)	(3)	(4)
$\mathbb{1}_{First\ indication}$	1.073***	0.617***	-0.386*	-0.591**
	(0.122)	(0.152)	(0.220)	(0.272)
Mean of dep. var	6.825	6.794	6.513	6.522
Observations	2,007	1,783	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 information-gathering investments (clinical trials), and the second two columns look at regulatory 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.

TABLE D2: ENTRY INVESTMENTS AND MARKET SIZE, INCORPORATING OFF-LABEL POTENTIAL

	Information-gathering investments		Regulatory investments	
	Focal market size (1)	Total market size (2)	Focal market size (3)	Total market size (4)
$\mathbb{1}_{First\ indication}$	0.617***	0.659***	-0.591**	-0.0954
	(0.152)	(0.152)	(0.272)	(0.233)
Mean of dep. var	6.794	7.657	6.522	8.568
Observations	1,783	1,783	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 information-gathering investments (clinical trials), and the second two columns look at regulatory 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

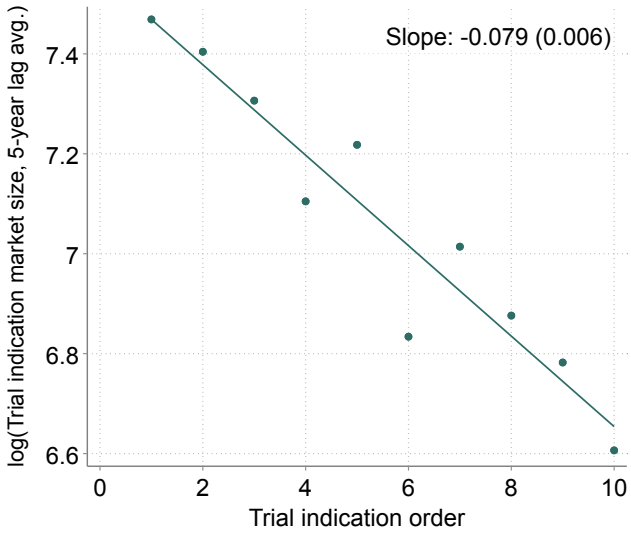
TABLE D3: REGULATORY INVESTMENTS AND TOTAL MARKET SIZE, USING ALTERNATIVE SIMILARITY MEASURES

	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	10.064
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 regulatory 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% (Columns 1 and 4), top 20% (Columns 2 and 5), or top 30% (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

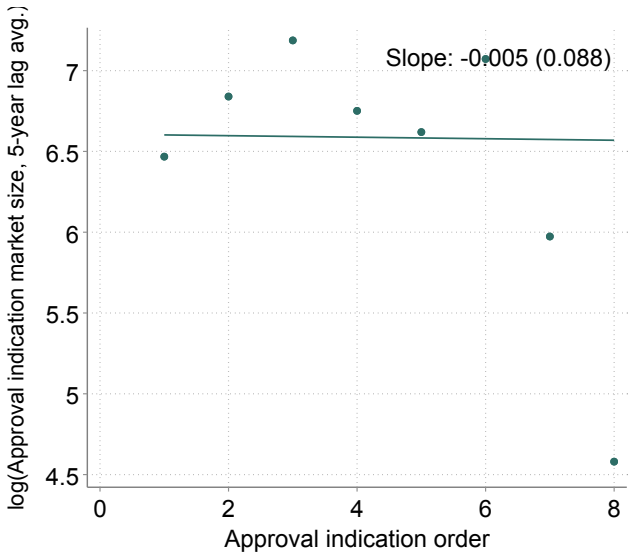
FIGURE D1: INFORMATION-GATHERING INVESTMENTS AND MARKET SIZE, WITH INDICATION ORDER DETERMINED BY TRIAL END DATES



NOTES: This figure shows the relationship between information-gathering 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: REGULATORY INVESTMENTS AND MARKET SIZE, WITH INDICATION ORDER DETERMINED BY SUBMISSION DATES



NOTES: This figure shows the relationship between regulatory 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.