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REGULATORY APPROVAL AND EXPANDED MARKET SIZE

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ABSTRACT

Regulatory review of new medicines is often viewed as a hindrance to innovation by increasing the hurdle to bring products to market. However, a more complete accounting of regulation must also account for its potential market expanding effects through quality certification. We combine data on FDA approvals for follow-on indications and patient-level data on utilization, and examine whether FDA approval of a follow-on indication increases the use of a drug for that indication. We find 5 facts for the market-expanding role of regulation: (1) follow-on approvals increase the share of patients taking a drug with that indication by 4.1 percentage points, or 40% increase over baseline use, at the time of approval; (2) there is little market learning prior to or following the approval of the follow-on indication, suggesting that such approvals fully certify the new use; (3) the effect of these approvals is larger for uses in a different disease area than previous indications, an increase equivalent to over 4 ½ years of market-learning; (4) it is FDA approval, not the initiation of clinical trials that generate the expansion in market size; (5) the market expansion is consistent with physicians prescribing the medicines more because of higher perceived benefits, not reduced administrative costs.

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The regulatory review of new medicines by agencies such as the United States Food and Drug Administration (FDA) is conventionally characterized as a tradeoff between an increase in product quality and a decrease in the number of new drugs (Peltzman 1973).[1] The reduced number of drugs is believed to result from lower expected profits, both because of higher direct regulatory costs and delayed market entry (Peltzman 1973; Budish, Williams, and Roin 2015; Stern 2017).[2] Concerns about this negative impact of regulatory burden have driven many reforms centered on decreasing the cost and length of FDA reviews – particularly for medicines believed to be provide new and unique value to the market.[3]

The view of regulatory review as purely a hindrance to innovation represents a partial equilibrium analysis. A more complete accounting of the impact of regulatory quality certification must also consider its potential market expanding effects and the subsequent impact on this expansion of R&D investments.[4] Medicines are largely experience goods about which, absent some type of credible quality disclosure or certification, market participants have little initial information about efficacy or safety. These market participants include not only patients but also physicians, who have medical expertise but little inherent knowledge about a new product's quality. This lack of information likely impacts their initial willingness to prescribe such products.[5] In contrast, manufacturers of these medicines possess far more information about the quality of their products, both from undisclosed internal testing and private information about the validity of those tests.[6] These manufacturers, however, may face difficulty in credibly communicating information about a product's value to the market (Dranove and Jin 2010).

This fundamental information asymmetry means that, absent some mechanism for certifying quality, new products might initially earn little revenue (Katz 2007). This is particularly concerning for manufacturers if market learning is slow, as pharmaceutical firms face a time-limited period of market exclusivity and therefore delays in take-up are not simply a question of shifting potential revenues across time periods but

[1] Historical concerns about the quality of pharmaceuticals have led to several regulations in the United States. Perhaps most important are the 1938 Food, Drug, and Cosmetic Act and its 1962 amendments. Together, these regulations grant the Food and Drug Administration (FDA) the power to regulate the *safety and efficacy* of new pharmaceutical products. In addition, the FDA has authority to regulate pharmaceutical advertising to consumers and physicians.

[2] The regulations also remove drugs the subset of medicines that do not clear a minimum threshold for safety and effectiveness

[3] Congress has passed numerous reforms aimed at decreasing the cost and length of the approval process. For instance, the Prescription Drug User Fee Act of 1992 (PDUFA) instituted fees on drug manufacturers to fund the process of drug approval. Laws have also attempted to accelerate development by giving special treatment to particular drugs. For instance, the Orphan Drug Act of 1983 gave drug manufacturers tax credits and exclusivity rights for developing drugs to treat rare diseases. It was later amended to also waive PDUFA user fees for these drugs. Moreover, FDA has numerous other drug designations including Priority Review, Accelerated Approval, Fast Track, and Breakthrough Therapy which are each aimed at reducing the time before drugs can be marketed.

[4] It is notable that given the long development times of new pharmaceutical products, an increase in products coming from a change in expected market size may take some time to occur. For this reason ,the relatively short 10 year window after the increase in regulatory standards that is considered in Peltzman (1973) may not have been enough time for new products to be developed and come to market.

[5] This potential phenomenon of demand being reduced because market participants undervalue products lacking regulatory certification is related to the McGuire et al. (1975) critique of Peltzman (1973) which, among other arguments, discusses how rather than believing the unverified claims of manufacturers consumers and physicians may underestimate drug quality in the absence of some external quality certification.

[6] Even at the extreme of truly "sham" products, firms possess private information that there is no possible way for the product to work.

instead represent a potentially meaningfully reduction in expected profits from investments in innovation. Given that firms make investments based on expected profitability, a smaller expected market size would result in fewer medicines being developed (Acemoglu and Lin 2004; Finkelstein 2004; Blume-Kohout and Sood 2013; DuBois et al. 2015; Dranove et al. 2020). These market conditions represent a channel through which a regulatory process that increased certainty in product quality could increase the expected market size and provide the necessary incentives for firms to invest in new product development. Any decrease in products from regulatory costs must be weighed against the potential market expanding benefits resulting from reduced information asymmetries.[7]

The existence of this potential market expanding effect of regulatory review hinges on whether the FDA certification increases the demand for pharmaceutical products. The recent behavior of firms investigating a vaccine against the SARS-COV-2 virus provides anecdotal evidence supporting this potential effect. In the summer of 2020, there were meaningful concerns that the FDA would bow to political pressure and approve such a vaccine without requiring firms to generate the traditional amount of required evidence demonstrating safety and efficacy (LaFraniere et al. 2020). Under the conventional view of FDA review as a pure burden, firms should have found this reduced evidence standard valuable because they could get their products to market faster and at a lower cost. However, the leading firms pursuing such a vaccine issued a public declaration asking for a "normal" (i.e. longer and more rigorous) FDA review (Lupkin 2020). This action is consistent with firms being cognizant of the difficulty that market participants have in determining the quality of pharmaceutical innovations and the ensuing effect of this uncertainty on demand.

Ideally, we would empirically demonstrate the potential market expanding benefits of FDA review by comparing the use of pharmaceuticals before and after their original approval. Unfortunately, this is not possible as products cannot be sold prior to original FDA approval.[8] We overcome this hurdle by exploiting FDA approvals for "follow-on indications"— or new medical uses for existing products — after launch. These indications are granted after "original indications" which are granted when drugs are first approved by the FDA.[9] Successful applications for follow-on indications require rigorous clinical trial evidence of efficacy that is similar to the standard for the original indication. Figure I demonstrates that these follow-on indications are an important and growing market feature.

We examine whether FDA approval of a follow-on indication increases the use of a drug for that indication. We then estimate whether the estimated increase in use surpasses what would reasonably have been expected to occur through natural market learning that occurs because physicians are free to prescribe

[7] A complete analysis would also weigh the welfare generated by the types of products that are lost and gained by these two economic channels.
[8] This is true even if there is demand for unapproved products. Evidence of some level of demand prior to FDA certification can be seen in continuing demand for the "compassionate use" of unapproved products (GAO 2019).
[9] An indication is the reason for which a medicine would be used. For example, breast-cancer would be the disease but first-line treatment of breast-cancer is an indication. Indications may not map onto diseases either, so should not be thought of as a more granular classification of diseases.

an approved product for *any indication* they believe is medically appropriate– a phenomenon commonly described as "off-label" use.[10] Off-label use is a prevalent market feature beginning early in drugs' marketable lives; in our data, original indications (those uses approved at the time of original approval) comprise only 57% of prescriptions only two quarters after original approval, while fewer than 3% of follow-on indications are approved in the first two quarters, implying that off-label use constitutes much of the remaining 43% of prescriptions.[11] Moreover, we find that prior to approval, off-label use for a soon-to-be approved follow-on indication is prevalent, constituting 10 percent of prescriptions in the quarter prior to their approval. Combined, the prevalence of off-label prescribing and the costliness of seeking follow-on indications gives firms an important strategic decision about whether to seek these indications or rely on off-label prescribing of unapproved uses.[12]

The coexistence of off-label prescribing, and regulatory approval of follow-on indications allows us to contrast the effect of regulatory quality certification relative to market-learning. We can also characterize whether the nature of the information conveyed by quality certification matters. First, we note that the additional information provided by a follow-on indication primarily involves questions of efficacy rather than safety.[13] While this means we cannot separately identify the effect of safety certification, our results inform whether efficacy certification alone is important.[14] This is not a minor question. It was not until 1962 that the role of the FDA was expanded to include efficacy certification, and the appropriate role of the FDA with respect to efficacy remains a source of debate.

Second, we are able to examine heterogeneity in the effect of additional quality certification based on the novelty of the information provided by the follow-on indication, by whether it is for a "new" or "previously approved" *diagnosis* (indications describe medical uses at a level that is narrower than the medical diagnosis, often including more detailed information on the proper circumstances for medical use within a diagnosis). Therefore, the effect of receiving a follow-on approval being larger when it is in a new diagnosis

[10] FDA approval constrains the marketing and advertising of manufacturers who are only allowed to communicate information about approved indications. We discuss the role of these marketing restrictions later in the paper.
[11] There are few studies that estimate off-label use prevalence with samples as large as ours. Perhaps the best comparison is Radley, Finkelstein, and Stafford (2006) who find that off-label uses comprise 21% of prescriptions, which is meaningfully less than our upper bound of 43%. There are a number of reasons for why our results differ. First, their data are based on survey evidence rather than administrative claims. The surveys they used asked physicians to report all diagnoses and the drug therapy used to treat those diagnoses for all patient encounters over two days. In contrast, we determined diagnoses using those billed to patients represented in the OptumLabs® Data Warehouse. Second, we report off-label use at the very beginning of drugs' marketable life when drugs have the fewest approved indications and thus more possible off-label uses. Radley et al. report a cross-section of drugs prescribed during a given year and thus observe both drugs that were recently approved and those that had been approved for decades (their sample includes generic drugs). Finally, our sample differs dramatically in the types of drugs included. For instance, about 15% of the drugs in our sample are chemotherapies while the Radley et al. sample includes none. To the extent that chemotherapies are often be used for unapproved uses, that would increase the gap in off-label share in our sample relative to Radley et al.
[12] While our paper focuses on the effects of indications, not the decision to seek them, analyzing firm strategy with respect to follow-on indications may be a promising avenue for future research.
[13] New indications primarily provide information about efficacy. To the extent that the new indication requires a meaningfully difference dose, there is also new safety information from this additional review process.
[14] In this way, our work also relates to Grennan and Town (2020) which examines the effect of the efficacy review of medical devices.

than when it is in the same diagnosis is consistent with potential market learning being slower when different physicians are responsible for the new diagnosis relative to the previously approved one.

To illustrate this approach, consider the example of Keytruda (pembrolizumab). This drug received approval for the treatment of melanoma in September 2014. In October 2015, it received approval for a follow-on indication to treat the diagnosis of non-small cell lung cancer (NSCLC) for the indication of *disease progression on or after platinum-based chemotherapy*. In May 2017, it received approval for an additional follow-on indication for the *first-line treatment of NSCLC in combination with two other drugs*. Although these follow-on indications are both for the diagnosis of NSCLC, the former indication was for a "new" diagnosis because NSCLC corresponds to a different ICD-diagnosis code than Melanoma, while the latter was for a "previously-approved" diagnosis (because an indication with the same ICD-diagnosis code was previously approved). If indications in new diagnosis provide better information to the market relative to new indications in existing diagnosis, we would expect a larger change in our event study specification in October 2015 than in May 2017.

Using this framework, we find that follow-on approvals increase the share of individuals with corresponding diagnoses by 4.1 percentage points on average. Given a pre-approval share of 9.6 percent, this estimate represents a 43 percent increase in the market share for the newly approved indication. It is, of course, possible that physicians would have ultimately discovered this information through off-label use (i.e. market-learning). If the market would have quickly learned the same amount of information, this would limit the welfare benefits of quality certification. In contrast, we estimate zero pre-existing trend in off-label use. In addition, we find that there is no additional market learning as measured by increased share of consumption following the approval of the follow-on indication, which points to the approval being complete in terms of information revelation.

