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ABSTRACT

Pharmaceutical innovation policy involves managing a tradeoff between high prices for new products in the short-term and stronger incentives to develop products for the future. Prior research has documented a causal relationship between market size and pharmaceutical research and development (R&D) activities. The existing literature, however, provides no evidence of how this relationship varies across markets. We investigate whether recent expansions in state Medicaid programs caused an increase in R&D. We find no evidence of a response, potentially a result of Medicaid's low reimbursement for pharmaceuticals, suggesting low(er) price markets may have different dynamics with respect to innovation policy.

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1. INTRODUCTION

The scientific knowledge generated when firms create new pharmaceutical products is largely a public good—i.e., absent non-market protections, much of this knowledge is non-rival and non-excludable. This leads to a fundamental "hold up" problem, in which, absent policy intervention, firms would be unwilling to make the large, upfront research and development (R&D) investments necessary for new product development. For this reason, governments use various forms of intellectual property protection to provide firms developing novel products with the temporary market power necessary to justify investments in innovation.

Optimal pharmaceutical innovation policy therefore involves managing a tradeoff between high prices for new products in the short-term and stronger incentives to develop new products for the future. When the social benefit of new products exceeds the deadweight loss resulting from monopoly prices charged in the product's early years on the market, this tradeoff is welfare enhancing. Therefore, understanding the degree to which expected economic returns impact the rate of development of new products is central to determining the optimal parameters of this policy tradeoff.

In a number of studies, economists have shown that firms' R&D investments and new product introductions are driven by expected returns (Acemoglu and Linn, 2004; Finkelstein, 2004; Blume-Kohout and Sood, 2013; Dubois et al., 2015; Dranove et al., 2020). With over 40 percent of the world market (and growing)[1], profits from the United States (U.S.) market are believed to play an outsized role in determining the level and nature of global pharmaceutical R&D investments. To the extent this is true, the existing literature primarily speaks to the magnitude of the innovative response to the decisions of U.S. commercial payers and Medicare.[2] As a corollary, if pharmaceutical firms largely respond to expected U.S. profits (either overall or those from a particular sector such as the commercial market), policymakers in other settings may have more freedom to constrain prices without impacting innovation. Unfortunately, empirical research to date says little about potential heterogeneity in pharmaceutical firms' innovative responses vis-à-vis different reimbursement systems. Yet, it is

[1] https://www.iqvia.com/insights/the-iqvia-institute/reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023
[2] While some studies examine changes in global disease burden (Dubois et al., 2015), these studies do not separate out the role of high potential American profits compared to profits earned elsewhere.

precisely these types of differences that will drive the welfare implications of market-specific drug pricing policy decisions.

As governments continue to refine pharmaceutical pricing policies and in the face of ongoing policy discussions in the United States, the question quickly becomes: which markets generate enough expected returns to impact marginal R&D investment decisions of pharmaceutical firms? Stated differently: if policymakers alter reimbursement rules in settings that have little effect on marginal investments in pharmaceutical innovation, they may have greater freedom to reduce prices from their current level without diminishing welfare (Lakdawalla, 2018). Importantly, this could be true not only across countries, but also across various segments of the U.S.'s multi-payer system.

We bridge the gap in the existing literature by examining the effect of the 2010 Patient Protection and Affordable Care Act's (ACA) Medicaid expansions on private sector investments in pharmaceutical R&D. The passage of the ACA caused a sudden and unanticipated increase in the expected market size for pharmaceuticals treating conditions afflicting individuals who would become newly eligible for Medicaid insurance coverage. We identify the ACA's causal effect on R&D investments by exploiting this variation in expected demand.

Across a variety of specifications, we find no evidence that greater anticipated demand from Medicaid expansions caused a change in R&D activities (i.e., clinical trials). This is true for both early stage investments (i.e., Phase I trials), later stage investments (i.e., Phase III trials), and for investments in new indications for existing drugs (i.e., trials for non-primary indications). These findings hold across a variety of measures of the demand shock caused by the ACA.

The absence of an observed effect of market expansion on innovation investments stands in contrast to the existing literature, which has repeatedly shown that R&D responds to changes in expected demand. Of particular relevance to our study, the creation of Medicare Part D (hereafter Part D), which provides prescription drug insurance to elderly Americans, was found to have a large impact on R&D investments for conditions afflicting the elderly (Blume-Kohout and Sood, 2013; Dranove et al., 2020). This raises an obvious question: what economic factors could cause this divergence in results?

The differences are unlikely to be based simply on the number of individuals affected by the policy change. While Medicare often garners the largest amount of national attention, Medicaid has grown from its modest origins to cover over 70 million Americans. This makes Medicaid larger than both Medicare and the British National Health Service (NHS, the world's eighth largest pharmaceutical market), and comparable in size to the statutorily insured population of Germany (the world's fourth largest pharmaceutical market).[3] In 2017, Medicaid spent approximately $29 billion on retail prescription drugs net of rebate—more than the entire NHS spent that same year on prescription drugs before rebates.

Part of Medicaid's formidable growth came from the ACA expansion, which made 12.7 million Americans newly eligible for Medicaid (Kaiser Family Foundation, 2019). This is more than the approximately 5 million individuals who received new coverage (after accounting for meaningful crowd-out) from the creation of Part D (Engelhart and Gruber, 2011). Perhaps more importantly, the increase in the number of new prescriptions filled because of these two insurance expansions was broadly similar. While more individuals received new coverage under the Medicaid expansion, the average Medicare recipient used more prescription drugs.[4]

While both program expansions resulted in a comparable increase in the number of prescriptions, a key difference between Part D and Medicaid is in how *prices* are determined under the two programs. Part D is a social insurance program run by private firms and subsidized by the government. These firms negotiate drug prices in a manner largely similar to the rest of the U.S. commercial market. Medicaid prices, however, are determined by strict regulations that reflect the U.S. government's choice to exert its economically meaningful buyer power. Specifically, federal law requires pharmaceutical firms to provide Medicaid with a flat rebate that ensures Medicaid pays a price *at least as low as* the lowest net price by to any private insurer. A second rebate further reduces prices paid when manufacturer list prices grow faster than inflation. Finally, state Medicaid agencies use additional hard and soft pressures to negotiate often substantial supplemental rebates (Dolan, 2019; Office of the Inspector

[3] https://www.iqvia.com/-/media/iqvia/pdfs/canada-location-site/top10worldwidesales_en_17.pdf
[4] See Appendix A for more information.

General, 2014). For products for which Medicaid is a large payer, the combination of these rules has been shown to have market-wide implications (Duggan and Scott Morton, 2006).

With these rebates, drug prices in Medicaid are often much lower than prices paid by any other commercial or federal insurer. For top selling drugs in 2017, the average net of rebate and subsidy price in Medicaid was 35% of the average net price in Medicare (CBO, 2021). For older drugs, inflation rebates can greatly reduce Medicaid prices further (Feng et al., 2020). This growth in the importance of inflation rebates also likely explains why a quarter of top selling drugs in 2017 had net Medicaid prices between zero and 5 percent of Medicare's net price.

The combination of its large overall program size and binding price controls means that, in many ways, Medicaid reimbursement is more similar to other developed markets with price controls (e.g., those in Canada and Europe) than to the U.S. commercial or Part D market. As a result, our estimates of the impact of Medicaid expansions on innovation activities may provide insight into how the policy decisions of a range of lower-reimbursing payers—such as those that are characteristic of other Organisation for Economic Co-operation and Development (OECD) countries—might (or might not) affect innovation incentives for pharmaceuticals.

Understanding heterogeneity in innovation response across markets is likely to be valuable given clear differences in how much pricing power different governments grant to branded pharmaceuticals.[5] The U.S. provides largely unfettered pricing power to pharmaceutical firms during the time a drug is covered by one or more types of market exclusivity. In contrast, other countries have prioritized lower prices for new drugs, primarily by using various forms of buyer power to curtail prices.[6] Yet while other developed countries have chosen policy regimes focused on lower prices relative to the United States, it does not necessarily follow that such policies reveal a willingness to accept decreased innovation. Rather, it could reflect these smaller markets recognizing they are largely inconsequential to the investment decisions of pharmaceutical firms and therefore policymakers realize they have more freedom to constrain prices without impacting innovative activity (Lakdawalla, 2018). It

[5] Branded pharmaceuticals are products covered by some form of intellectual property protection.
[6] Such policies include explicit price controls, reference pricing, cost-benefit analyses, and government-supported coalitions of buyers empowered to walk away in the face of high prices relative to clinical value (Paris and Belloni, 2013; Stern et al., 2019).

could also simply reflect the fact that global innovation incentives are not as price elastic as estimates from settings that include the U.S. commercial and/or Part D markets.

Our results provide support for the argument that lower-reimbursing insurers may have more freedom to increase access without impacting innovation incentives. Vis-à-vis the existing literature, they also accord with the common contention that higher-reimbursing markets such as those characterized by many U.S. payers play an outsized role in driving the investment decisions of pharmaceutical firms.

2. The ACA Medicaid Expansion

The passage of the ACA in March 2010 launched the largest U.S. expansion of health insurance coverage since the creation of Medicare and Medicaid (Dranove et al., 2016). Additionally, it changed the very nature of U.S. social health insurance. Traditionally, Medicaid covered only low-income persons that also fell into distinct eligibility categories – members of families with children, pregnant women, and persons with disabilities. While eligibility rules have historically varied by state and expansions and contractions in coverage have occurred over time, low-income individuals who did not fit into one of these categories, such as those who were both non-disabled and childless, largely did not qualify for Medicaid, regardless of income (Finkelstein et al., 2012; Baicker et al., 2013; Garthwaite et al., 2014). The ACA provided federal financing for states to expand Medicaid coverage to non-elderly adults earning less than 138 percent of the federal poverty level (FPL). Following the ACA, residents living in states that chose to expand Medicaid programs could gain access to health insurance based solely on income.[7] Estimates suggest that over 12 million Americans gained new Medicaid access through these expansions (Kaiser Family Foundation, 2019).

3. Data

To identify the expected demand shock from the ACA, we use data from the 2007-2010 Medical Expenditure Panel Survey (MEPS) to estimate the prevalence of different medical conditions. This

[7] Following a 2012 Supreme Court decision, states were given the option of implementing the reform. In 2014, 27 states plus the District of Columbia (D.C.) adopted the expansion, a number that has grown to 37 states.

provides an *ex-ante* (i.e., pre-ACA) measure of demand for pharmaceuticals in the newly-eligible Medicaid population. The MEPS is a publicly available, nationally representative survey of the U.S. civilian non-institutionalized population. It contains information on health insurance status, demographics, medical conditions, and prescription drug use.[8]

We use the MEPS data to identify medical conditions for which pharmaceutical firms would have anticipated demand increases following the ACA's passage. Many newly eligible enrollees did not have access to prescription drug coverage prior to the expansion and therefore their prior use of pharmaceuticals may not reflect the demand associated with insurance. This is particularly true for drugs that are either very expensive or for conditions where treatment may be more discretionary. Therefore, we our primary measure of expected demand focuses on the prevalence of medical conditions reported in the MEPS rather than pharmaceutical utilization.

We develop an additional measure of the expected demand shock using Medicaid State Drug Utilization Data from 2004-2013 to identify changes in drug spending for three states (California, Connecticut, and Massachusetts) that expanded their Medicaid programs prior to 2014. For every National Drug Code (NDC), we observe quarterly utilization and (pre-rebate) spending in all 50 state programs.[9] We link these data to detailed information on drug products and their typical uses from four databases employed by professional pharmacists.[10] By combining data on utilization and spending with information on typical use, we analyze the conditions that experienced the largest drug spending increases in ACA Medicaid expansion states. Appendix B provides more detail on these data.

Our final data source, the Clarivate Analytics *Cortellis Competitive Intelligence* database (Cortellis), provides detailed data on pharmaceutical R&D activities. In the Cortellis data, we identify all U.S. clinical trials that began between 2004-2016 (totaling almost 58,000 clinical trials in this period), which can be used to estimate pharmaceutical innovation activities by disease area.[11] Cortellis assembles data on drug candidates from public records including company documents, press releases, financial listings, clinical trial registries, publications, and FDA submissions. From 2005 onwards, our data contain

[8] For more information, see https://www.meps.ahrq.gov/mepsweb/about_meps/survey_back.jsp
[9] We aggregate NDC codes by active ingredient to simplify analysis. Data on active ingredients comes from Drugs@FDA.
[10] Importantly, these databases include both approved and "off-label" uses for each drug in our sample.
[11] We restrict our focus to U.S.-based clinical trials since manufacturers pursuing U.S. regulatory approval typically conduct one or more U.S.-based clinical trials as part of an FDA submission.

the near universe of drugs that entered clinical trials.[12] Since the dataset covers all known registered and published trials, our analysis captures several stages of the drug development process.

4. Conceptual Framework

To date, the literature on how firms respond to pharmaceutical demand shocks has largely focused on identifying the presence and magnitude of the (causal) relationship between expected profits and investments in drug development. This focus has produced evidence of a consistent connection between future returns and various measures of R&D activity (Acemoglu and Linn, 2004; Finkelstein, 2004; Blume-Kohut and Sood, 2013; Dubois et al., 2015; Dranove et al., 2020). However, there has been little focus on whether markets with different reimbursement characteristics (i.e., those with lower prices) demonstrate variation in the presence or magnitude of this R&D response. Given each market (or payer in a multi-payer system) must determine its respective pricing policy, understanding the degree to which such decisions impact R&D investments is important for understanding the implications of market policies.

It is often asserted that the U.S. market drives the majority of pharmaceutical innovation (Carroll and Frakt, 2017; Easton, 2018; Goldman and Lakdawalla, 2018). Civan and Maloney (2009) provide initial descriptive evidence that supports this oft-stated belief. These authors document an association between investments in drug development and diseases which are more prevalent in the U.S. population. However, this descriptive work falls short of establishing a causal relationship between market size and R&D investment. Estimating this causal relationship requires identifying an economically meaningful demand shock that is isolated to markets whose fundamental economics differ from those that have been previously studied. For two reasons, the ACA's Medicaid expansions present a useful empirical setting to make progress on this question.

First, the ACA expansion was expected to increase pharmaceutical demand from individuals with a particular and *ex-ante* knowable set of conditions. This allows us to identify the subset of R&D investments most likely to be affected by the demand shock. Given the passage of the ACA was largely

[12] Starting in 2005, sponsors were required to register trials to an approved clinical trial registry prior to patient enrollment in order to be considered for publication in any International Committee of Medical Journal Editors journals (See De Angelis et al., 2004). See Chandra et al., 2018 for more information.

uncertain and unexpected (and as such, in the years prior to its passage, firms did not have enough information to make anticipatory investments), post-ACA changes in R&D for conditions prevalent among the newly-eligible population (compared to those that were less affected, such as conditions primarily seen among senior citizens) can reasonably be interpreted as a causal effect of ACA expansions.

Second, while located in the U.S., the Medicaid program's reimbursement policies for prescription drugs bear little resemblance to other parts of the U.S. pharmaceutical market that are commonly believed to drive investments in innovation. Unlike private insurers or Part D, state Medicaid programs benefit from a series of explicit and implicit pharmaceutical price controls. Due to federal regulations, Medicaid programs pay prices *at least as low as* any commercial insurer in the market. In addition to this statutory guarantee, state Medicaid agencies operate under increasing budgetary pressure, which is expected to continue to increase demands for additional price concessions in the form of supplemental rebates. This combination of explicit and implicit price controls renders Medicaid more similar to the lower-reimbursing markets of other developed countries than it is to the rest of the U.S. market. Theoretically, this feature of Medicaid should dampen the innovative response to any program expansions *relative* to what would be expected from a similarly sized increase in covered lives in more generously-reimbursing insurance programs such as Part D. Depending on the cost structure of private pharmaceutical firms (in particular the fixed costs of developing a new product) and the distribution of potential development projects, anticipated change in sales volumes and associated revenues from Medicaid could be below the level that is relevant to the marginal clinical trial investment decision.

There could be a concern that other features of the ACA limited the magnitude of the expected demand shock. Specifically, in addition to expanding coverage, the ACA increased the minimum rebate pharmaceutical manufacturers were required to give to state Medicaid agencies. If this higher minimum rebate increased overall rebates, this could outweigh the expected increase in revenues from the program's expansion.[13] However, actual changes to average rebates post-ACA were minimal and

[13] An increase in overall rebates is a function of how many products were expected to be subject to the minimum rebate requirement versus Medicaid's "best price" rebate.

net-rebate pharmaceutical prices continued to grow between 2010 and 2018 (Feng et al., 2020). This implies that even after accounting for the effect of the minimum rebates, the observed increases in total Medicaid drug utilization resulting from ACA expansion (shown in Appendix C) caused an increase in pharmaceutical revenue. Furthermore, given the largely mechanical nature of the Medicaid rebate requirements, even relatively unsophisticated firms had the ability to predict *ex ante* the likely change in average rebates based on the ACA.

In considering the nature of potential changes in R&D activity, it is also important to recognize how the impact of policy changes may vary across stages of clinical development. Firms move products through the clinical development and regulatory approval processes in phases. At any point in time, firms likely have a number of products in development that have already cleared early-stage trials (Phase I or Phase II trials) but did not have sufficiently compelling results and/or expected demand to justify a subsequent (Phase III) investment. For such products, relatively small changes in expected future demand could change the anticipated return to additional investments from negative to positive. If this were the case, we might see a change in investments in later-stages (e.g., Phase III trials) without any new activity in earlier stages.

Similarly, firms may have knowledge about additional indications that could be pursued for their existing (marketed or in-development) products. While prescriptions can be written for conditions that are not approved by the FDA, firms face meaningful restrictions on marketing and reimbursement for such "off label" use. Firms can apply for an extension of their existing label but must fund clinical trials to demonstrate efficacy for new indications. This decision is driven by expected returns (Berger et al, 2021). Thus, a change in expected market size could also lead firms to pursue new clinical trials for additional indications.[14]

[14] The welfare implications of such investments are unclear. See Bagley et al. (2018) for a discussion of this in the context of the orphan drug market.

5. ESTIMATION

5.1 PRIMARY MEASURE OF DEMAND SHOCK

Given the passage of time, we can now observe how disease-specific demand of newly eligible Medicaid patients changed as a result of the ACA's Medicaid expansions.[15] However, this *ex-post* observation likely does not accurately represent the information available to firms making investment decisions immediately in the wake of the ACA's passage. Therefore, we develop a measure of *expected* demand based on the known disease burden of individuals made newly eligible for Medicaid under the ACA.

Estimating the size of the demand shock requires correctly identifying the newly-eligible population, a population meaningfully different than those previously eligible. The movement away from categorical eligibility means conditions prevalent in the historical Medicaid population may not be reflected in the new eligible population. Therefore, our preferred method of estimating demand uses data from the 2007-2010 MEPS on the disease burden of individuals who would gain new Medicaid eligibility as a result of the ACA. These are individuals who were uninsured for at least part of the year and earned less than 138 percent of the FPL.

Under this definition, we estimate the ACA would have increased the size of the eligible Medicaid population by 18 million individuals. Considering that 12.7 million individuals eventually gained new access to Medicaid (despite many states choosing not to expand their Medicaid programs), this estimate is broadly consistent with what has been documented elsewhere and what was likely expected by firms as they made decisions about forward-looking R&D investments. In Appendix E, we present our findings using alternative definition of the demand shock, one of which includes individuals eligible for ACA nongroup coverage expansions.[16]

There are two ways to calculate the Medicaid market share (MMS) to capture demand. The first calculates demand as a relative measure, in which it is represented as the share of those with a given disease that are newly covered. This provides some sense of a social insurer's impact on that

[15] Appendix C details this approach.
[16] Our upper and lower bound definitions detailed in Appendix E give estimates of 14.6 and 48.3 million individuals respectively.

disease, but little evidence about the expected return (or changes in the return) from a product targeting that condition. Therefore, we prefer the second definition of MMS, which focuses on the percentage of the overall U.S. population that both has a condition and gained new coverage as a result of Medicaid expansions. Given that firms care about absolute, rather than relative market opportunities, this measure is likely to be more relevant to their investment decisions.[17]

Figure 1 shows the distribution of our preferred MMS measure. We focus on International Classification of Diseases (ICD)-9 Sub-Chapters, which group ICD-9 three-digit codes into smaller categories that are more representative of the R&D decisions firms face.[18] Appendix Figure D1 shows the distribution of MMS across ICD-9 subchapters.

5.2. Alternate Measure of Demand

To address potential concerns that measures generated from public data are inferior to information about expected demand that sophisticated firms would have possessed, we also generate a measure of demand based on the *realized* change in the use of drugs following early Medicaid expansions. While firms clearly did not have access to this *ex-post* measure in 2010, the observed changes could potentially more accurately reflect other types of proprietary estimates to which firms had access. In addition, early expansions provided market information during a time period that could reasonably impact trial decision in our data.

To generate this alternate measure, we focus on three states that expanded Medicaid prior to 2014: California, Connecticut, and Massachusetts.[19] To calculate realized demand for pharmaceuticals across conditions, we combine total drug spending on active ingredients in early expansion states and other states within the relevant Census Division in the year prior to and following expansion in the

[17] Estimating the negative binomial model in this paper with condition fixed effects should generate qualitatively similar results for each condition. Appendix F presents results using the first definition, the share of individuals with a disease that were made newly eligible by the expansion, for completeness. The results are remarkably similar across both definitions.

[18] For instance, while Endocrine Diseases, Nutritional and Metabolic Diseases, and Immunity Disorders are all part of ICD-9 Chapter 3, the Sub-Chapters break these diseases into four distinct categories: Diseases of the Thyroid Gland, Diseases of other Endocrine Glands, Nutritional Deficiencies, and Other Metabolic Disorders and Immunity Disorders.

[19] We focus on these three early expansion states because a large literature has documented these expansions increased Medicaid coverage and evaluated their effect on care utilization, health, and providers (Kolstad and Kowalski, 2012; Sommers et al., 2014; Golberstein and Gonzales, 2015; Nikpay et al., 2015; Sommers et al., 2016).

Medicaid State Drug and Utilization Data.[20] We allocate drug spending to associated conditions in the year prior to and following expansion and calculate the relative increase in spending on these products. The difference between these ratios represents the growth in drug spending for that condition resulting from Medicaid expansion. To isolate conditions with high vs. low demand in in the newly-eligible Medicaid population, we divide conditions into the top vs. bottom three quartiles by growth in drug spending.[21]

5.3. Estimating Changes in Clinical Trial Activity

Since our outcome data are primarily count-based measures of clinical trials, we estimate a negative binomial specification.[22] Specifically, we model whether increases in expected pharmaceutical demand increased clinical trial activity by running the following regression for each condition in the MEPS:

$$Trials_{it} = f\left(\alpha + \sum_{t=2004}^{2016} \beta_t * MMS_i * 1(year = t)_{it} + \lambda_t + \eta_i\right)$$

Where $Trials_{it}$ measures the number of trials for condition *i* in year *t*. MMS_i is the demand for drugs treating condition *i* in the newly-eligible population, λ_t are year fixed effects, and η_i are condition fixed effects.