We also find that the largest estimates of an increase in use are for follow-on indications in a different disease area than previous indications, and find no significant change for follow-on indications that modify approved use for an already-approved indication (e.g. when the original and follow-on indications are both for the same cancer, but differ in what stage the medicine is appropriate in).[15] This provides evidence that regulatory certification of more novel information has a greater impact on the activities of market participants. Diagnoses for indications in a new disease area do increase prior to approval at a rate of 0.3 percentage points per quarter. However, this means that it would take almost 4.5 years to achieve the 5.5 percentage point increase that the approval causes in two quarters. Since new pharmaceutical products have an effective patent life of only 11.7 years, this rapid increase in use is economically meaningful (Grabowski and Vernon 2000).

[15] More detail on how disease groups are identified is contained in the data and methods sections.

There are two potential mechanisms for these results. The first relates to the actual certification of the product by the FDA as opposed to simply firms conducting the clinical trials necessary for the approval.[16] We find no evidence that a firm registering its pivotal clinical trial for a follow-on indication causes a large increase in use. This provides evidence that regulatory approval rather than simply new information drives our results.[17]

The second potential mechanism relates to features of the health insurance contract. Insurers have latitude to place restrictions on payment for the off-label use of expensive drugs, and it is possible that the increase in use is mostly a consequence of these restrictions being relaxed. However, our estimates are of the same magnitude for drugs that are identified as typically being subject to utilization management and those with fewer restrictions on prescribing behavior. This means it is the increase in the benefits of prescribing provided by the FDA regulatory review and not a decrease in the costs of prescribing from a relaxing of constraints from insurance firms that is driving our results.

We next describe the data used for our analysis, including the process by which we are able to link the use of the drug to a medical diagnosis. In Section II we describe our methods and in Section III we present out main results. We then explore potential mechanisms in Section IV and discuss the economic and policy implications of our results in our concluding Section V.

I. **Data**

For our primary analysis, we combine data from two assets that allow us to identify the timing of indications and utilization of drugs for those indications, which are necessary for an event study design. The first asset, is dataset encompassing all indications for new molecular entities and biologic drugs approved by FDA from 1995 to 2019 and listed on FDA's Drugs@FDA website. Assembling this dataset required examining several thousand drug labels and letters from FDA to manufacturers (all available publicly on the Drugs@FDA website) to assess the clinical content of the new indications and determine the dates they were approved.[18]

Using these indication data, we harmonized indication descriptions across different formulations of each active ingredient, the drug unit that we use throughout our analysis. Table I shows that this process allows us to identify 1,552 distinct indications across 784 drugs; of these, 619 indications (39.9%) were follow-on indications. However, Figure II shows that while follow-on indications are fairly prevalent, they are

[16] We note that firms presumably apply for new indications that they believe will increase profits, therefore at any point the set of follow-on indications represent a selected sample. We discuss the implications of this selection below.

[17] While it is true that FDA approval also allows firms to advertise for the follow-on indication, we note that our estimated increase in use occurs in the quarter immediately following approval. Furthermore, while FDA approval is a public event we note that applying for a new indication and to a lesser extent registering clinical trials are also events that are well known to informed market participants such as medical specialists. We discuss the potential role of marketing and advertising later in the paper.

[18] Although Drugs@FDA reliably includes recent documentation about drugs originally approved after 1995, documentation is often missing in the years before 1995, making it difficult to ascertain the entire approval history of these drugs. Because our empirical analysis depends on accurate identification of approval histories, we therefore limited our data collection to indications for drugs approved since 1995.

also concentrated in relatively few drugs. Only 21% of drugs have at least one follow-on indication within 5 years of their original approvals, and many follow-on indications are for one of only a handful of blockbuster chemotherapies, with one drug (Keytruda) alone receiving 20 follow-on indications within 5 years of its original approval.[19]

Next, to understand how often the 619 follow-on indications were approved for new diagnoses as opposed to previously-approved diagnoses, we assigned ICD-10-CM diagnosis codes to each indication. Table I shows that of the 619 follow-on indications we identify, 317 (51.2%) are for new diagnoses.[20] Then, we measure the extent to which a new diagnosis for a drug is different from its previously-approved diagnoses by exploiting the hierarchical nature of ICD-10-CM codes. The ICD-10-CM hierarchy groups codes into 3-digit groups (roughly corresponding to a disease), sub-chapters (corresponding to a diverse group of diseases), and chapters (corresponding to an even more diverse group of diseases). For example, ICD-10 code C91.1 "Chronic lymphocytic leukemia of B-Cell type" falls in 3-digit group C91 "Lymphoid leukemia," sub-chapter "Malignant Neoplasms Of Lymphoid, Hematopoietic And Related Tissue," and chapter "Neoplasms." By using the ICD-10-CM hierarchy, we determine whether each approved indication links to a diagnosis code that was the first approved in its hierarchical group. Table I breaks approvals down into these categories: only 32.5% of follow-on indications are in a new ICD-10 sub-chapter, and only 14.9% fall in an entirely new chapter.[21] For our analysis, we further aggregate the ICD-10 hierarchy groupings into "New Disease Group" category for indications that fall in a new chapter or sub-chapter and "New Diagnosis within Disease Group" category for indications that remain within the same sub-chapters as a drug's previous indications.

Our second asset is de-identified administrative claims data from the OptumLabs® Data Warehouse (henceforth OLDW) which allows us to measure the use of drugs overall and across indications. This database includes medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage (MA) enrollees between 1993 and 2019. The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities and geographical regions across the United States..[22] We focus on patients receiving first prescriptions (prescriptions for individuals who have no previous claims for the relevant drug) rather than all prescriptions.[23] To calculate the number of first prescriptions, we first identify every pharmacy and medical claim for each drug in our dataset of indications. Then, for each drug-beneficiary pair, we determine the date the beneficiary first filed a claim

[19] Given the prominent role of oncology in the market for follow-on indications, we separately analyze this set of products and find qualitatively similar results to our main estimates.
[20] See the appendix for a description of how we assigned diagnosis codes to indications.
[21] Indications in a new chapter necessarily fall in a new sub-chapter, so these are included in this figure.
[22] We restrict the data to only include beneficiaries of commercial plans – which means excluding beneficiaries of Part D prescription drug plans — and only claims filed by beneficiaries enrolled in both medical and pharmacy coverage through the plan.
[23] Our goal is to track how prescribing behavior evolves before and after indication approval, not to analyze the persistence of utilization which is an important but different question that is an important area for future research.

for the drug. We drop drug-beneficiary pairs if the beneficiary was not continuously enrolled for 6 months prior to their first claim for the drug.[24] Second, because our pharmacy claims data do not report diagnoses and therefore are not themselves indicative of the diagnosis for which a drug was prescribed, we use diagnoses from medical claims data to infer the prescribing diagnosis. Specifically, we consider all diagnoses in the 180-day window prior to each drug-beneficiary's first prescription and assign the prescription to each indication with a matching diagnosis.[25]

Finally, our data-use-agreement requires us to censor all cells with between 1 and 10 individuals. Our primary specification assumes utilization in censored cells is equal to the actual mean of all censored cells (i.e. 4 individuals). We also estimate models assuming all censored cells are equal to 1 or 10, respectively.

II. Methods

We assess the impact of indication approval on utilization using an event study design that measures how the share of patients who receive a drug in a particular diagnosis (e.g. Keytruda for lung-cancer) increases when the drug formally gets FDA approval for that follow-on indication (e.g. Keytruda receives a follow on indication for *disease progression on or after platinum-based chemotherapy)*. We use the share because it reflects the changing composition of use across indications while accounting for time trends in overall use of the product. The event-study naturally measures how this increase evolves over time relative to the time-trend before approval, which we interpret as market-learning.

We estimate event study models of the following form:

$$y_{imt} = \alpha + \gamma_{im} + \mu_t + \sum_{\ell=-10}^{6} \beta_\ell 1\{t - A_{im} = \ell\} + \varepsilon_{imt}. \quad (1)$$

In this specification, y_{imt} is the share of patients who are taking medicine m in time-period t with a diagnosis corresponding to indication *i*. On the right hand side, α is an intercept term, γ_{im} is an indication-drug fixed effect, β_ℓ is the coefficient for quarter ℓ relative to approval that measures the difference in utilization between quarters ℓ and -1 (β_{-1} is normalized to 0 at the time of the new indication), μ_t is a calendar quarter-and-year fixed effect, and ε_{imt} is an idiosyncratic error term.

To estimate the effect of approvals based on the nature of the information provided, we estimate the equation above with two different samples of follow-on indications. The first model uses approvals for follow-on indications that happen in new diagnoses after the original diagnosis (in the Keytruda example, this

[24] This restriction increases the likelihood that the first claim for the drug was truly the beneficiary's first use of the drug; if we used a shorter continuous enrollment window — say 30 days — then the prescriptions of beneficiaries who switched from another insurer's plan only 31 days prior would often erroneously appear to be beneficiaries' first prescriptions due to the lack of claims from the previous insurer.

[25] A limit of this procedure is that we are only able to determine whether individuals have a diagnosis that is consistent with a drug's labelled indication and not whether drugs are taken in perfect accordance with their labeled indication (e.g. as first- or second-line therapy). Because of this, much of our analysis focuses on indication approvals for previously unapproved diagnoses. Note that this method may (and often will) assign a claim to more than one of a drug's indications. In fact, if all of a drug's indications are for the same disease, the indications will all link to the same claims.

would be looking at the increased share of Keytruda use for NSCLC after receiving approval in NSCLC). The second uses approvals for follow-on indications for previously-approved diagnoses (for example Keytruda for first-line therapy in NSCLC, which was the second NSCLC indication).[26]

Our event study specification allows us to examine both immediate impact of a follow-on indication approval as well as the trends of market learning before and after the regulatory action. We examine 17 quarters around the quarter of approval of each indication beginning 10 quarters prior and ending 6 quarters after and estimate the model using fixed-effects regression. We quantify the impact of receiving an indication by the FDA on utilization as β_1, the change in utilization from the quarter before approval to the quarter after approval. We note that β_{-10} represents the average level of utilization 10 quarters (2.5 years) prior to approval relative to the level in the quarter before approval. Therefore, $-\beta_{-10}/9$ is the average quarterly change in utilization over the pre-approval portion of the study window. Similarly, $(\beta_6 - \beta_1)/5$ represents the average quarterly change over the post-approval portion of the study window. Lastly, we quantify the level of utilization prior to approval as the average utilization across indications in quarter -1. [27] In all models, we cluster standard errors at the drug level, allowing for arbitrary correlation of residuals within-drug.

III. Results

We present our key results in Table II. Panel A summarizes the dynamics of utilization for follow-on indications that represent new diagnoses. Our preferred specification (Column 1) indicates that in the quarter prior to their follow-on approval, prescriptions for diagnoses related to yet-to-be-granted indications comprise about 9.6 percent of prescriptions for any use. Approval of the follow-on indication sharply increases utilization for new diagnoses, raising their share of overall utilization by 4.1 percentage points (95% confidence interval [CI], 2.3 to 5.9; $p<0.001$). Relative to pre-approval off-label use, the new indication increases the diagnosis share by 43%. This sharp and persistent increase provides evidence that FDA approval increases utilization of an existing medicine in a follow-on indication.

This increase in demand was economically significant compared to the trends of prior use. In Figure III we show that in the 10 quarters prior to approval, the change in the diagnosis share is not statistically different from zero (95% CI, -0.12 to 0.23). Even if the share increased linearly at a rate equal to the upper bound of the confidence interval, it would take almost 18 quarters (4 ½ years) to achieve the same increase in

[26] We include only the first repeat of a diagnosis in this sample. For example, while Keytruda received a follow-on indication for NSCLC in October 2018, it received multiple NSCLC indications beforehand and is therefore not included in this sample.
[27] We balance the panel so that for each drug there are 11 or more first prescriptions in each quarter of the study window. This imposes a lower bound on the denominator of the diagnosis share, removing indications for hyper-orphan drugs and indications that were approved 10 or fewer quarters after drug launch. We also drop indications for influenza drugs, which have largely seasonal utilization, as well as indications that were approved alongside new drug formulations. Imposing these restrictions reduces our sample to 245 follow-on indications for 129 drugs, or 39.6% of all follow-on indications in our unrestricted sample. The third set of columns in Table I (labeled "Estimation Sample") shows that this sample is broadly similar on observable dimensions to the wider set of follow-on indications. We also estimate our main specifications using an alternate unbalanced panel. Appendix Figure IV graphically presents these coefficient estimates which are broadly similar to the balanced panel.

diagnosis share that the approval of the follow-on indication causes in only 2 quarters. To place this length of time into context, Grabowski and Vernon (2000) estimate that new pharmaceutical products have an average effective patent life of only 11.7 years, and each new indication receives only 5 years of post-approval market exclusivity from the FDA.[28, 29] Therefore, the increase in use from the new indication is economically significant to manufacturers. In contrast, we find no evidence of additional market learning in the 6 quarters after indication approval which we note is similar to the lack of pre-approval market learning. As we discuss below, this lack of post-approval increase suggests that our estimates are not primarily driven by the ability of firms to actively market their products for the new indication.

Columns 2 and 3 of Panel A show that these results are robust to assuming different values for censored cells. In both specifications we estimate indication effects that are quite close to our preferred specification. The only exceptions are (1) we estimate a small positive and significant coefficient for the pre-approval diffusion rate when we assume censored values are equal to 1 and (2) we estimate a negative and significant coefficient on the post-approval diffusion rate when we assume censored values are equal to 10 (which is meaningfully different than the average value of 4).[30] However, even if indications remained a constant fraction of utilization prior to approval, we still find compelling evidence of substantial off-label use.[31]

Panel B performs the same analysis but for approvals for previously-approved diagnoses, i.e. an indication for a new course of treatment within an existing diagnosis. We expect that these indications provide the smallest amount of new information to the market and therefore we should see a substantially smaller and possibly even no effect from the new indication approval. Accordingly, we find that the change in the diagnosis share is not statistically different from zero (CI, -0.85 to 2.04 percentage points). Moreover, there is little evidence of diffusion in the pre-period, and these results hold regardless of the assumed censored cell size. Taken together, our results suggest that new indications inject little consumer-relevant information into the market when the indication extends approved usage within-disease.

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[28] Grabowski and Vernon's estimates are based on a sample of New Chemical Entities that were approved in the years 1990–1995.
[29] While follow-on indications grant a five year period of exclusivity to drugs, this exclusivity is specific to the approved use. Therefore when the drug's patent exclusivity ends, another manufacturer may market the drug as a generic with a so-called "skinny label," that omits some number of follow-on indications. Doctors may still prescribe the generic version off-label for uses that are only approved for the brand name formulation. Therefore the effectiveness of this follow-on exclusivity may be limited.
[30] In the specification in which we assume censored values equal 1, we find that the pre-approval diffusion rate is 0.20 percentage points per quarter (95% CI, 0.03 to 0.37). This means that even if this assumption best approximates the true uncensored data, we find that market learning would still take over five years to increase the diagnosis share by the amount a new indication does in half of one year. In fact, even if utilization increased at a rate equal to the upper bound of the 95% confidence interval, it would take nearly three years — a significant fraction of the drug's life — to achieve the indication-induced increase
[31] In Appendix Figure V, we also examine the sensitivity of our results to dropping indications with any censored cells. This imposes that the fewest prescriptions for any indication and in any quarter is 11, thus effectively conditioning on a minimum level of off-label utilization. This amounts to conditioning on a minimum level of off-label utilization, positively biasing off-label utilization and negatively biasing the estimated indication effect. As expected, we find that this specification yields the highest level of utilization prior to approval, and while we still identify a statistically significant effect from indication approval, the estimated increase is approximately half as large.

We should expect a similar pattern of differential estimates based on whether the follow-on indication is in a new disease area rather than expansion within a group of similar diseases. Panel A of Figure IV shows that the effect of a follow-on indication approval for a new diagnosis within a disease group is 2.4 percentage points (CI, 0.7 to 4.1; $p<0.01$). In contrast, Panel B shows that when the follow-on indication is for a new diagnosis in *new disease area*, the increase in the share of patients using the drug for that indication increases by 5.5 percentage points (CI, 3.1 to 8.0; $p<0.001$). A test of the difference in effects rejects the null hypothesis of equal effects ($p=0.037$). This result, shows that "more novel" indications (i.e. those for diagnoses that are medically dissimilar to previously-approved ones) increase utilization for those diagnoses more than "less novel" indications.

Together, our estimates suggest that the demand response is in part a function of the novelty of the information consumers and providers gain from the regulatory action. Indications in new disease areas also show statistically significant pre-approval diffusion, with the diagnosis share increasing an average of 0.3 percentage points per quarter. Thus, for these approvals, the indication effect is equivalent to the effect of about 18 quarters or 4 ½ years of market learning.

A notable feature of our data on secondary indications is that prominent role of the oncology market, with 27 percent of our follow-on indications being for cancer. In order to determine whether our results are primarily driven by these oncology products we next analyze how the consumer response to follow-on approvals varies across cancer and non-cancer indications. In addition to demonstrating whether our main results are driven by oncology, these estimates also provide evidence regarding the role of disease severity in the use of products for follow-on indications.

Panels A and C of Figure V show that the utilization dynamics around cancer and non-cancer new diagnosis approvals are fairly similar: the diagnosis share is mostly stable prior to approval and increases by around 4 percentage points by the quarter after approval.[32] In contrast, we find no evidence of an indication effect for either non-cancer or cancer indications when the indication is for a new course of treatment for a previously-approved diagnosis. This provides clear evidence demonstrating our main results are not driven solely by oncology. It also demonstrates that there are not meaningfully different patterns for oncology products. This is especially surprising for cancer indications as cancer is a major source of mortality in the United States and other OECD countries, meaning effective treatment may literally be the difference between life and death. Moreover, cancer drugs are quite expensive, and thus insurers have strong incentives to curtail cancer drug utilization that they view as ineffective, even if they view some use for the same diagnosis as

[32] One key difference in utilization dynamics is that the diagnosis share for cancer indications declines to the pre-approval share within 6 quarters of approval whereas no clear decline is seen among non-cancer indications (see Panels A and C of Figure V). This could be the result of a couple different factors. First, due to the relative frequency of new indications among cancer drugs, other uses for cancer drugs may increase substantially as the post-period drags on, reducing the diagnosis share while preserving absolute increases in utilization. Second, this could be a result of spillovers: an initial increase in use of a drug for one diagnosis may produce information about its effectiveness at treating other diagnoses, similarly decreasing the diagnosis share of the newly-approved diagnosis as time progresses.

effective. If the insurer only covered prescriptions for individuals undergoing treatment in exact accordance with the FDA-approved indications, we should expect an increase in the diagnosis share when drugs receive a new indication, even when the diagnosis is already approved under a different indication. The fact that we do not observe such a significant increase in the share suggests that, even if the insurer perceives new indications as signals of efficacy, they may have limited ability to restrict utilization within-diagnosis.

IV. Mechanisms

Understanding the economic and policy significance of the post-approval utilization increase requires understanding more about the potential mechanisms that could drive our results. Here, we explore two potential mechanisms, each of which requires additional data.

We first examine the source of information provided by the approval. A new indication provides information both from the supporting clinical trials and the actual regulatory decision. It is possible that clinical trial information on its own could contribute to market learning and this would limit the importance of the formal regulatory review. In order to provide some evidence about the separate role of these factors, we use data from ClinicalTrials.gov, a publicly available online clinical trial registry that allows us to identify when trials for follow-on indications were publicly registered.[33] If we believe that the trial registration sends a signal on potential effectiveness, because profit-maximizing firms do not start expensive trials randomly, then a large part of the approval effect should show up at the time that the trial is registered.

We modify our framework to analyze the contributions of clinical trial registration to changing utilization. To analyze trial impacts, we simultaneously consider the impacts of the indication approval and pivotal trial registration, where pivotal trials are those clinical trials that are listed in the clinical studies section of the drug label providing evidence of its efficacy for a particular indication. For indications with multiple pivotal trials, we consider the latest phase of the trial that was registered first. We include drugs that have 11 or more first prescriptions in each quarter in two distinct windows: a first window beginning 5 quarters prior to trial registration and ending 2 quarters after and a second window beginning 2 quarters prior to indication approval and ending 5 quarters after. Moreover, we require that there be at least 5 quarters between trial registration and indication approval so that the two windows do not overlap. Note that requiring a positive number of prescriptions in each quarter rules out pivotal trials that occur before primary approval. We also consider only new diagnosis approvals. We estimate quarter coefficients as in our previous estimating equation but now include quarters both relative to the indication and to the trial. Using the estimated

[33] Trials are generally first posted publicly a few days after the study sponsor submits registration. The Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) requires drugmakers to submit registration information within 21 days of enrolling the first trial subject; however, this rule has only been in place since January 2017. (https://clinicaltrials.gov/ct2/manage-recs/fdaaa#WhenDoINeedToRegister). Note that in principle, we could also use the date of the trial readout, but there is no systematic source for these.

coefficients $\beta_{Trial,t}$ and $\beta_{Ind,t}$, we compute the trial effect $\beta_{Trial,1} - \beta_{Trial,-1}$and, as before, the indication effect $\beta_{Ind,1} - \beta_{Ind,-1}$.[34]

Figure VI shows coefficient estimates for utilization relative to the quarter prior to approval using a sample of 48 follow-on indications for new diagnoses with trials registered after original approval. The estimated short-term effect of the trial is a statistically insignificant 1 percentage point (CI, -0.7 to 2.7, p=0.254) increase in the share. In contrast, we observe an indication approval effect of 5.1 percent, which is largely in line with the estimates from our main sample. These estimates suggest that the short-term impact of a new indication on diagnosis share is nearly 5 times the impact of a new trial registration. We also observe increasing utilization after the trial is registered, but we cannot reject that this increase is statistically different from zero. Regardless, the approval of the indication itself tends to have the most substantial impact on utilization.

Our primary results showed that there is a strong short-term demand response to new diagnosis approvals. We next examine whether this is because approvals permit insurers to relax constraints on prior-authorization which governs off-label use (prior authorization is a requirement mandated by the health plan than requires doctors obtain approval from the plan before it will cover the costs of medicine). This requirement is intended to lower costs by deterring inappropriate use. Insurers, however, have less latitude to refuse coverage for indications that are approved by the FDA.[35] Comparing follow-on indication responses for drugs with different prior authorization requirements amounts to a useful test of mechanisms because if utilization changes are similar among drugs with different utilization restrictions then any increase in utilization is likely to be driven entirely by the indication shifting demand.

To examine this question, we use prescription drug plan formulary data from Managed Markets Insight & Technology (MMIT) to determine how restrictions imposed by the insurer on prospective users of different medications interact with follow-on indications to impact utilization. This data contains information on drug coverage, restrictions (including prior authorization), and enrollment in prescription drug plans for a subset of drugs in our sample for which the FDA approved at least one follow-on indication in the years 2011–2019. For each drug, we determine the number of individuals enrolled in prescription drug plans that cover that drug, and then further determine how many of those individuals are on plans that require prior authorization, using these counts to compute the share of covered individuals who require prior authorization: our measure of exposure to prior authorization requirements which we term the prior authorization (PA) share.

[34] We must also normalize one of the coefficients to zero as before. For consistency, we set $\beta_{Ind,-1} = 0$.
[35] This assumption is supported by the fact that prior authorization forms from various health plans often cite FDA approval of an indication as a sufficient criterion for its coverage; however, they often also cover off-label uses listed in medical compendia, meaning that FDA approval is not always necessary for coverage.