The coefficients of interest, β_t, measure how a 1 percentage point higher MMS_i for a condition impacts the number of trials conducted for potential drugs intended to treat that condition. The year prior to the ACA's passage, 2009, serves as the omitted category. Coefficients from this negative binomial model can be interpreted as the change in log trials. Using an event study specification allows us to examine both pre-trends in the data as well as the time path of the change in clinical trial activity after the passage of the ACA.

[20] For each expansion, we focus on drugs that together account for 95% of total drug spending two years prior to expansion. The remaining 5% of spending consists of a large number of low-volume drugs.
[21] Appendix Table D1 lists these conditions.
[22] In the case of count data such as ours, a negative binomial is better suited to the data-generating process than an ordinary least squares (OLS) model. We determined we do not need to use a zero-inflated negative binomial, as 90 percent of our observations are for conditions with at least one trial overall.

6. Effect of Medicaid Expansion on Clinical Trial Activity

We begin by graphically examining clinical trial activity over time. Figure 2 presents the share of trials per year in each clinical trial phase targeting conditions above the median MMS. There is no clear difference in the pattern of clinical trial investments in this category. For example, the first panel of Figure 2 contains the share of Phase I trials by category and shows a largely stable distribution of clinical trials targeting conditions above the median measure of the demand shock variable. This is true whether we consider trials for primary indications or for secondary indications that could expand the set of conditions on a drug's FDA label.[23] We also observe stability over time in shares of both Phase II and Phase III trials.

Since the decision to move forward with drug development involves a large and fixed investment, it is possible pharmaceutical firms only respond to the largest demand shocks. Thus, Figure 2 also includes a measure of clinical trials for conditions in the top quartile of the demand shock variable. Again, there is no observable change in clinical trial activity resulting from the passage of the ACA for even those drugs targeting the conditions most affected by the expansion. This is true across all phases and for both primary and secondary conditions.

While there is little graphical evidence of a change in clinical trial activity, there could still be a response that is not visually apparent. To account for that possibility, Figure 3 presents the event study coefficients from the negative binomial model described above. The figure contains the estimated coefficient on the interaction between the MMS demand shock variable and a series of indicator variables for each year. Prior to the passage of the ACA, the event study coefficients are flat and close to zero and they remain so following the passage of the ACA.

Table 1 contains the estimates from a model that collapses all of the post-expansion variables into a single indicator variable. Given that the R&D spending for each stage of development is meaningfully different, heterogeneity in the clinical trial response across phases may be obscured. To account for this, negative binomial results are presented for both the entire sample and for each clinical

[23] If anything, in the upper right panel of Figure 2, it would appear that phase I trial activity is increasing in those diseases with the smallest increases in Medicaid demand and slightly decreasing in diseases where the greatest increases in Medicaid demand were observed.

development phase. Regardless of the phase of development, there is no evidence of any change in clinical trial activity in response to the demand shock from the ACA's Medicaid expansions.

6.1 Estimates Using Alternative Measures of Demand Shocks

The evidence using our preferred *ex-ante* measure of the ACA-driven demand shock demonstrates no change in clinical trial investments related to the increase in the number of potential insured customers. However, it is possible this could be the result of our preferred estimate of the demand shock ineffectively measuring the change in firm expectations about future profits. Therefore, we next present results where the change in expected demand is estimated using the *ex-post* utilization of pharmaceuticals by newly insured patients in early expansion states. While firms could not directly observe this change in the actual use of drugs when making their investment decisions, it is possible that sophisticated firms had a better understanding of which conditions would likely see more demand than could have been seen in the MEPS.[24] For this specification, we estimate the change in clinical trial activity based on a binary variable for whether a condition, *i,* is in the top quartile of the change in spending as a result of the earlier expansion:

$$Trials_{it} = f\left(\alpha + \sum_{t=2004}^{2016} \beta_t * TopQuartile_i * 1(year = t)_{it} + \lambda_t + \eta_i\right)$$

Where $Trials_{it}$ measures the number of trials for condition *i* in year *t*. $TopQuartile_i$ indicates whether the condition was in the top quartile of conditions with increased spending due to early Medicaid expansion in the state, λ_t are year fixed effects, and η_i are condition fixed effects.

Figure 4 plots the event study coefficients for the change in clinical trials for conditions based on whether they are in the bottom three quartiles vs. top quartile for early expansions in California, Connecticut, and Massachusetts. Again, there is no statistically significant or consistent evidence of an increase in trials targeting the top quartile of conditions, as observed in these states.

[24] It is also possible firms may respond to changes in market share rather than the absolute shock. Given firm investment decisions represent an attempt to have a positive return on a fixed cost investment, we do not believe this is the case. For completeness, Appendix F presents results for this definition. Using this alternative definition does not produce different results. While we see a significant effect for one outcome in Table F1, that result is driven by trials targeting malignant neoplasms. Such conditions are in the bottom quartile of market share.

7. Discussion and Conclusion

Across a variety of specifications and stages of clinical development, we find no evidence that ACA Medicaid expansions changed the pattern of private sector investments in R&D for new pharmaceutical products. This lack of effect emerges persistently and robustly, despite the fact that this expansion represented a large increase in the number of U.S. patients with health insurance, associated with several billion dollars more in annual revenues for pharmaceutical firms (MACPAC, 2016).

The lack of a response to such a change in demand stands in stark contrast to the existing health care economics literature, which has consistently found increases in both R&D activity and new product introductions in response to greater expected demand for pharmaceuticals. Our findings demonstrate that R&D activity does not respond to demand changes in all markets. While Medicaid represents a large market in terms of the number of covered individuals, explicit and implicit government price controls decrease the potential returns for products used by patients in this system, similar to pharmaceutical markets in other developed countries. As such, the lack of a detectable effect of Medicaid expansions on innovation activity provides some insight into the degree to which revenues earned in lower reimbursing markets drive—or more accurately fail to drive—investments in pharmaceutical development.

Given various types of price controls in most OECD markets, an interpretation of our results is that the revenues earned in low-reimbursing markets might have little impact on R&D investments at the margin. As a corollary, policymakers in these markets (both Medicaid and in other developed countries) likely have more ability to constrain prices without decreasing the current global rate of pharmaceutical innovation.

However, it is important to note that to the extent this is true, this relative freedom is likely driven by 1) sustained high levels of reimbursement by other U.S. payers and 2) previous policy decisions to exert price controls in Medicaid that drove market returns below the level that would impact the marginal R&D investment by pharmaceutical firms.

Policymakers setting prices in non-U.S. markets may still face decreased access to medicines from firms being unwilling to sell existing products at lower prices.[25] However, given the relatively low marginal costs of production, there likely exists a set of low(er) prices that would still be profitable for firms that have already laid out R&D costs. Additional research is necessary to understand implications for R&D in a world where additional payers reduce prices from current levels.

[25] For example, Vertex refused to provide its cystic fibrosis products to the United Kingdom for many years.

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Which Markets (Don't) Drive Pharmaceutical Innovation? Evidence from U.S. Medicaid Expansions

By Craig Garthwaite, Rebecca M. Sachs, Ariel D. Stern

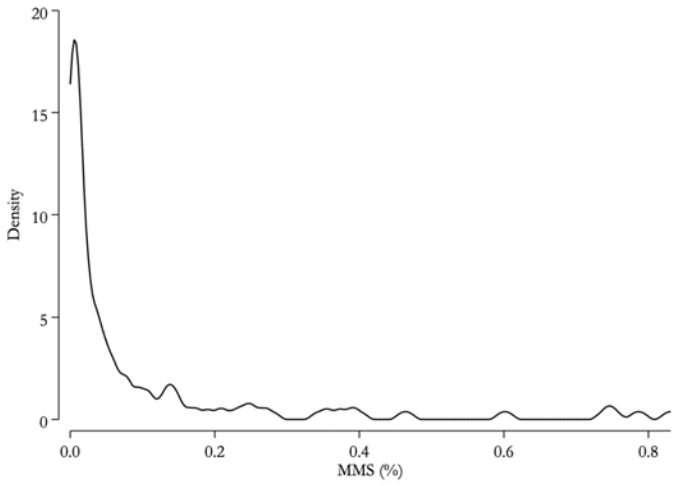

Figure 1. Kernel Density of Newly-Eligible Medicaid Market Share (MMS) Across Conditions 2007 - 2010

Note: This figure demonstrates that there is substantial variation in demand for pharmaceuticals treating different conditions in the newly-eligible Medicaid population. It specifically plots the kernel density of our demand measure among the newly-eligible (MMS) for conditions at the ICD-9 Sub-Chapter level. MMS is defined as the share of the total US population that both has a condition and was expected to gain coverage due to ACA Medicaid expansion. Estimates of MMS are derived from the 2007-2010 MEPS for individuals in the Northeast, West, and Midwest Census Divisions.

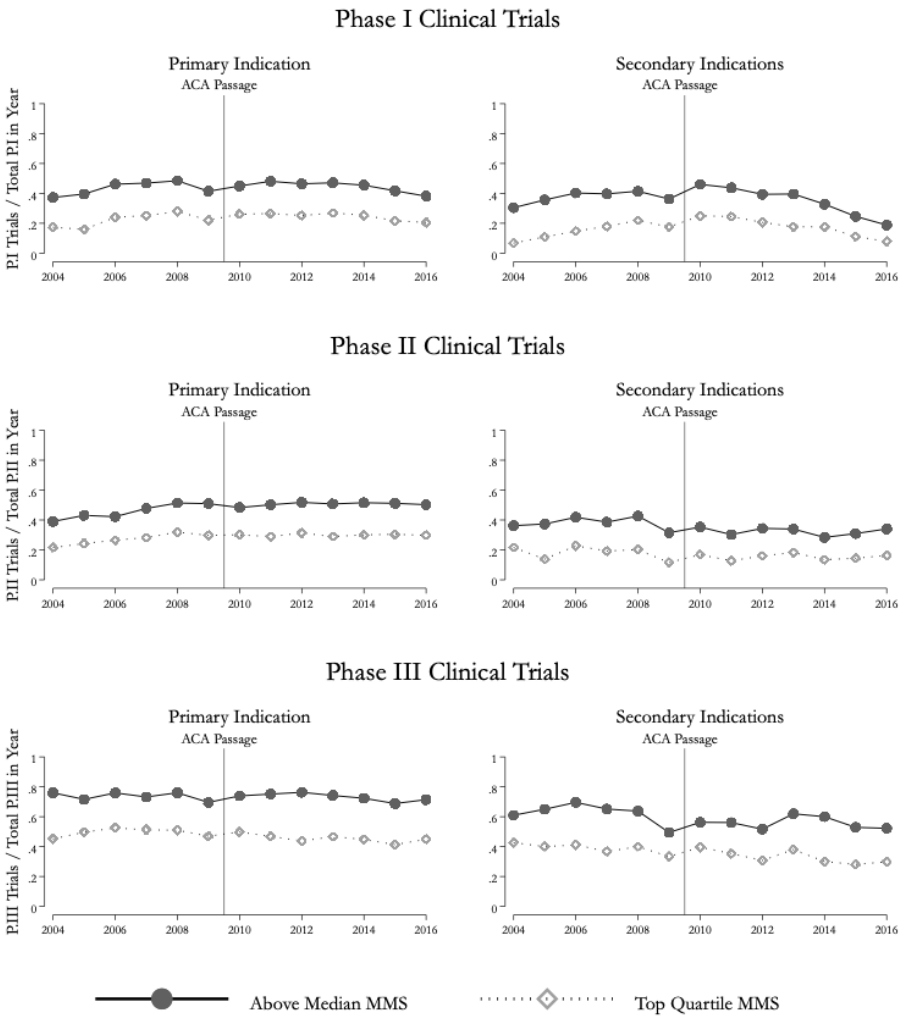

Figure 2. Share of Trials with Above Median Newly-Eligible Medicaid Market Share (MMS)

Note: This figure plots clinical trial activity over time. It shows the share of Phase I, II, and III trials with primary or secondary indications targeting conditions with high Medicaid Market Share (MMS). The figure provides no graphical evidence that clinical trials targeting conditions with high demand among the newly-eligible (i.e. high MMS) increased following the ACA's passage. MMS is defined as the share of the total US population that has a condition and was expected to gain coverage due to ACA Medicaid expansion. MMS is calculated at ICD-9 Subchapter level. Clinical trial activity is shown for conditions with MMS above the median or in the top quartile of all conditions. All data on MMS comes from 2007-2010 panels of the MEPS for individuals living in the Northeast, West, and Midwest Census Divisions. Data on the universe of clinical trials, along with information on trial phase and indications come from Clarivate Analytics Cortellis Competitive Intelligence Database (Cortellis). The sample of clinical trials is limited to U.S.- based trials between 2004 and 2016 with at least one reported indication.