We test for the role of insurer constraints by assessing the differential indication effects of drugs with different prior authorization requirements. To assess the impact of prior authorization requirements on the indication effect, we limit our sample to drugs covered by their plan's pharmacy benefit: drugs must have 11 or more first prescriptions covered by pharmacy benefit in each quarter in the approval window. (We use the same 17-month window as our primary analysis, but now based off of only pharmacy claims.) We also limit to new diagnosis approvals in years since 2011, since this is as far back as our prior authorization data extends, and drop any other indications with missing prior authorization shares. We then estimate the following equation:

$$y_{imt} = \alpha + \gamma_{im} + \mu_t + \sum_{\ell=-6}^{10}(\beta_\ell + \rho_\ell \times PA_m)1\{t - A_{im} = \ell\} + \varepsilon_{imt}\,. \qquad (2)$$

In the equation, PA_m is a measure of drug m's prior authorization exposure and ρ_ℓ is a time-dependent coefficient that allows prior authorization to mediate time trends. We specifically measure prior authorization as the PA share (as we have previously defined) in the quarter prior to approval and alternatively estimate Equation 2 by including it as a continuous interaction variable or discretized into high prior authorization share (PA Share >= 0.5) or low prior authorization share (PA Share < 0.5).

Table III reports our estimates of Equation 2. While the estimates are admittedly noisy, we find no evidence that prior authorization restrictions lead to larger indication effects and thus no evidence that these restrictions prevent beneficiaries from accessing drugs for approved uses prior to their approval. Column 1 reports estimates from the regression interacting quarter dummies with PA Share. We find an imprecise negative effect from prior authorization when it is included as a continuous interaction (-0.8 percentage points; CI, -6.4 to 4.8; p=0.768). Column 2 then estimates Equation 2 by interacting the quarter dummies with a dummy for a high PA share. We find that indication effects for drugs with a high PA share are only 0.5 percentage points greater than drugs with a low PA share (CI, -3.8 to 4.8; p=0.823). The confidence intervals on these interaction terms contain economically meaningful magnitudes; however, the overall similarity of the time trends for drugs with high and low prior authorization shares, depicted in Figure VII, further suggests that FDA approval increases utilization principally by shifting demand.

V. Conclusion

FDA regulations are often thought of as purely a means of consumer protection, where society sacrifices the number of drugs in order to enjoy increased product quality and safety. Certainly, the clinical trial process is costly and, holding all else constant, would result in a reduced number of products coming to market. Our results demonstrate that all else is not held constant., because FDA approval grows the market size for pharmaceutical products beyond what otherwise would have existed. FDA approvals have two effects. First,

they provides information to the market in the form of both FDA certification and the result from new clinical trials demonstrating efficacy. Second, they allows firms to market their product for the new indication. These efforts could increase demand independent of any information conveyed by the FDA. Indeed, Shapiro (2018) finds that direct advertising to physicians in the month of an informational shock increased prescriptions and tilted use towards on-label uses. Our results reflect a combination of the effects of these two forces, and we believe that the totality of our results suggests that the increase in sales is not solely driven by increased marketing efforts and instead reflects an independent effect from product certification by the FDA. We offer three reasons for this interpretation:

We first note that our main specification finds a 4.1 percentage point increase in market share off of a baseline of 9.6 percent – an increase of nearly 45 percent. This is a far larger increase than is suggested by the literature on both direct-to-consumer (DTC) advertising and physician detailing (Iizuka and Jin 2007; Shapiro 2018). Second, the increase in sales that we observe is immediate, and after two quarters we observe negligible differential market learning for the new indication (compared to the existing approved indications). This would suggest that if the sales effect were driven by DTC advertising and/or detailing there would need to be an immediate and complete effect from these efforts within 6 months of approval. Finally, our results are largest when the indication appears to provide the most novel information to the market, i.e. when the indication is for a new medical diagnosis. This demonstrates that there is something important about the novelty of the information provided by the FDA action. It also suggests that detailing efforts in response to the new approval are not solely about a pharmaceutical representative discussing new indications with the same physicians. Instead, these efforts would likely involve setting up new relationships with physicians.

Taken together, these factors make it likely that a meaningful portion of the change in sales we observe is driven by the actual act of FDA approval providing information to the market about quality. This would be consistent with the statements and actions of vaccine manufacturers during the COVID-19 pandemic who joined together to ask for the normal and rigorous though costly review. This suggests market participants have a belief that the market expanding effects that we estimate are related to the FDA certification. Importantly, future work could seek to improve our understanding of how firms strategically decide to expand use by seeking new indications.

In this way, our results contribute to a broader economics literature about the economics of quality disclosure and verification. Questions of the optimal amount of quality certification and disclosure date back to at least Spence (1975). As discussed in Dranove and Jin (2010), quality certification can take many forms ranging from voluntary disclosure by sellers to the mandated FDA process at the center of our study.

We interpret the totality of our results as providing evidence of a value creating role for the information required as part of the FDA process. These provide a channel for the for the FDA process increasing welfare even in a setting where the process imposes meaningful delays on market entry. For example, to the extent that lost sales from this earlier period are outweighed by the higher revenue from a

more robust market, the review process could be valued by firms rather than being perceived as a pure burden.[36] This could also increase welfare to the extent that it shifts research and development investments towards higher quality products.

This opens the question of whether the increase in use is welfare enhancing. To the degree that our estimates reflect a change in demand resulting from a reduction of information asymmetries, that would suggest an increase in welfare. Of course, greater use of medicines could also reflect overuse, in the sense of the marginal benefits from these medicines being less than the cost of providing them (Chandra and Skinner 2012), which would limit the welfare benefits. We note that we find no increase in attempts by insurers to limit the wasteful use of medications after indication approval which we might expect if insurers viewed the increased use as potentially wasteful.[37] Measuring the welfare effects of expanded market size more completely remains a fruitful area for future research.

[36] Peltsman (1973) does examine the possibility that new drugs are of higher quality. However, this study uses a relatively short period after the policy change to examine this effect. The pace of scientific and drug development suggests a much longer time period for firms to develop new and higher quality products.

[37] See Appendix Figure II.

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Appendix I. Data

Indications

After identifying drugs using tabular data available on Drugs@FDA,[38] we used the same data to access all original and supplemental approval documents for each drug, including new indication approvals as well as approvals of numerous other drug labelling changes. While new indication approval documents are sometimes labelled as such, some supplemental approval documents either are not classified (especially for biologic drugs) or are misclassified. Due to these oversights, we read the content of each letter issued by the FDA to (1) identify if a new indication was granted, (2) determine the wording of that indication, and (3) determine the date it was approved. This data was then manually entered in a spreadsheet program.

We harmonized indication descriptions within-drug (i.e. within-active ingredient) to account for small differences in wording across formulations but maintained all relevant information about the drug's intended uses including the targeted diseases, patient populations, genotypes, therapy goals (treatment vs. prevention), and more.

We manually assigned diagnosis codes for each indication by comparing the text of the indication to the description of the ICD code as defined by the World Health Organization. Instead of assigning diagnosis codes at a fixed level of hierarchy (e.g. 3-digit ICD-10 codes), we assigned diagnosis codes to indications at the most specific level possible so that utilization is measured with as little error as possible. For instance, if an indication most closely corresponds to a 5-digit ICD-10 code, we would use that code, and not the more aggregate 3-digit code, to determine claims for that indication. Note that because a single indication may occasionally describe treatment for multiple closely related diagnoses, some indications are assigned multiple ICD codes. For indications for preventive uses, a very small sample of our data, we ascribed codes to characterize the diagnosis that justifies use of the drug. For example, an indication for "reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis" will be linked to osteoporosis, not breast cancer because diagnoses for prevented diseases do not appear in claims data, making it impossible to identify individuals based on that criteria. We did not code diagnoses for drugs with diagnostic uses (such as radiocontrast agents) and those primarily used in perioperative settings (such as anaesthetics) due to the difficulty of identifying and grouping individuals based off of their diagnoses in these settings.

ICD-10-CM Hierarchy

The ICD-10-CM hierarchy groups codes into 3-digit groups (roughly corresponding to a disease), sub-chapters (corresponding to a diverse group of diseases), and chapters (corresponding to an even more diverse

[38] Access this data at https://www..gov/drugs/drug-approvals-and-databases/drugsfda-data-files.

group of diseases). For example, ICD-10 code C91.1 "Chronic lymphocytic leukemia of B-Cell type" falls in 3-digit group C91 "Lymphoid leukemia", sub-chapter "Malignant Neoplasms Of Lymphoid, Hematopoietic And Related Tissue," and chapter "Neoplasms." By using these three highest levels of the ICD-10-CM hierarchy, we determine whether each approved indication links to a diagnosis code that was the first approved in its hierarchical group. For more information on the ICD-10-CM hierarchy, visit https://icd.who.int/browse10/Help/Get/hierarchy/en.

OptumLabs Data Warehouse

We link the drugs in our indication data to claims data using the RxNorm database to create crosswalks between each drug in our dataset and the NDC and HCPCS codes used for reimbursement.

Clinical Trials

To link indication approvals to trials, we determined the National Clinical Trial (NCT) codes that uniquely identify the "pivotal trials" that led to the approval. FDA details the pivotal trials for each indication in the drug's label, but trial identifiers (including NCT codes) are not reliably reported, especially in the earlier years of our study. To determine the correct NCTs, two research assistants independently read FDA labels for each indication and compared information in the label to information documented about the trial on ClinicalTrials.gov. Discrepancies were then addressed by one of the authors.

Table I
Indication Summary Statistics for NMEs and Biologics Approved 1995-2019

	All Indications			Follow-on Indications			Estimation Sample		
	# Drugs	# Inds	% Inds	# Drugs	# Inds	% Inds	# Drugs	# Inds	% Inds
All Indications	784	1552	100.0	287	619	100.0	129	245	100.0
Follow-on Indication Novelty									
New Diagnosis	166	317	20.4	166	317	51.2	77	136	55.5
Previously-Approved Diagnosis	166	264	17.0	166	264	42.6	79	109	44.5
New Disease Group	121	201	13.0	121	201	32.5	55	84	34.3
Previously-Approved Disease Group	215	380	24.5	215	380	61.4	103	161	65.7
Approval Period									
1995-1999	193	309	19.9	23	36	5.8	5	6	2.4
2000-2004	180	265	17.1	73	107	17.3	35	47	19.2
2005-2009	183	268	17.3	91	146	23.6	55	87	35.5
2010-2014	197	267	17.2	74	109	17.6	37	50	20.4
2015-2019	298	443	28.5	125	221	35.7	40	55	22.4
Drug Class									
Anti-Epileptics	16	30	1.9	6	12	1.9	3	6	2.4
Anti-Infectives	71	143	9.2	25	37	6.0	7	10	4.1
Anti-Thrombotic Drugs	23	49	3.2	10	24	3.9	4	7	2.9
Chemotherapies	122	344	22.2	73	207	33.4	28	67	27.3
Endocrine Drugs	13	27	1.7	7	14	2.3	5	9	3.7
Immunosuppresants	44	107	6.9	20	58	9.4	13	34	13.9
Insulins & Other Diabetes Drugs	30	50	3.2	11	17	2.7	9	11	4.5
Lipid-Modifying Drugs	9	29	1.9	6	15	2.4	4	10	4.1
Opthalmologicals	19	30	1.9	6	11	1.8	4	8	3.3
Psycholeptics	18	48	3.1	8	26	4.2	5	17	6.9
Other	419	695	44.8	115	198	32.0	47	66	26.9

Notes: The estimation sample drops follow-on indications that are approved in conjunction with a new drug formulation and indications for drugs with fewer than 11 prescriptions in any year of the study window. Diagnosis novelty categories are nested so that, for example, an approval in a new ICD-10 subchapter includes approvals in a new chapter. Indication novelty sums to less than 100% in Column 2 because of unknown values.

Table II
Main Regression Estimates

Dependent Variable: Diagnosis Share of Prescriptions

Panel A: Indications for New Diagnoses

	Censored Values Assumed		
	(1) Censored=4	(2) Censored=1	(3) Censored=10
Indication Effect	0.0410***	0.0419***	0.0391***
	(0.0090)	(0.0091)	(0.0118)
Pre-Approval Quarterly Diffusion Rate	0.0006	0.0020*	-0.0023
	(0.0009)	(0.0009)	(0.0012)
Post-Approval Quarterly Diffusion Rate	-0.0019	-0.0002	-0.0053**
	(0.0015)	(0.0014)	(0.0020)
Pre-Approval Diagnosis Share	0.0958	0.0820	0.1234
# Indications	136	136	136
# Drugs	77	77	77

Panel B: Indications for Previously-Approved Diagnoses

	Censored Values Assumed		
	(1) Censored=4	(2) Censored=1	(3) Censored=10
Indication Effect	0.0059	0.0093	-0.0009
	(0.0072)	(0.0085)	(0.0071)
Pre-Approval Quarterly Diffusion Rate	-0.0002	0.0005	-0.0015
	(0.0016)	(0.0023)	(0.0012)
Post-Approval Quarterly Diffusion Rate	-0.0074*	-0.0092*	-0.0037
	(0.0033)	(0.0041)	(0.0029)
Pre-Approval Diagnosis Share	0.4966	0.4924	0.5051
# Indications	64	64	64
# Drugs	55	55	55

Standard errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Notes: This table reports estimates of β_1, the short-term causal effect of an indication on utilization; $-\beta_{10}/9$, the quarterly rate of diffusion in the 10 months prior to approval; and $(\beta_6 - \beta_1)/5$, the quarterly rate of diffusion in the 6 months after approval. Utilization is measured as the diagnosis share of initial prescriptions. We additionally report the average diagnosis share in the quarter prior to approval. All models include calendar year-and-quarter fixed-effects. Panels A and B report estimates for new diagnoses and previously-approved diagnoses, respectively. Columns 1, 2, and 3 in both panels report the coefficients given different values assumed for censored cells. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.

Table III
Prior Authorization Regressions

Dependent Variable: Diagnosis Share of Prescriptions

	(1) Continuous PA	(2) Discrete PA
$\mathbb{1}\{t = 1\}$	0.0563*	0.0489*
	(0.0225)	(0.0181)
$\mathbb{1}\{t = 1\} \times$ PA Share	-0.0080	
	(0.0266)	
$\mathbb{1}\{t = 1\} \times \mathbb{1}\{\text{PA Share} \geq 0.5\}$		0.0046
		(0.0205)
# Observations	510	510
# Indications	30	30
# Drugs	19	19

Standard errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Notes: This table reports regression coefficients from a fixed-effects model (with indication-level intercepts) that characterize the differential indication effect from differential use of prior authorization restrictions. The outcome variable is diagnosis share of new prescriptions in a retail or mail-order pharmacy setting. We include only drugs that have at least 11 total pharmacy prescriptions in each quarter of our sample and indications that were approved between 2011 and 2019 (the years we observe prior authorization status). Moreover, we only include indications for new diagnoses. Censored cells are assumed to equal 4. Column 1 interacts quarter dummy variables with the PA Share in Quarter -1, while Column 2 instead interacts the quarter dummies with another dummy for PA Share being greater than or equal to 0.5. Quarter -1 is omitted in both specifications; therefore, the utilization change is with respect to $t = -1$. To focus on the short-run indication effect, we report only the estimates for Quarter 1. Note that although the models are estimated using all periods, the reported parameters are identified from just 2 quarters of data, so the effective number of observations is just # Indications $\times$ 2. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.

Figure I: Cumulative Indications Per Drug

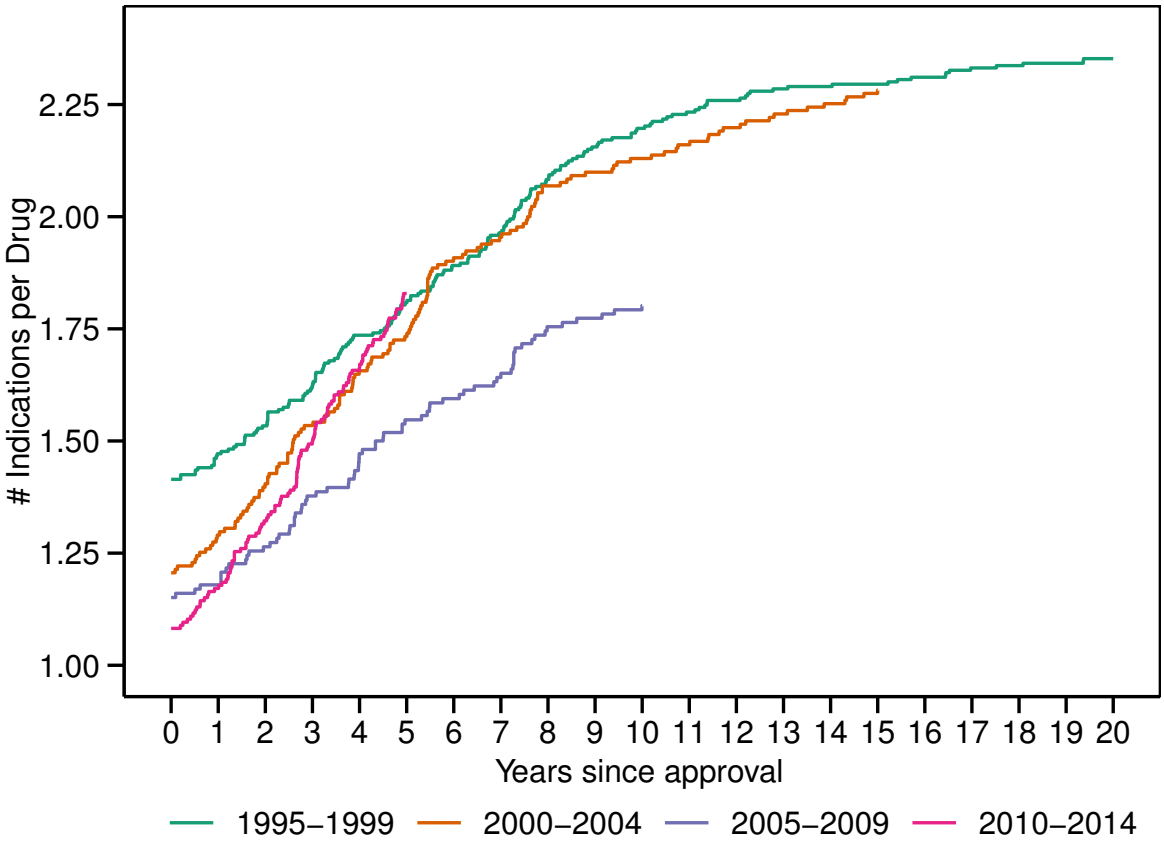
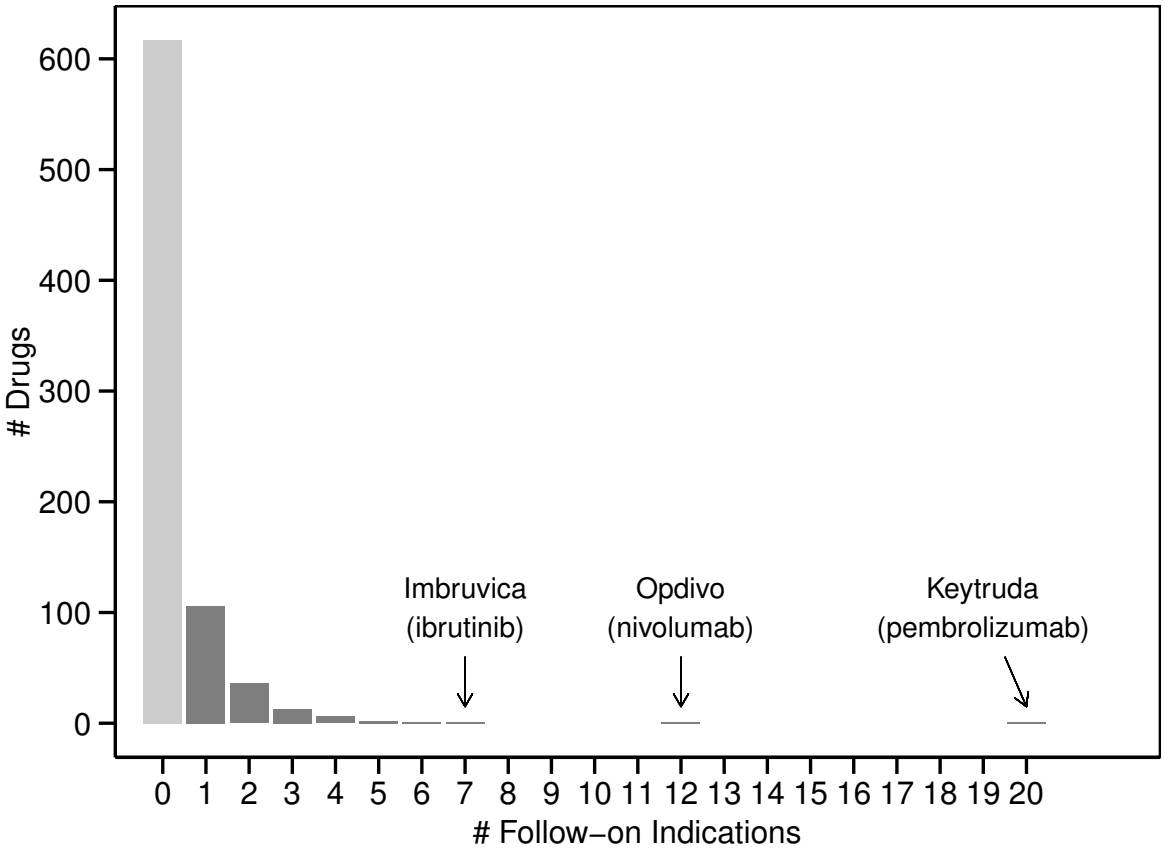
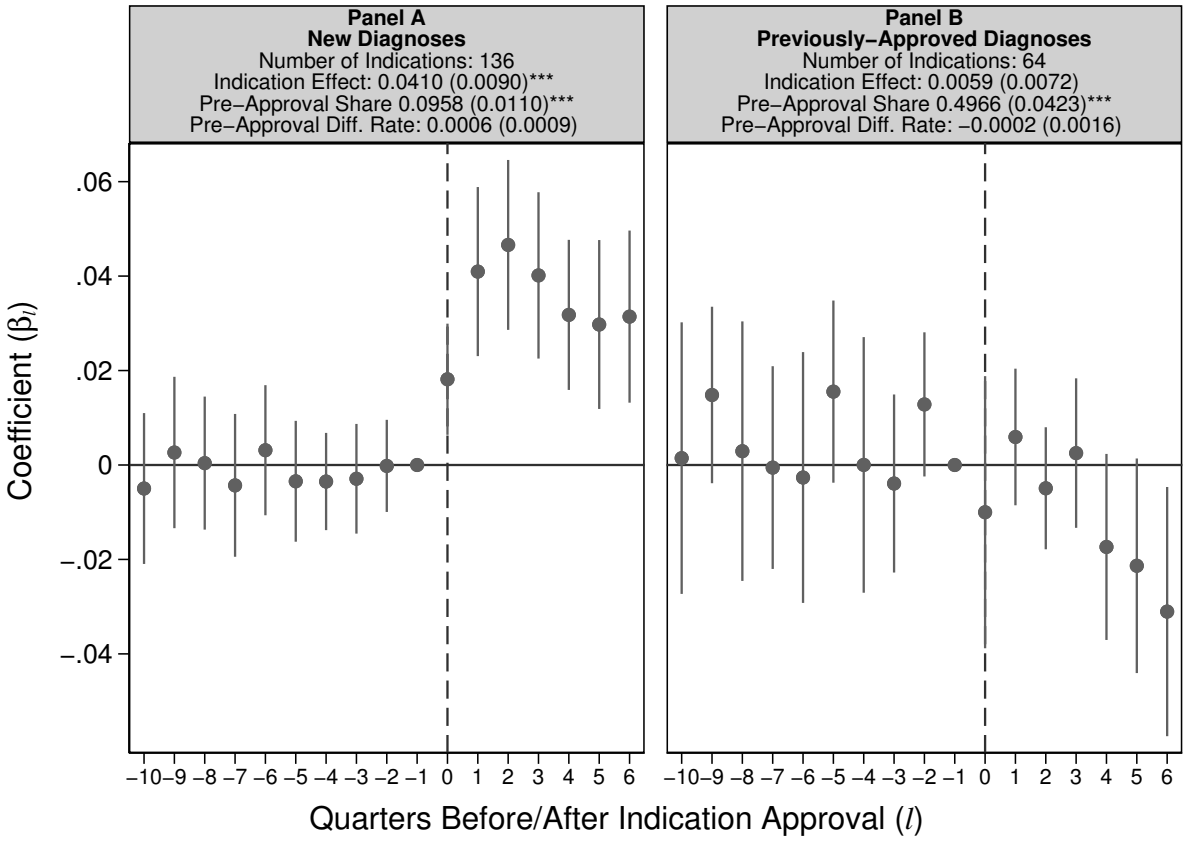