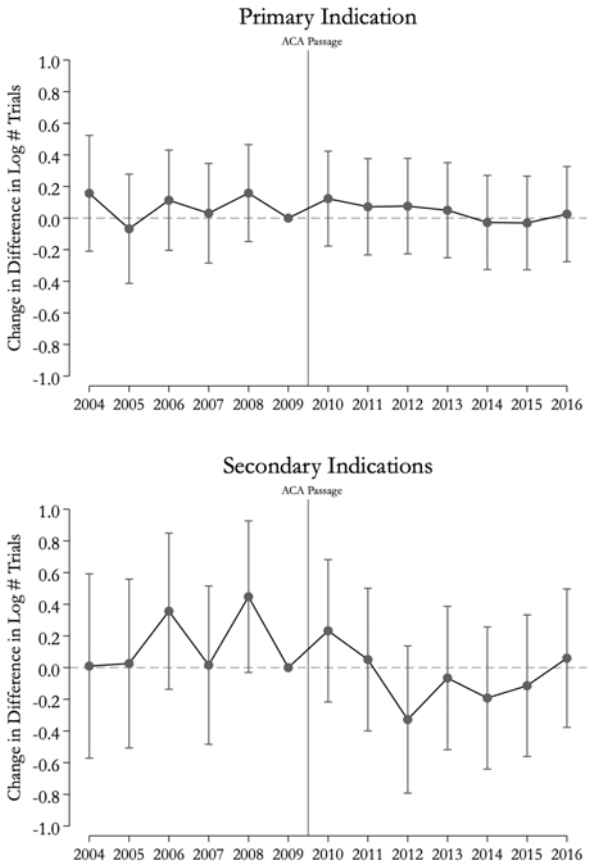

Figure 3. Trends in Total Clinical Trials for One Percentage Point Higher Newly-Eligible Medicaid Market Share (MMS)

Note: This figure plots event negative binomial event study estimates for the effect of a one percentage point higher newly-eligible Medicaid Market Share (MMS) on clinical trials in the years surrounding the passage of the ACA. The outcome is the total clinical trials per condition. The points are regression coefficients from a negative binomial specification with calendar year and condition fixed effects. All effects are plotted as changes relative to the year before ACA passage (2009). The top chart contains the total number of of trials with primary indication for a condition and the bottom chart contains the total number of trials with a secondary indication for a condition. The figure provides no graphical evidence that clinical trials targeting conditions with higher MMS increased following the ACA's passage. MMS is defined as the share of the total U.S. population that has a condition and was expected to gain coverage due to ACA Medicaid expansion. The MMS ranges between 0.00% and 0.79%, so a one percentage point change is a unit of magnitude higher than we see in our data. The average number of total trials with a primary indication for a given condition over the whole 13 year period is 37.85. The average number of total trials with at least one secondary indication for a given condition is 12.85. Estimates of MMS are derived from the 2007-2010 MEPS for individuals in the Northeast, West, and Midwest Census Divisions. Data on clinical trials comes from Cortellis and includes all U.S.-based trials with at least one reported indication.

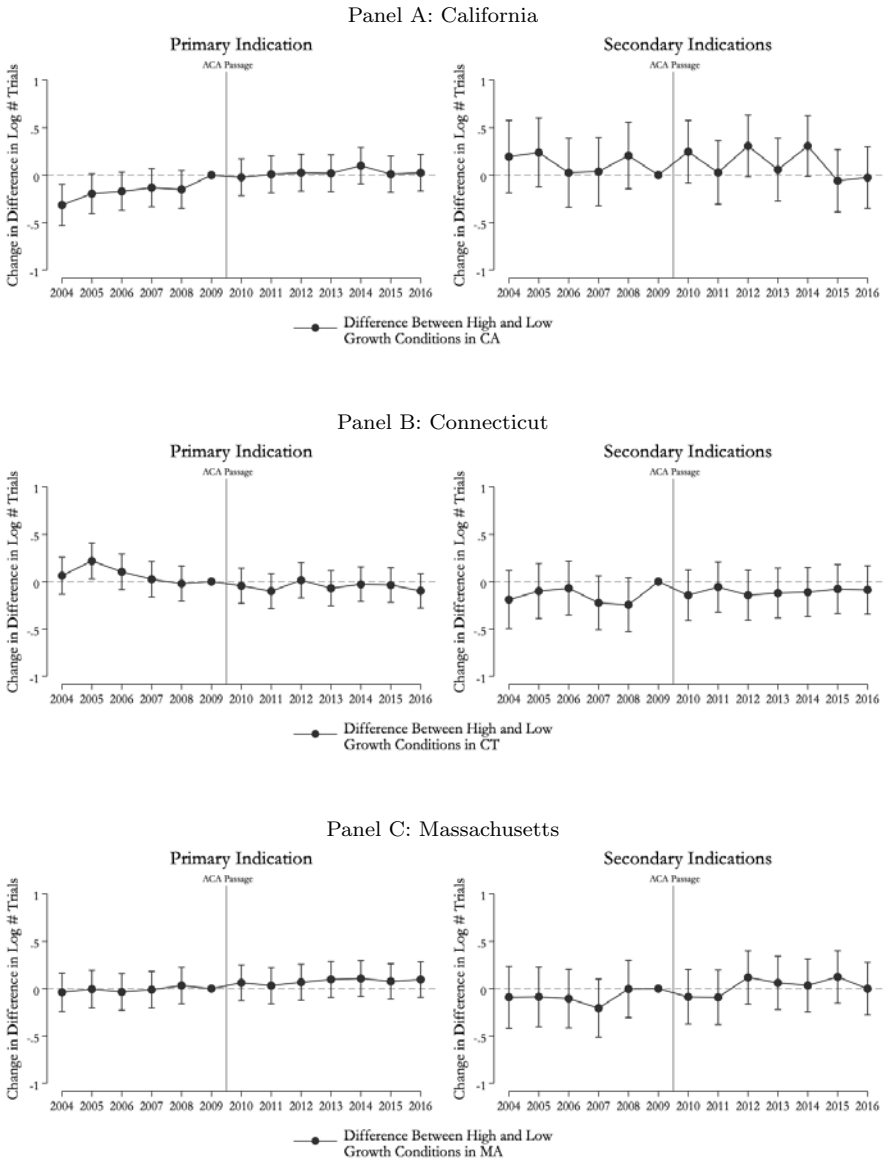

Figure 4. Comparing Clinical Trials Targeting Conditions with Large and Small Changes in Medicaid Spending Under Early State Medicaid Expansions

Note: This figure plots the event study coefficients for the change in clinical trials for conditions based on whether they are in the bottom three quartiles or top quartile of spending growth among Medicaid beneficiaries in early expansion states (CA, CT, MA). There is no statistically significant or consistent increase in trials targeting the conditions with high expected demand among the newly-eligible. The regression uses a negative binomial specification to estimate the change in clinical trial activity based on a binary variable for whether a condition is in the top quartile of Medicaid spending growth following early state Medicaid expansions. Conditions in the top quartile of spending in early expansion states are identified by comparing ex-post utilization of pharmaceuticals by Medicaid beneficiaries in CA, CT, and MA and surrounding control states following early Medicaid expansions. Medicaid pharmaceutical product expenditures come from the Medicaid State Drug Utilization Data and pharmaceutical products are linked to conditions using databases employed by professional pharmacists (See Appendix B). Data on clinical trial activity comes from Cortellis and includes all U.S.-based trials with at least one reported indication.

Table 1—Difference-in-Differences Estimates of Clinical Trial Activity

	P. I Trials	
	Primary Indication	Secondary Indications
Post 2009	0.866***	1.241***
	(0.071)	(0.124)
Post 2009 × MMS	0.109	0.152
	(0.115)	(0.203)
Observations	1274	1274

Standard errors in parentheses

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

	P. II Trials	
	Primary Indication	Secondary Indications
Post 2009	0.565***	0.988***
	(0.057)	(0.084)
Post 2009 × MMS	0.168	-0.154
	(0.092)	(0.149)
Observations	1274	1274

Standard errors in parentheses

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

	P. III Trials	
	Primary Indication	Secondary Indications
Post 2009	0.212**	0.354**
	(0.076)	(0.126)
Post 2009 × MMS	-0.280*	-0.317
	(0.119)	(0.204)
Observations	1274	1274

Standard errors in parentheses

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

Note: This table contains estimates from a negative binomial difference-in-differences specification for the effect of a 1 percentage point higher newly-eligible Medicaid Market Share (MMS) on innovation post-ACA passage. Since responses to Medicaid Expansion may vary across clinical trial stage, Phase I, Phase II, and Phase III trials are presented in separate panels. The first column contains the total number of trials with primary indication for a condition and the second column contains the total number of trials with a secondary indication for a condition. Regardless of the phase of development, there is no detectable change in clinical trial activity in response to the demand shock from the ACA's Medicaid expansions. The MMS ranges between 0.00% and 0.79%, so a 1 percentage point change is a unit of magnitude higher than we see in our data. The outcome is the total trials per condition. The average number of total trials with a primary indication for a given condition over the whole 13 year period is 37.85. The average number of total trials with at least one secondary indication for a given condition is 12.85. Estimates of MMS are derived from the 2007-2010 MEPS for individuals in the Northeast, West, and Midwest Census Divisions. Data on clinical trials comes from Cortellis and includes all U.S.-based trials with at least one reported indication.

APPENDICES

Which Markets (Don't) Drive Pharmaceutical Innovation? Evidence from U.S. Medicaid Expansions

By Craig Garthwaite, Rebecca M. Sachs, Ariel D. Stern

Appendix A: Comparing the ACA's Medicaid Expansion to Medicare Part D Expansion

The ACA's Medicaid Expansions and Prescription Drug Utilization

Several studies have examined the relationship between Medicaid expansions under the ACA and prescription drug utilization. Research by Mulcahy et al. (2016) suggests that gaining insurance through ACA Medicaid expansions had a larger effect on prescription drug utilization than gaining coverage through other insurers: individuals transitioning from no insurance to Medicaid increased their drug utilization at a threefold higher rate than individuals transitioning from no insurance to private coverage.

Other studies directly compare utilization increases between expansion and non-expansion states. Using data from a nationally representative prescription drug transaction database, Ghosh et al. (2019) find that Medicaid prescriptions increased by 19 percent in states that expanded Medicaid in 2014 and the first quarter of 2015 relative to states that did not. This increase translates to approximately nine additional prescriptions per year for each newly enrolled beneficiary. Other studies report utilization increases of a similar magnitude.[1] Data from IMS Health (2015) show that Medicaid prescriptions increased by 25.4 percent in states that expanded Medicaid relative to 2.8 percent in states that did not in 2014. Based on a subset of expansion and non-expansion states, Mahendraratnam (2016) finds that one year after ACA implementation, expansion states had 17 percent more Medicaid prescriptions than were seen in the quarter proceeding the expansion.[2]

Our study's estimates, which are based on the Medicaid State Drug Utilization Data, align with these estimates. Between 2013 and 2014, we find an 18 percent

[1] While Wen et al (2016) also look at drug utilization using the Medicaid State Drug Utilization data, the estimates they present are not directly comparable to ours since they are normalized by the number of residents in each state.

[2] Mahendraratnam (2016) reports that prescription drug utilization grew on an upwards trajectory throughout 2014, which is consistent with the continued growth we observe in 2015.

increase in expansions states relative to 3 percent in non-expansion states. These increases translated into 24 million new Medicaid prescriptions in 2014. When we expand our sample through 2015, which other studies do not report on, we observe 60 million new prescriptions.

Medicare Part D and Prescription Drug Utilization

While a large literature has examined how Medicare Part D's implementation affected prescription drug utilization and spending, the precise size of this utilization increase is difficult to pinpoint.

Both Litchenberg and Sun (2007) and Yin et al. (2008) use a difference-in-differences approach to study drug utilization in Walgreens pharmacy claims data. Comparing utilization among the elderly to the non-elderly, Litchenberg and Sun (2007) find that Medicare Part D implementation increased prescription drug use among the elderly by 13 percent. When only comparing the elderly to the near-elderly (60-63), Yin et al. (2008) find a five percent increase in utilization. Using prescription drug transaction data between 2004 and 2007 for those over 66 years to those below 58, Ketcham and Simon (2008) find Part D increased elderly prescription drug utilization by 4.7 percent. Khan and Kaestner (2009) estimate that Part D would increase utilization 4-10 percent among the elderly using a nationally representative sample of Medicare beneficiaries and a fixed-effect estimator. While Khan and Kaestner provide information on projected instead of realized increases, the benefit of their study design is that they can vary parameters and think about the overall Medicare population instead of subsamples. Back-of-the-envelope calculations using predicted drug spending in the absence of Part D in 2006 derived from Litchenberg and Sun (2007) suggest a 4-13 percent increase in prescriptions among the elderly translated into 46 million to 158 million new prescriptions due to Part D.[3]

Medicare Part D vs. the ACA's Medicaid Expansions

[3]Duggan and Scott Morton (2010) are outliers in this literature. They document an increase of 51 percent, although it is not significant and imprecisely estimated.

Notably, there are two key reasons why it is difficult to compare utilization increases in Medicare vs. Medicaid: price effects and crowd-out effects.

The creation of Medicare Part D led to substantial declines in average branded pharmaceutical prices, especially among drugs with high sales to individuals eligible for Part D (Duggan and Scott Morton, 2010). This price decrease contributed to increased consumption. Meanwhile, there is no evidence of price decreases following Medicaid expansion (Feng et al., 2019). In fact, due to the structure of Medicaid rebate rules, we would expect commercial branded pharmacuetical prices to rise for drugs with high sales to Medicaid following expansion (Duggan and Scott Morton, 2006).

Medicare Part D also included substantial crowd-out of other drug coverage, while Medicaid expansion did not. Results from Ghosh et al. (2019) suggest that new coverage under Medicaid did not substitute for other payment sources.[4] When prescriptions paid for by Medicaid increase, they find no evidence of reductions in prescriptions paid for by private insurance or by those with no insurance. In Part D, on the other hand, there is substantial crowd-out. Englehardt and Gruber (2010) estimate that Part D resulted in a 75 percent crowd-out of prescription drug insurance coverage and expenditures among the elderly population. In their data, Litchenberg and Sun (2007) find that for every seven new prescriptions paid for by the government, there was a reduction of five prescriptions paid for by the private sector. The reduction also implies a large crowd-out of private insurance by Part D. Levy and Weir (2010) also report high crowd-out of other private insurance by Part D.

[4] A review of the literature finds limited crowd out of insurance among the newly eligible Medicaid population (KFF, 2020)

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Appendix B: Typical Use of Products in Medicaid State Drug Utilization Data

To link drugs listed in the Medicaid State Drug Utilization data to ICD-9 codes, we employed a two-step process. We first obtained information on the active ingredients of the drugs in the Medicaid State Drug Utilization data from current and historical versions of the Drugs @ FDA database and the FDA's National Drug Code (NDC) Directory. We then removed all active ingredients with at least one NDC listed as available over the counter. To limit our sample to a reasonable number of active ingredients, we focus on the set of drugs that together account for 95% of total drug spending two years prior to each expansion studied. The remaining 5% of spending consists of a large number of low-volume drugs.

Next, we hired a Doctor of Pharmacy (PharmD) candidate in the final stages of her studies to research the most common uses (both on and off-label) for relevant active ingredients. The PharmD candidate identified the primary indications for each active ingredient using four tertiary pharmacy databases.

1) MicroMedix - owned by Truven Health Analytics, an IBM Watson Health company

2) DynaMed Plus - owned by EBSCO Health

3) Clinical Pharmacology - powered by ClinicalKey, owned by Elsevier

4) Lexicomp – owned by Wolters Kluwer

All four pharmacy databases are used by licensed pharmacists and other health-care providers for clinical guidance in practice along with student pharmacists for educational purposes accessed via an institutionally paid subscription plan. The companies that own these sources supply health information supported by peer-reviewed studies.

When the databases listed multiple indications, the PharmD candidate identified consensus across the four databases and used her clinical judgement to narrow down the indications to the primary one to three indications. In cases where the primary uses of an active ingredient varied by route of administration, the PharmD candidate referenced the indications for the route of administration compromising the majority of spending in the Medicaid population (information on each NDC code came from Drugs FDA).

To link drug indications to three-digit ICD-9 codes, the PharmD candidate relied on ICD-9-CM codes listed at findacode.com. In cases where the drug was primarily used as a contraception, an antibiotic, or as part of general medical and surgical procedures (e.g. anesthesia, contrast fluid, saline), the drug was not linked to a specific ICD-9 code or disease. For example, Lidocaine is often used for medical anesthesia. Because this does not correspond to a disease, it not linked to a specific ICD-9 code. Contraception similarly does not correspond to a disease. In the case of antibiotics, the list number of diseases they can treat are too large to able to be able to accurately learn about specific conditions in the newly-eligible Medicaid population from their utilization. Given that a lack of innovation in antibiotics is well documented, their exclusion cannot explain our null results for innovation.

Appendix C: Increases in Medicaid Drug Utilization Post-ACA

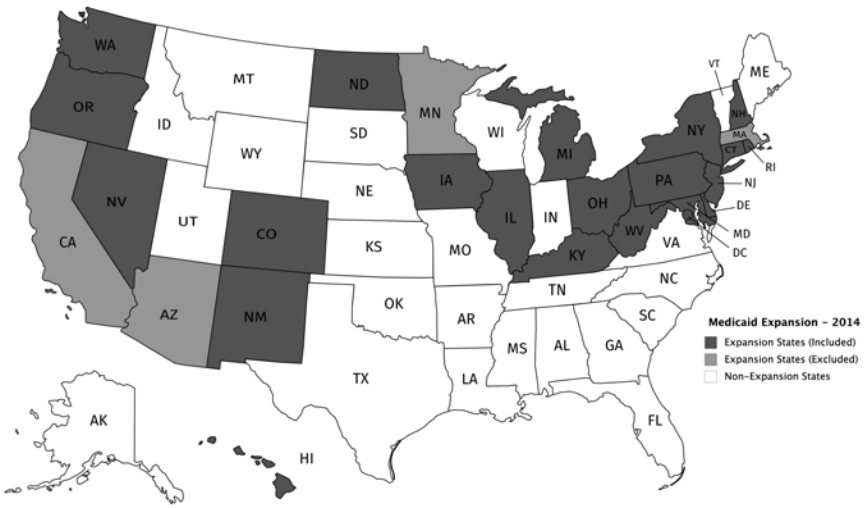
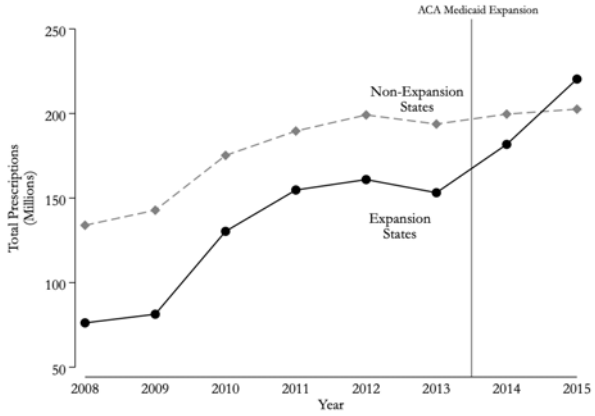


Figure C1. States Expanding Medicaid in 2014

Note: This figure illustrates which states chose to expand Medicaid under the ACA and which chose not to expand. Expansion states are in dark gray, non-expansion states are in white, and states that expanded, but are excluded from our sample due to the nature of their early expansion, are in light gray. The list of excluded states comes from Dranove, et al (2016).

Panel A: Total Prescriptions Reimbursed by Medicaid



Panel B: Total Pre-Rebate Drug Spending in Medicaid

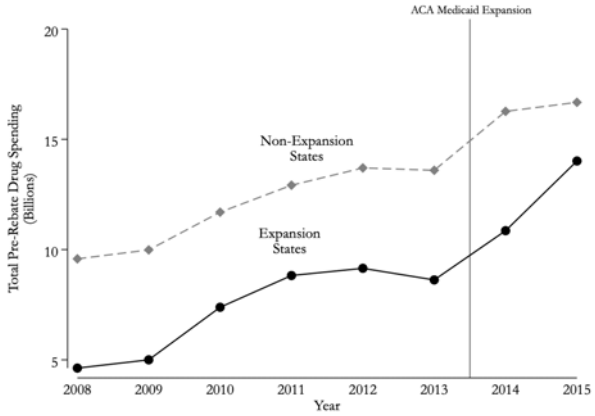


Figure C2. Medicaid Prescriptions and Pre-Rebate Spending in Expansion and Non-Expansion States

Note: This figure plots measures of drug utilization and spending across expansion and non-expansion states over time. It shows that both utilization (total prescriptions) and spending increased more in states that expanded Medicaid than those that did not. Total prescriptions includes any prescription for which Medicaid paid a portion of the claim, as well as those prescriptions for which Medicaid paid the full claim. Total spending include the total amount reimbursed by both Medicaid and non-Medicaid entities to pharmacies or other providers for drugs prescribed to Medicaid beneficiaries. This total does not include Medicaid rebates and represents both federal and state reimbursement. All data on drug spending comes from the Medicaid State Drug Utilization Data and includes information for both Medicaid Fee-For-Service and Medicaid Managed Care Organization beneficiaries.