Figure II: Distribution of Follow-on Indication Count



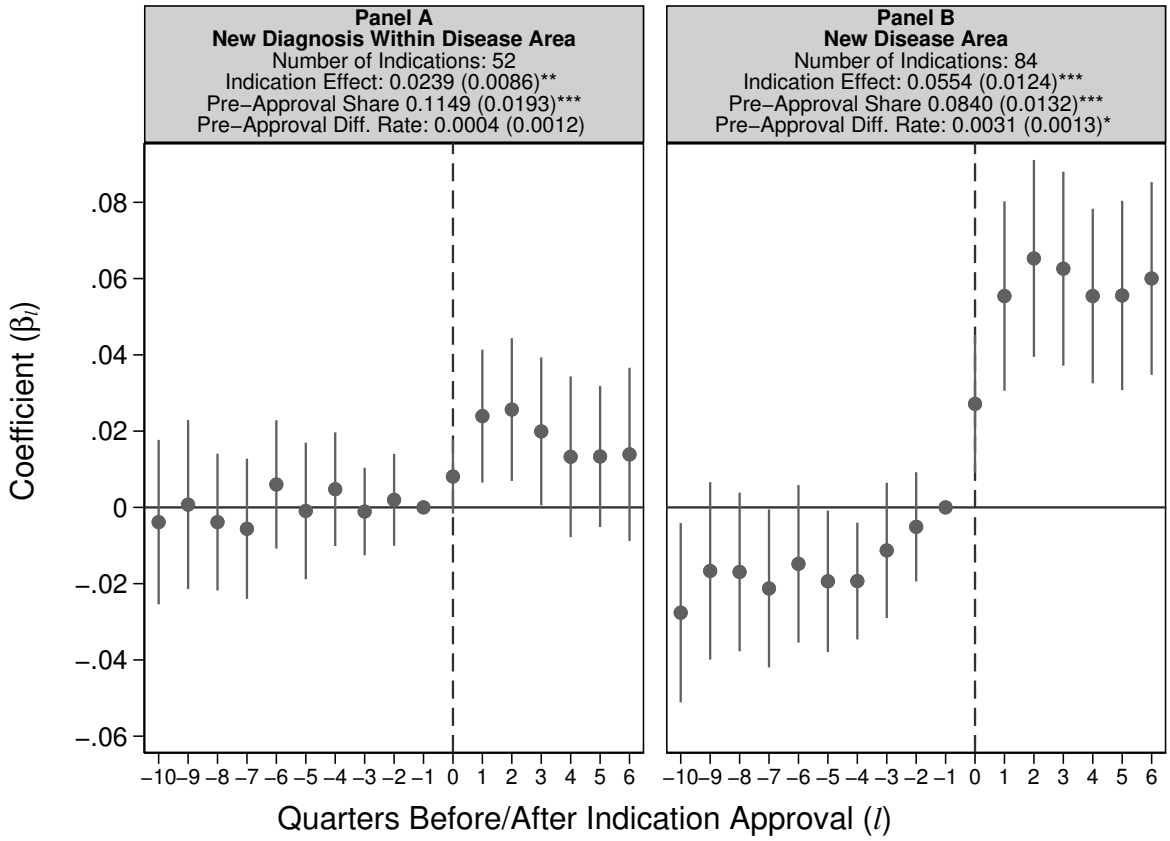
Notes: Follow-on indication count is based on the number of indications approved within 5 years of original approval for drugs with original approvals between 1995 and 2014.

Figure III: Diagnosis Share for New and Previously-Approved Diagnoses



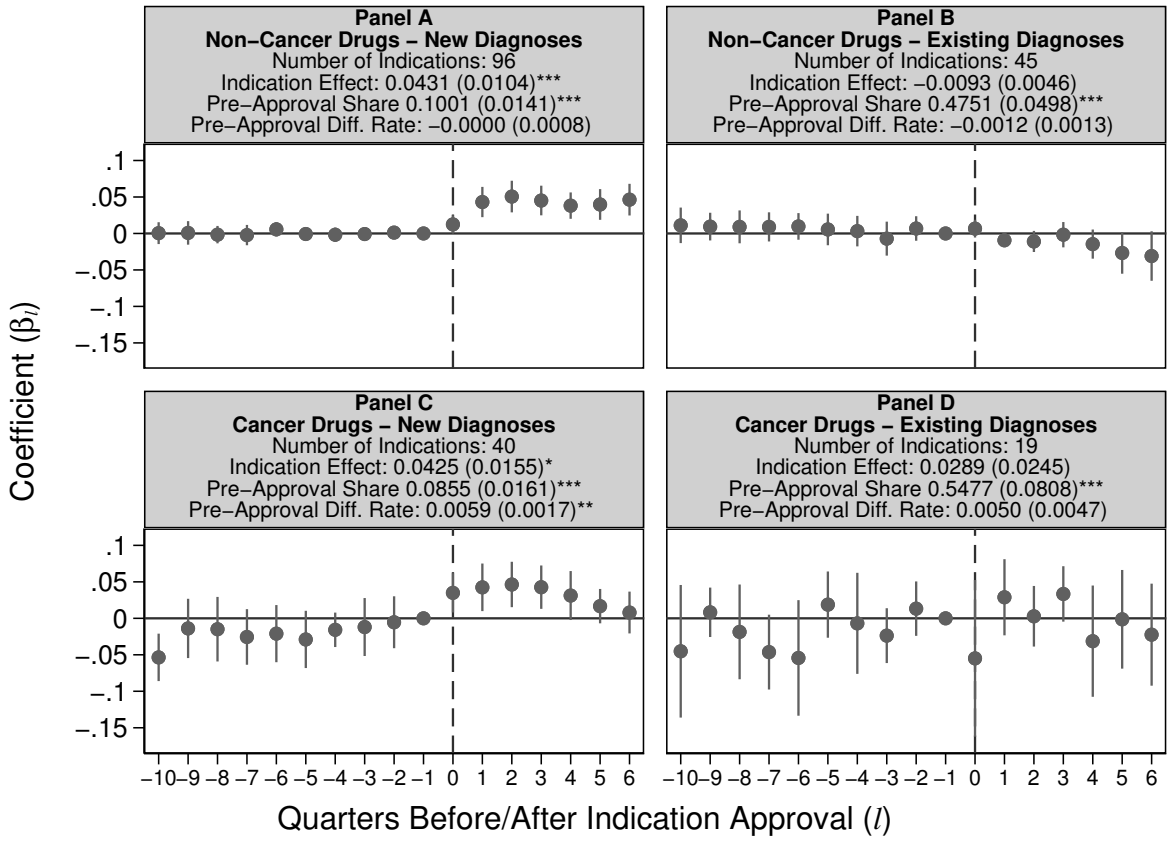
Notes: Panel A reports the diagnosis share of prescriptions around indication approvals for new diagnoses. Panel B, in contrast, reports the diagnosis share for repeat diagnoses — those that had already been approved under another indication for the same drug. Diagnoses were defined by manually assigning diagnosis codes to each indication. In Panel B we include only the first previously-approved diagnosis indication for each drug and diagnosis. That is, for drug-diagnosis pairs with three or more indications, our samples include only the first two: the first indication in Panel A and the second in Panel B. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.

Figure IV: Diagnosis Share by Treatment Novelty



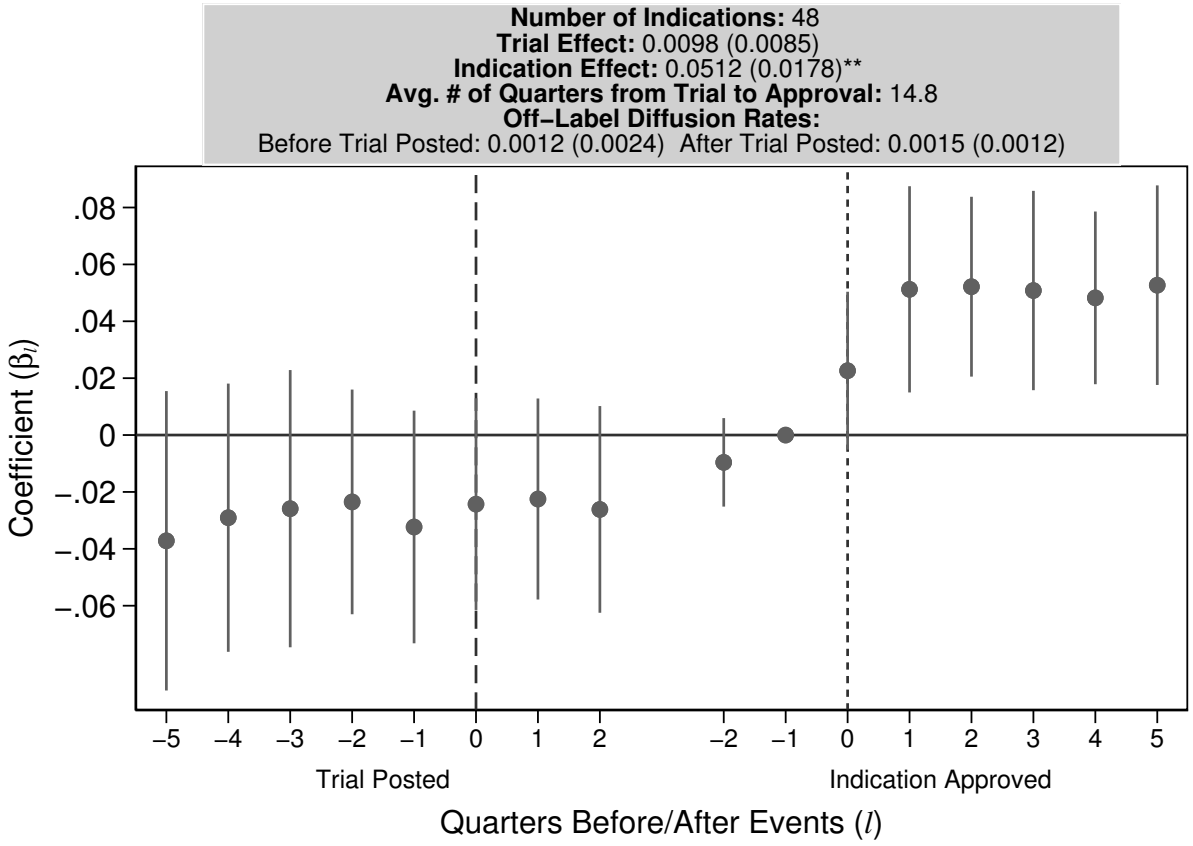
Notes: Panel A reports the diagnosis share of prescriptions around indication approvals for new diagnoses that lie in the same disease area as previous indications for the same drug. Panel B, in contrast, reports the diagnosis share for new diagnoses that lie in a new disease area. Here we define disease area as an ICD-10-CM sub-chapter. A sub-chapter is a fairly coarse grouping of diseases. For example, all cancers fall into one of 21 sub-chapters that are differentiated by the organ system the cancer affects. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.