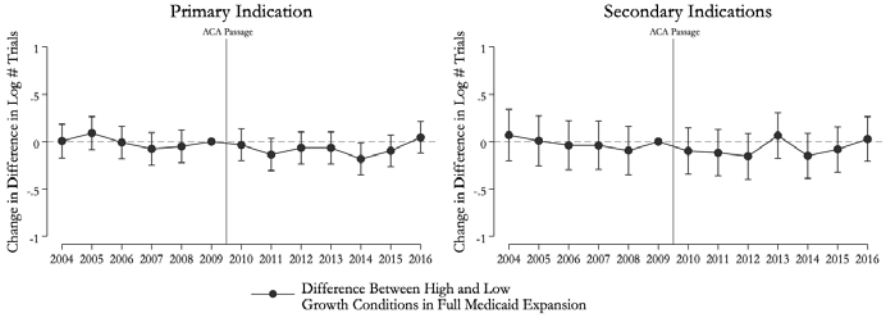
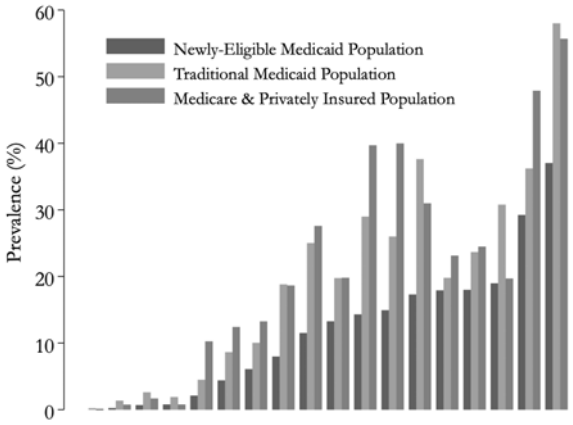


Figure C3. Comparing Clinical Trials Targeting Conditions with Large and Small Changes in Medicaid Spending Under 2014 ACA Medicaid Expansion

Note: This figure plots the event study coefficients for the change in clinical trials for conditions based on whether they are in the bottom three quartiles or top quartile of spending growth among Medicaid beneficiaries under the full 2014 Medicaid expansion. There is no statistically significant or consistent increase in trials targeting the conditions with high expected demand among the newly-eligible. The regression uses a negative binomial specification to estimate the change in clinical trial activity based on a binary variable for whether a condition is in the top quartile of Medicaid spending growth following early state Medicaid expansions. Conditions in the top quartile of spending in early expansion states are identified by comparing ex-post utilization of pharmaceuticals by Medicaid beneficiaries. Medicaid pharmaceutical product expenditures come from the Medicaid State Drug Utilization Data and pharmaceutical products are linked to conditions using databases employed by professional pharmacists (See Appendix B). Data on clinical trial activity comes from Cortellis and includes all U.S.-based trials with at least one reported indication.

Appendix D: Additional Tables and Figures from Text



Order	ICD Chapter	Newly-Eligible Medicaid Prevalence	Traditional Medicaid Prevalence	Medicare & Privately Insured Prevalence
1	Certain Conditions Originating In The Perinatal Period	0.00	0.21	0.04
2	Congenital Anomalies	0.24	1.35	0.74
3	Diseases Of The Blood And Blood-Forming Organs	0.68	2.60	1.68
4	Complications Of Pregnancy, Childbirth, And The Puerperium	0.78	1.90	0.78
5	Neoplasms	2.11	4.48	10.25
6	Diseases Of The Skin And Subcutaneous Tissue	4.38	8.62	12.41
7	Diseases Of The Genitourinary System	6.08	10.03	13.25
8	Supplementary Classification Of Factors Influencing Health Status And Contact With Health Services	7.97	18.80	18.64
9	Diseases Of The Nervous System And Sense Organs	11.50	25.01	27.58
10	Diseases Of The Digestive System	13.27	19.75	19.81
11	Diseases Of The Circulatory System	14.30	28.98	39.68
12	Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders	14.92	25.99	39.97
13	Symptoms, Signs, And Ill-Defined Conditions	17.29	37.61	30.97
14	Injury And Poisoning	17.90	19.78	23.12
15	Infectious And Parasitic Diseases	17.98	23.66	24.49
16	Mental Disorders	18.96	30.77	19.68
17	Diseases Of The Musculoskeletal System And Connective Tissue	29.23	36.20	47.89
18	Diseases Of The Respiratory System	37.02	58.01	55.68

Figure D1. Comparing Disease Prevalence Across Insurance Groups

Note: This figure shows how the prevalence of conditions differs across the newly-eligible Medicaid, traditional Medicaid, and Medicare and privately insured populations. Prevalence is defined as the share of the eligible population with a particular condition, defined at the ICD-9 Chapter level. There is large variation in prevalence across both diseases and populations. Since prevalence across conditions in the newly-eligible population differs from prevalence in other populations, pharmaceutical utilization across the newly-eligible population cannot be accurately predicted using data from other populations. Overall prevalence across diseases may be mechanically lower in the newly-eligible Medicaid population due to infrequent interactions with the medical system. All data come from the 2007-2010 Medical Expenditure Panel Survey (MEPS) for individuals living in the Northeast, West, and Midwest Census Divisions.

Table D1—Early Expansion State Growth in Pharmaceutical Spending by Condition

Relevant Conditions	CA		CT		MA	
	Spending Growth	Rank	Spending Growth	Rank	Spending Growth	Rank
Acute Respiratory Infections	-3.47	55	-	-	-	-
Arthropathies And Related Disorders	-0.63	47	-0.29	37	0.13	9
Benign Neoplasms	-0.64	49	-	-	0.11	11
Cerebrovascular Disease	0.20	10	-	-	0.07	15
Chronic Obstructive Pulmonary Disease And Allied Conditions	-0.05	19	-0.30	38	0.04	25
Complications Of Surgical And Medical Care, Not Elsewhere Classified	-0.24	33	0.66	4	0.07	16
Diseases Of Arteries, Arterioles, And Capillaries	-0.22	30	0.50	7	0.01	31
Diseases Of Esophagus, Stomach, And Duodenum	-0.28	37	0.55	5	-0.30	49
Diseases Of Male Genital Organs	0.12	14	0.71	3	0.07	18
Diseases Of Oral Cavity, Salivary Glands, And Jaws	0.78	3	-	-	-	-
Diseases Of Other Endocrine Glands	-0.17	28	-0.10	31	0.00	34
Diseases Of Pulmonary Circulation	0.15	11	-	-	0.16	8
Diseases Of The Blood And Blood-Forming Organs	0.02	18	0.51	6	-0.07	44
Diseases Of The Ear And Mastoid Process	0.23	7	-	-	-	-
Diseases Of Veins And Lymphatics, And Other Diseases Of Circulatory System	0.07	15	0.26	10	0.20	3
Disorders Of The Eye And Adnexa	-0.36	39	0.82	2	-0.03	40
Disorders Of Thyroid Gland	-0.45	44	0.18	15	0.00	33
Dorsopathies	-0.42	43	-0.34	39	0.19	5
Hereditary And Degenerative Diseases Of The Central Nervous System	-0.10	23	0.13	18	0.06	20
Human Immunodeficiency Virus (Hiv) Infection	-0.24	32	-0.11	32	-0.03	38
Hypertensive Disease	-0.66	50	0.15	17	0.03	27
Infections Of Skin And Subcutaneous Tissue	0.86	2	0.04	24	0.36	2
Injury To Nerves And Spinal Cord	-0.22	31	-0.70	48	0.06	21
Ischemic Heart Disease	-0.05	20	0.00	27	0.06	22
Malignant Neoplasm Of Bone, Connective Tissue, Skin, And Breast	-0.64	48	0.19	13	-0.02	36
Malignant Neoplasm Of Digestive Organs And Peritoneum	-0.75	52	0.12	19	0.02	29
Malignant Neoplasm Of Genitourinary Organs	-0.15	26	1.01	1	0.07	19
Malignant Neoplasm Of Lymphatic And Hematopoietic Tissue	-0.79	53	-1.37	50	0.40	1
Malignant Neoplasm Of Other And Unspecified Sites	-0.09	22	0.18	14	-0.04	42
Malignant Neoplasm Of Respiratory And Intrathoracic Organs	-0.67	51	0.19	12	0.11	10
Mycoses	-0.13	25	-0.55	44	0.01	30
Nephritis, Nephrotic Syndrome, And Nephrosis	0.21	9	0.04	23	0.17	6
Neurotic Disorders, Personality Disorders, And Other Nonpsychotic Mental Disorders	-0.07	21	-0.15	33	-0.02	37
Noninfectious Enteritis And Colitis	-0.16	27	-0.40	42	0.05	23
Nutritional Deficiencies	0.12	13	0.09	20	-	-
Organic Sleep Disorders	-0.46	45	-0.59	45	-0.12	48
Osteopathies, Chondropathies, And Acquired Musculoskeletal Deformities	-0.50	46	-0.38	40	0.07	17
Other And Unspecified Effects Of External Causes	1.11	1	-0.85	49	0.19	4
Other Diseases Due To Viruses And Chlamydiae	-0.32	38	-0.64	47	-0.03	39
Other Diseases Of Digestive System	-0.24	34	-0.17	35	0.09	13
Other Diseases Of Intestines And Peritoneum	-0.21	29	0.16	16	0.09	14
Other Diseases Of Skin And Subcutaneous Tissue	-	-	-0.43	43	-0.75	50
Other Diseases Of The Upper Respiratory Tract	0.06	16	-0.63	46	0.17	7
Other Diseases Of Urinary System	-	-	0.45	9	-	-
Other Disorders Of Female Genital Tract	-0.26	36	0.03	25	-0.02	35
Other Disorders Of The Central Nervous System	-0.24	35	-0.05	28	0.01	32
Other Forms Of Heart Disease	0.43	5	0.45	8	-0.04	43
Other Infectious And Parasitic Diseases	-1.43	54	-	-	-	-
Other Inflammatory Conditions Of Skin And Subcutaneous Tissue	-0.38	40	-0.15	34	0.11	12
Other Metabolic And Immunity Disorders	-0.42	42	0.05	22	-0.09	46
Pain	-0.12	24	-0.06	29	-0.09	45
Pneumonia And Influenza	0.22	8	-0.26	36	0.04	24
Poisoning By Drugs, Medicinal And Biological Substances	0.27	6	0.21	11	-	-
Psychoses	0.45	4	-0.06	30	0.03	28
Rheumatism, Excluding The Back	0.04	17	0.02	26	-0.10	47
Symptoms	-0.41	41	-0.39	41	-0.03	41
Viral Diseases Generally Accompanied By Exanthem	0.13	12	0.07	21	0.03	26

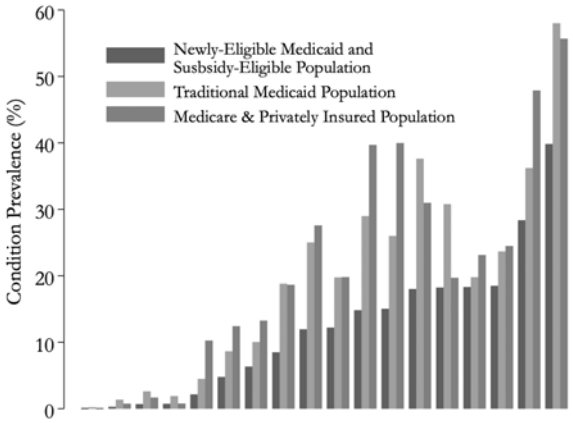
Note: This table reports the difference-in-difference estimation results for conditions in early expansion states. Conditions are defined at the ICD-9 Sub-Chapter level and spending growth is derived using the proportional growth difference-in-differences methodology in Appendix Figure C3. Rank is the relative ranking of each condition's growth. All information on pharmaceutical product expenditures come from the Medicaid State Drug Utilization Data. Pharmaceutical products are linked to conditions using databases employed by professional pharmacists (see Appendix B) and spending on products is split equally among conditions linked to each product. Not all conditions are present in this table, as some conditions were not primarily targeted by pharmaceutical products in the set of drugs that together account for 95% of total drug spending in the two years prior to early state expansion. Some conditions are also only targeted by excluded categories of pharmaceutical products (see Appendix B).