Figure V: Diagnosis Share of New and Previously-Approved Diagnoses by Cancer/Non-Cancer



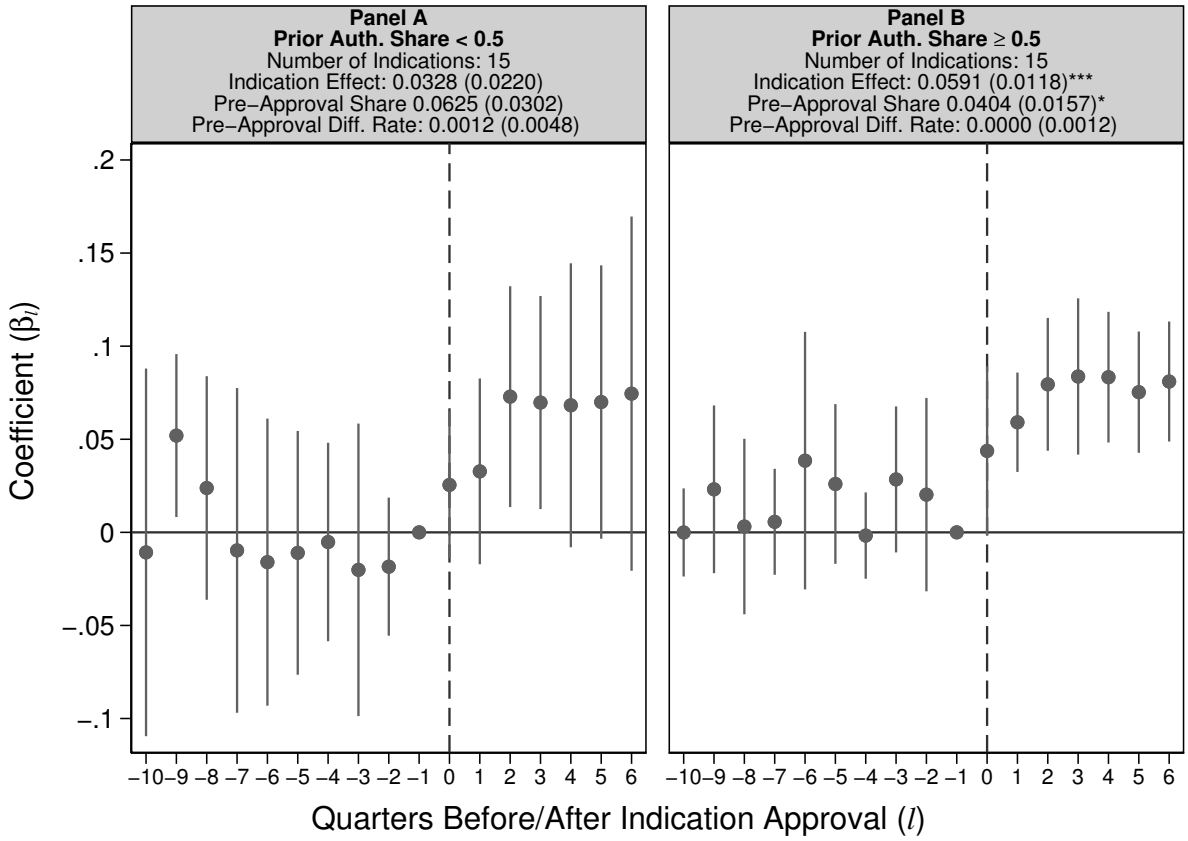
Notes: In the left panels (A and C) we report estimates using new diagnosis approvals while in the right panels (B and D) we report estimates using approvals of previously-approved diagnoses. Moreover, in the top panels (A and B) we report estimates for non-cancer drug indications and in the bottom panels (C and D) we report estimates for cancer drug indications. Cancer drugs are defined as those with an ATC code of L01 for *Antineoplastic agents*. In all specifications, we include calendar year and quarter fixed effects and cluster standard errors at the drug level.

Figure VI: Diagnosis Share with Trial Posting Milestone



Notes: We report estimates from a model including dummies for quarters relative to two distinct events, trial registration and indication approval. We include only indications for new diagnoses. We define a window starting 5 quarters prior to trial registration and ending and 2 quarters after and another window starting two quarters prior to indication approval and ending five quarters after. We require that each drug must have at least 11 total prescriptions in each quarter of the two windows. Moreover, we require there to be at least 5 quarters between trial registration and indication approval. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.

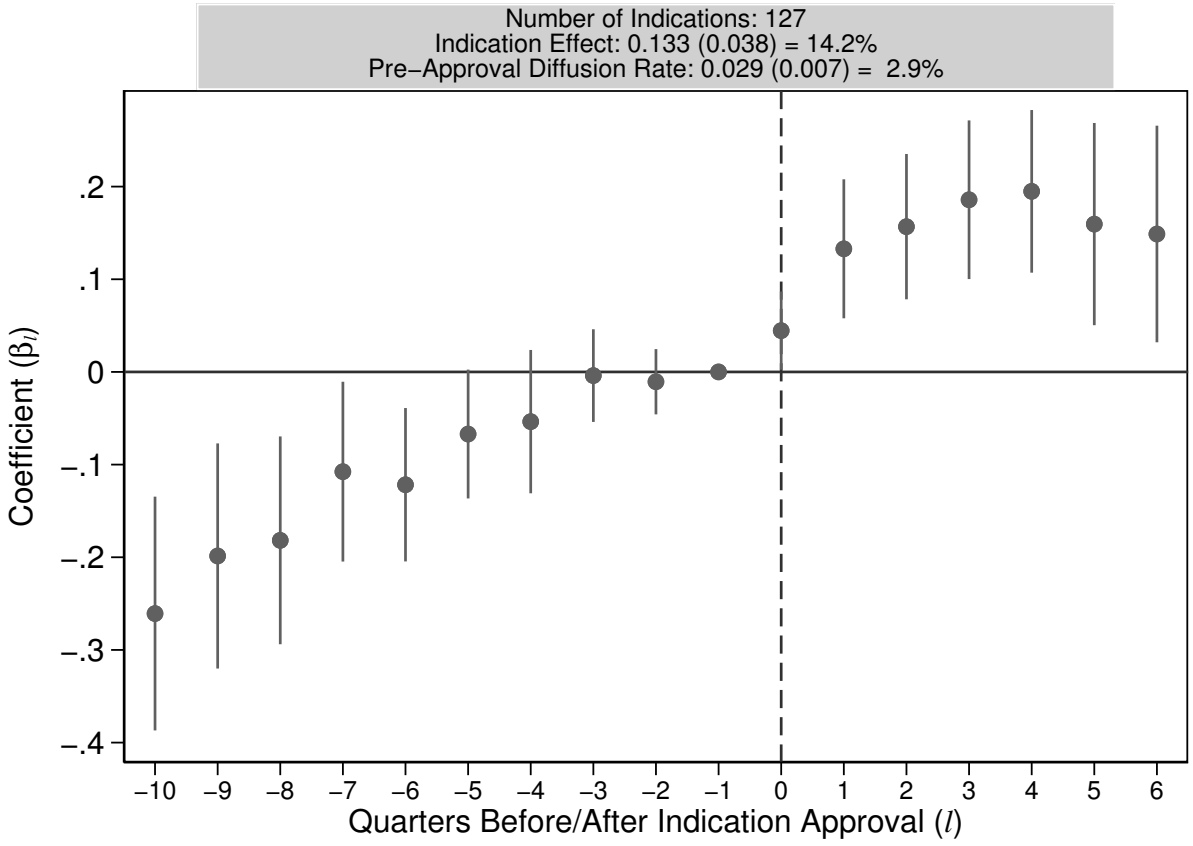
Figure VII: Diagnosis Share by Prior Authorization Share - New Diagnoses



Notes: Panel A reports the diagnosis share of prescriptions around indication approvals drugs with a low prior authorization (PA) share. Panel B, in contrast, reports the diagnosis share for drugs with a high prior authorization share. We include only indications for new diagnoses. The PA Share is equal to the fraction of beneficiaries enrolled in plans captured in the OptumLabs® Data Warehouse (OLDW) who were subject to prior authorization for a drug in the quarter prior to indication approval. We define a low PA share as falling below 0.5 and a high PA share as 0.5 or greater. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.