Appendix E: Estimates using Demand from Expanded Newly-Eligible Medicaid and Subsidy-Eligible Population

Table E1—Newly Eligible (NE) Medicaid Population Sample Selection

Description	Income	Medicaid Status	Insurance Status	Estimated Population Size
NE Medicaid (strict)	Under 138% FPL	Not on Medicaid	Uninsured full year	14.6 Million
NE Medicaid	Under 138% FPL	Not on Medicaid	Uninsured at some point in year	18 Million
NE Medicaid & Subsidy-Eligible Population	Under 400% FPL	Not on Medicaid	Uninsured at some point in year	48.3 Million

Note: This table displays three different sample selection criteria that can be used to identify individuals newly eligible for Medicaid under the ACA. The analysis in this paper uses the second sample, since the definition and estimated population size most accurately align with ACA-era Medicaid expansion, but later tables in this section present results for the most generous sample selection - newly-eligible Medicaid and marketplace subsidy-eligible. The three criteria – income, Medicaid status, and insurance status – all translate to variables collected in the Medical Expenditure Panel Survey (MEPS) between 2007 and 2010. The sample selection criteria for three potential groups are listed from most to least restrictive. All calculations include individuals from every region of the United States. The estimated population size calculations are averaged over the 2007 - 2010 panels of the MEPS.



Order	ICD Chapter	Newly-Eligible Medicaid & Subsidy-Eligible Prevalence	Traditional Medicaid Prevalence	Medicare & Privately Insured Prevalence
1	Certain Conditions Originating In The Perinatal Period	0.05	0.21	0.04
2	Congenital Anomalies	0.28	1.35	0.74
3	Diseases Of The Blood And Blood-Forming Organs	0.70	2.60	1.68
4	Complications Of Pregnancy, Childbirth, And The Puerperium	0.73	1.90	0.78
5	Neoplasms	2.14	4.48	10.25
6	Diseases Of The Skin And Subcutaneous Tissue	4.77	8.62	12.41
7	Diseases Of The Genitourinary System	6.33	10.03	13.25
8	Supplementary Classification Of Factors Influencing Health Status And Contact With Health Services	8.48	18.80	18.64
9	Diseases Of The Nervous System And Sense Organs	11.94	25.01	27.58
10	Diseases Of The Digestive System	12.19	19.75	19.81
11	Diseases Of The Circulatory System	14.82	28.98	39.68
12	Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders	15.04	25.99	39.97
13	Symptoms, Signs, And Ill-Defined Conditions	18.02	37.61	30.97
14	Mental Disorders	18.23	30.77	19.68
15	Injury And Poisoning	18.31	19.78	23.12
16	Infectious And Parasitic Diseases	18.49	23.66	24.49
17	Diseases Of The Musculoskeletal System And Connective Tissue	28.36	36.20	47.89
18	Diseases Of The Respiratory System	39.82	58.01	55.68

Figure E1. Expanded Population - Comparing Disease Prevalence Across Insurance Groups

Note: This figure shows how the prevalence of conditions differs across the newly-eligible Medicaid and subsidy-eligible, traditional Medicaid, and Medicare and privately insured populations. Prevalence is defined as the share of the eligible population with a particular condition, defined at the ICD-9 Chapter level. There is large variation in prevalence across both diseases and populations. Since prevalence across conditions in the newly-eligible Medicaid and subsidy-eligible population (i.e. those uninsured with incomes below 400% FPL) differs from prevalence in other populations, pharmaceutical utilization across the newly-eligible population cannot be accurately predicted using data from other populations. Overall prevalence across diseases may be mechanically lower in the newly-eligible Medicaid and subsidy-eligible population due to infrequent interactions with the medical system. All data come from the 2007-2010 Medical Expenditure Panel Survey (MEPS) for individuals living in the Northeast, West, and Midwest Census Divisions.

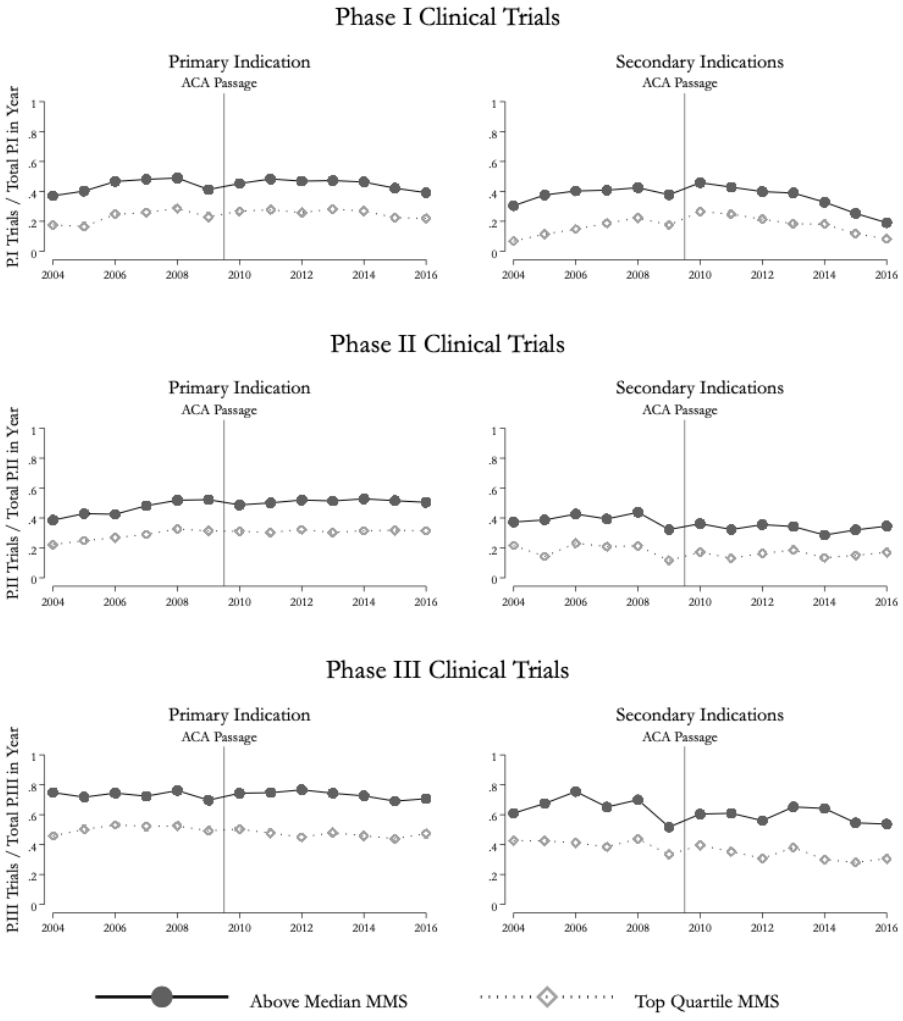


Figure E2. Expanded Population - Share of Trials Below and Above Median MMS

Note: This figure plots clinical trial activity over time. It shows the share of Phase I, II, and III trials with primary or secondary indications targeting conditions with high or low Medicaid Market Share (MMS). The figure provides no graphical evidence that clinical trials targeting conditions with high demand among the newly-eligible Medicaid and subsidy-eligible population (i.e. high MMS) increased following the ACA's passage. MMS is defined as the share of the total US population that has a condition and was expected to gain coverage due to ACA Medicaid expansion or marketplace exchange subsidies. MMS is calculated at ICD-9 Subchapter level. Clinical trial activity is shown for conditions with MMS above the median or in the top quartile of all conditions. All data on MMS comes from 2007-2010 panels of the MEPS for individuals living in the Northeast, West, and Midwest Census Divisions. Data on the universe of clinical trials, along with information on trial phase and indications come from Clarivate Analytics Cortellis Competitive Intelligence Database (Cortellis). The sample of clinical trials is limited to U.S.-based trials between 2004 and 2016 with at least one reported indication.

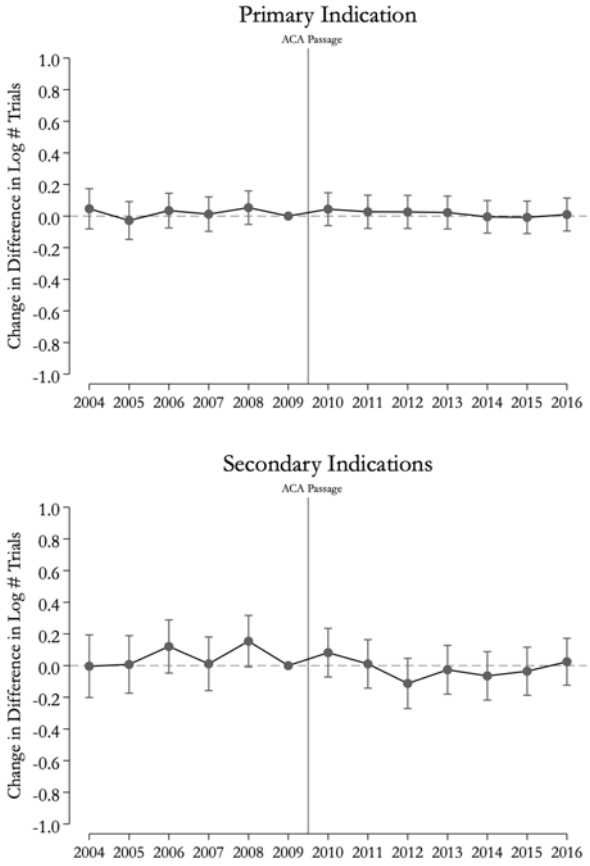


Figure E3. Expanded Population - Trends in Total Clinical Trials for One Percentage Point Higher MMS

Note: This figure plots negative binomial event study estimates for the effect of a one percentage point higher newly-eligible Medicaid and subsidy-eligible Market Share (MMS) on clinical trials in the years surrounding the passage of the ACA. The outcome is the total clinical trials per condition. The points are regression coefficients from a negative binomial specification with calendar year and condition fixed effects. All effects are plotted as changes relative to the time year before ACA passage (2009). The top chart contains the total number of of trials with primary indication for a condition and the bottom chart contains the total number of trials with a secondary indication for a condition. The figure provides no graphical evidence that clinical trials targeting conditions with higher MMS increased following the ACA's passage. MMS is defined as the share of the total US population that has a condition and was expected to gain coverage due to ACA Medicaid expansion or marketplace exchange subsidies. The MMS ranges between 0.00% and 2.38% (mean: 0.27, sd: 0.50), so a one percentage point change is a unit of magnitude higher than we see in our data. The average number of total trials with a primary indication for a given condition over the whole 13 year period is 37.85. The average number of total trials with at least one secondary indication for a given condition is 12.85. Estimates of MMS are derived from the 2007-2010 MEPS for individuals in the Northeast, West, and Midwest Census Divisions. Data on clinical trials comes from Cortellis and includes all U.S.-based trials with at least one reported indication.

Table E2—Expanded Population - Difference-in-Differences Estimates of Clinical Trial Activity

	P. I Trials	
	Primary Indication	Secondary Indications
Post 2009	0.864***	1.240***
	(0.071)	(0.124)
Post 2009 × MMS	0.042	0.056
	(0.039)	(0.070)
Observations	1274	1274

Standard errors in parentheses

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

	P. II Trials	
	Primary Indication	Secondary Indications
Post 2009	0.562***	0.987***
	(0.057)	(0.084)
Post 2009 × MMS	0.064*	-0.050
	(0.032)	(0.051)
Observations	1274	1274

Standard errors in parentheses

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

	P. III Trials	
	Primary Indication	Secondary Indications
Post 2009	0.211**	0.355**
	(0.076)	(0.126)
Post 2009 × MMS	-0.094*	-0.110
	(0.041)	(0.070)
Observations	1274	1274

Standard errors in parentheses

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

Note: This table contains estimates from a negative binomial DID for the effect of a 1 percentage point higher newly-eligible Medicaid and subsidy-eligible Market Share (MMS) on innovation post ACA passage. Since responses to the ACA may vary across clinical trial stage, Phase I, Phase II, and Phase III trials are presented in separate panels. The first column contains the total number of of trials with primary indication for a condition and the second column contains the total number of trials with a secondary indication for a condition. Regardless of the phase of development, there is no consistent and detectable change in clinical trial activity in response to the demand shock from the ACA's Medicaid expansions and marketplace exchange subsidy implementation. The MMS ranges between 0.00% and 2.38% (mean: 0.27, sd: 0.50), so a one percentage point change is a unit of magnitude higher than we see in our data.The outcome is the total trials per condition. The average number of total trials with a primary indication for a given condition over the whole 13 year period is 37.85. The average number of total trials with at least one secondary indication for a given condition is 12.85. Estimates of MMS are derived from the 2007-2010 MEPS for individuals in the Northeast, West, and Midwest Census Divisions. Data on clinical trials comes from Cortellis and includes all U.S.-based trials with at least one reported indication.