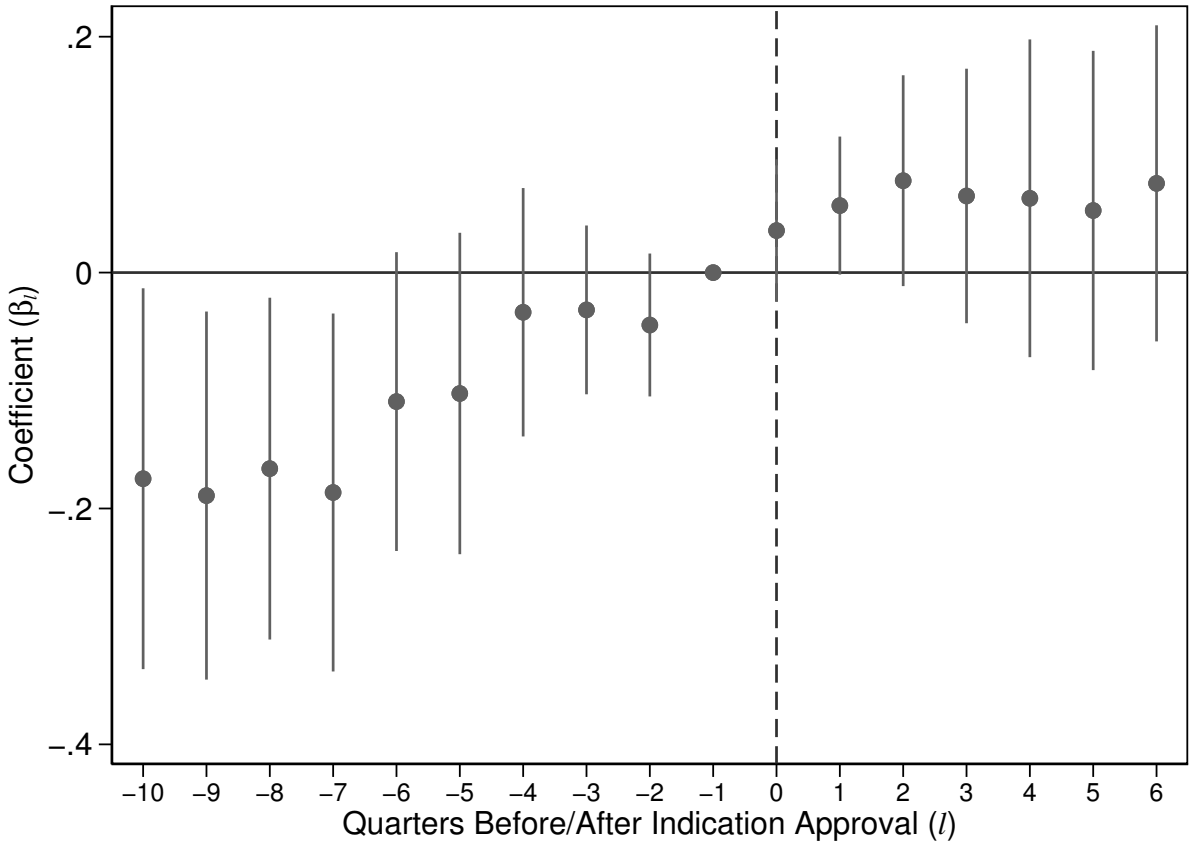
Appendix

Figure A.I: Log Prescribing Rate for Any Diagnosis



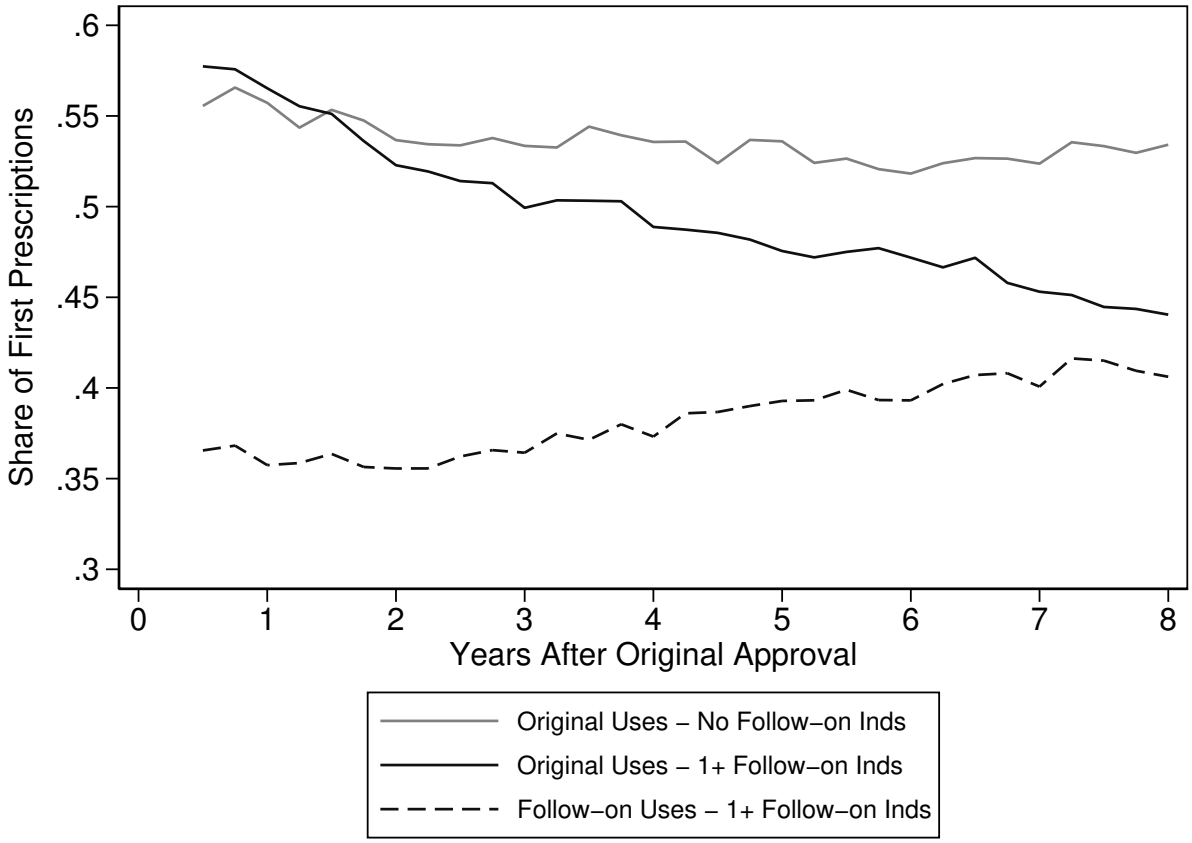
Notes: We report estimates using the log *any use* prescribing rate to measure utilization. Only indications for new diagnoses are included. The prescribing rate is measured as the number of prescriptions for any use as a fraction of the total number of beneficiaries in that quarter. If multiple indications were approved in the same quarter, we drop all but one from the sample. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.

Figure A.II: Prior Authorization or Step Therapy Prevalence



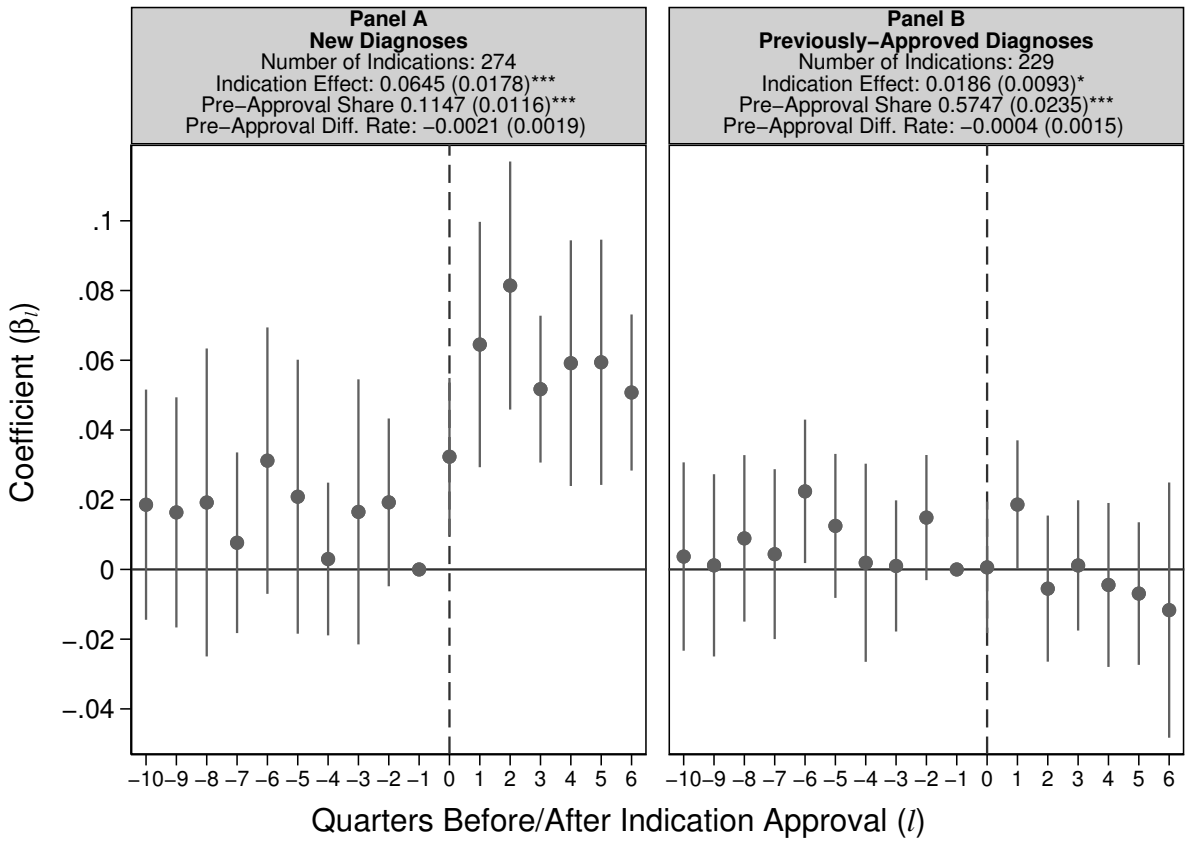
Notes: We report estimates using the prevalence of prior authorization or step therapy restrictions for a drug as the dependent variable. Only indications for new diagnoses are included. If multiple indications were approved in the same quarter, we drop all but one from the sample. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.

Figure A.III: Original Indication Diagnosis Share



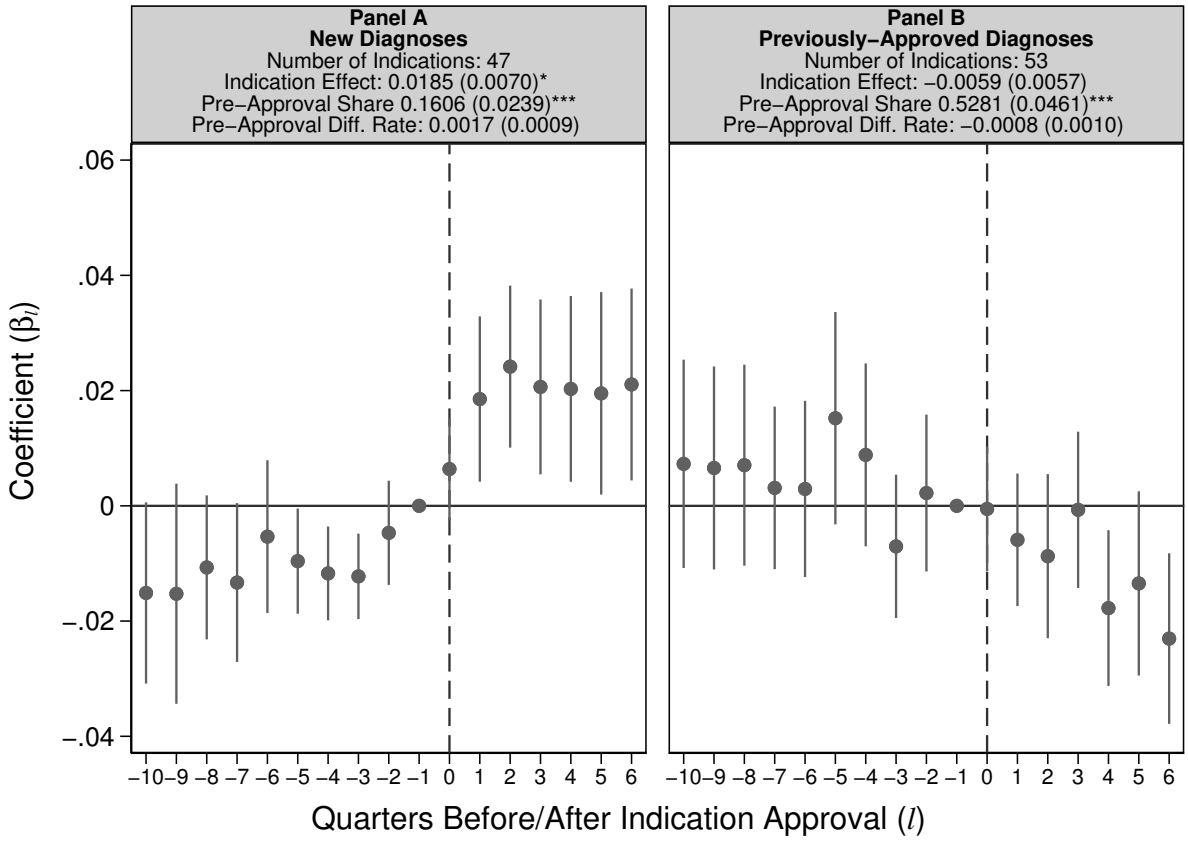
Notes: This figure depicts the share of first prescriptions accounted for by original and follow-on uses over the first 8 years of a drug's lifecycle. We split utilization into original and follow-on uses (indications) and calculate the share of individuals with diagnoses matching those indications. We additionally separately tabulate utilization for drugs with no follow-on indications at any time in our sample and drugs with at least one. We exclude flu medications and drugs with fewer than 11 initial prescriptions in any quarter beginning 2 quarters after approval. Shares do not add up to 1 because some individuals do not have diagnoses matching either original or follow-on uses and others have diagnoses that match both.

Figure A.IV: Diagnosis Share for New and Previously-Approved Diagnoses Unbalanced Panel



Notes: We report estimates of the same equations as Figure III, but with an unbalanced panel. Specifically, instead of dropping indications altogether if the drug's total utilization falls below 11 patients, we include those observations whenever they fall above the 11 patient threshold. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.

Figure A.V: Diagnosis Share for New and Previously-Approved Diagnoses Censored Cells Omitted



Notes: We report estimates of the same equations as Figure III, but dropping indications if any diagnosis share in the window is constructed using a numerator less than 11. Therefore we omit all censored observations. We include calendar year and quarter fixed effects and cluster standard errors at the drug level.