Appendix F: Estimates using Alternative Definition of Newly-Eligible Medicaid Market Share (Alt. MMS)

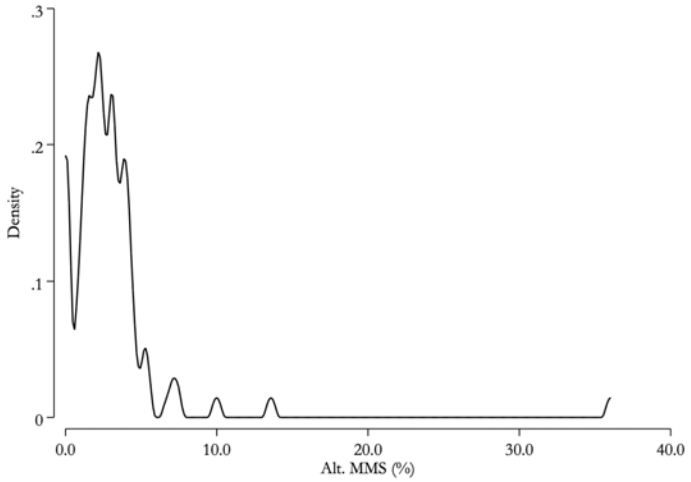


Figure F1. Kernel Density of Alternative MMS Across Conditions 2007 - 2010

Note: This figure demonstrates that there is substantial variation in demand for pharmaceuticals treating different conditions in the newly-eligible Medicaid population. It specifically plots the kernel density of our alternative demand measure among the newly-eligible (Alt. MMS) for conditions at the ICD-9 Sub-Chapter level. Alt. MMS is defined as the share of the population with a disease that are newly-covered by ACA Medicaid expansion. Estimates of Alt. MMS are derived from the 2007-2010 MEPS for individuals in the Northeast, West, and Midwest Census Divisions.

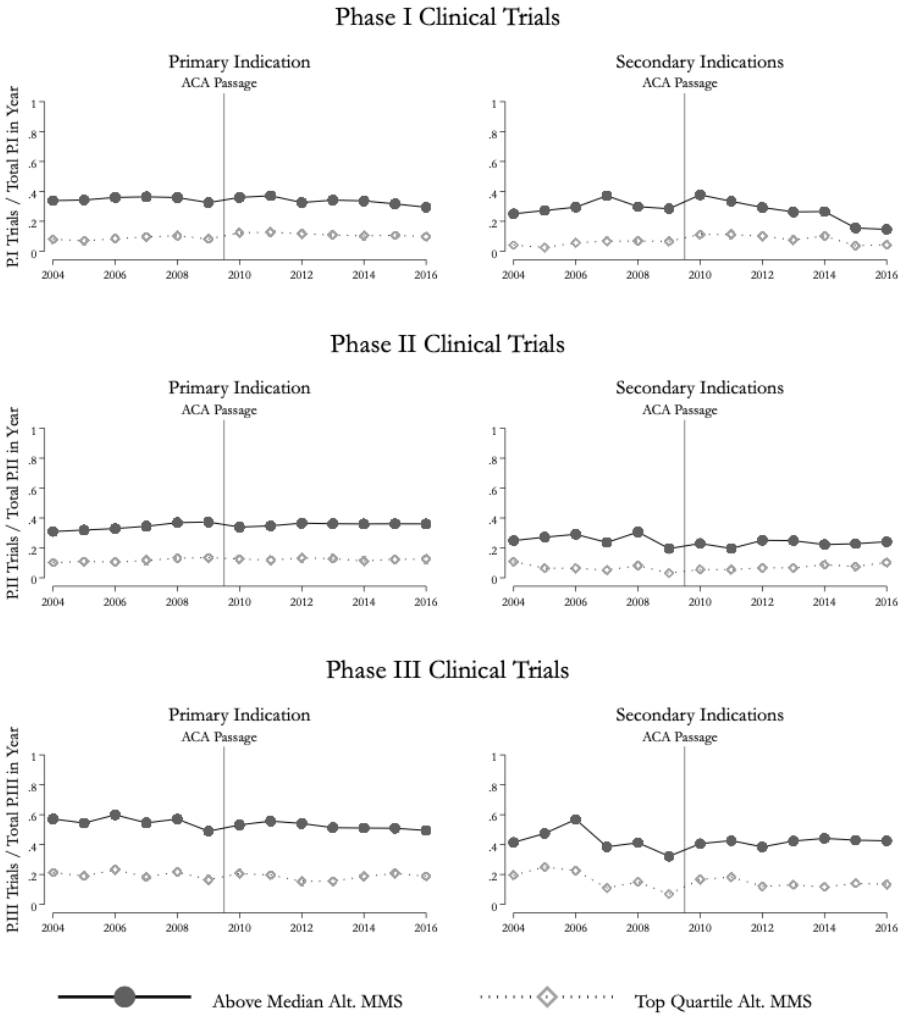


Figure F2. Share of Trials Below and Above Median Alternative MMS

Note: This figure plots clinical trial activity over time. It shows the share of Phase I, II, and III trials with primary or secondary indications targeting conditions with high or low Alternative Medicaid Market Share (Alt. MMS). The figure provides no graphical evidence that clinical trials targeting conditions with high demand among the newly-eligible (i.e. high MMS) increased following the ACA's passage. Alt. MMS is defined as the share of the population with a disease that are newly-covered by ACA Medicaid expansion. Alt. MMS is calculated at ICD-9 Subchapter level. Clinical trial activity is shown for conditions with Alt. MMS above the median or in the top quartile of all conditions. All data on Alt. MMS comes from 2007-2010 panels of the MEPS for individuals living in the Northeast, West, and Midwest Census Divisions. Data on the universe of clinical trials, along with information on trial phase and indications come from Clarivate Analytics Cortellis Competitive Intelligence Database (Cortellis). The sample of clinical trials is limited to U.S.- based trials between 2004 and 2016 with at least one reported indication.

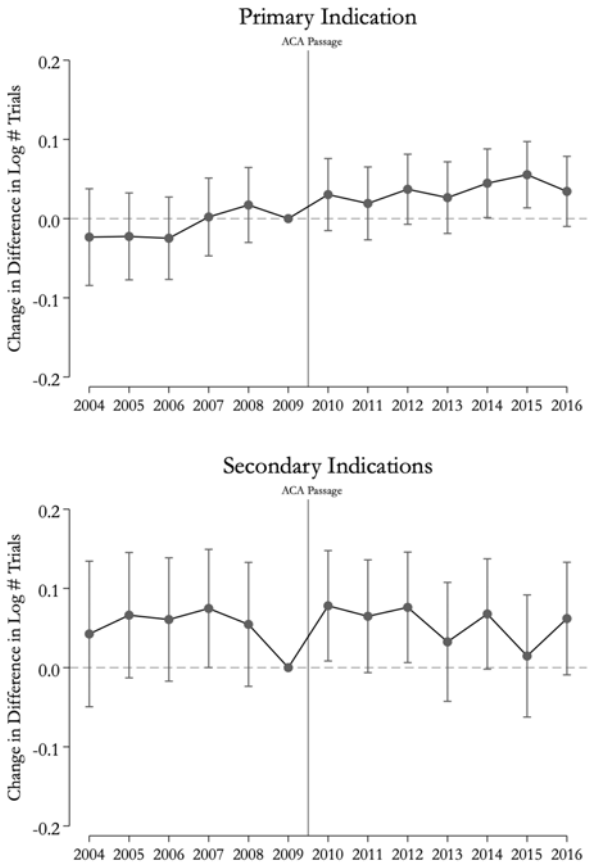


Figure F3. Trends in Total Clinical Trials for One Percentage Point Higher Alt. MMS

Note: This figure plots event negative binomial event study estimates for the effect of a one percentage point higher alternative newly-eligible Medicaid Market Share (Alt. MMS) on clinical trials in the years surrounding the passage of the ACA. The outcome is the total clinical trials per condition. The points are regression coefficients from a negative binomial specification with calendar year and condition fixed effects. All effects are plotted as changes relative to the time year before ACA passage (2009). The top chart contains the total number of of trials with primary indication for a condition and the bottom chart contains the total number of trials with a secondary indication for a condition. The figure provides no graphical evidence that clinical trials targeting conditions with higher Alt. MMS increased following the ACA's passage. Alt. MMS is defined as the share of the total US population that has a condition and was expected to gain coverage due to ACA Medicaid expansion. The Alt. MMS ranges between 0.00% and 36.03% (mean: 2.93, sd: 3.75), so a one percentage point change is a reasonable magnitude of change in our data. The average number of total trials with a primary indication for a given condition over the whole 13 year period is 37.85. The average number of total trials with at least one secondary indication for a given condition is 12.85. Estimates of Alt. MMS are derived from the 2007-2010 MEPS for individuals in the Northeast, West, and Midwest Census Divisions. Data on clinical trials comes from Cortellis and includes all U.S.-based trials with at least one reported indication.

Table F1—Difference-in-Differences Estimates of Clinical Trial Activity for Alt. MMS

	P. I Trials	
	Primary Indication	Secondary Indications
Post 2009	0.797***	1.187***
	(0.077)	(0.131)
Post 2009 × Alt. MMS	0.039*	0.036
	(0.016)	(0.025)
Observations	1274	1274

Standard errors in parentheses

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

	P. II Trials	
	Primary Indication	Secondary Indications
Post 2009	0.477***	1.025***
	(0.063)	(0.089)
Post 2009 × Alt. MMS	0.050***	-0.030
	(0.014)	(0.020)
Observations	1274	1274

Standard errors in parentheses

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

	P. III Trials	
	Primary Indication	Secondary Indications
Post 2009	0.125	0.491***
	(0.086)	(0.147)
Post 2009 × Alt. MMS	0.016	-0.083*
	(0.018)	(0.037)
Observations	1274	1274

Standard errors in parentheses

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

Note: This table contains estimates from a negative binomial DID for the effect of a 1 percentage point higher alternative newly-eligible Medicaid Market Share (Alt. MMS) on innovation post ACA passage. Since responses to Medicaid Expansion may vary across clinical trial stage, Phase I, Phase II, and Phase III trials are presented in separate panels. The first column contains the total number of of trials with primary indication for a condition and the second column contains the total number of trials with a secondary indication for a condition. Regardless of the phase of development, there is no consistent and detectable change in clinical trial activity in response to the demand shock from the ACA's Medicaid expansions. The Alt. MMS ranges between 0.00% and 36.03% (mean: 2.93, sd: 3.75), so a one percentage point change is a reasonable magnitude of change in our data. The outcome is the total trials per condition. The average number of total trials with a primary indication for a given condition over the whole 13 year period is 37.85. The average number of total trials with at least one secondary indication for a given condition is 12.85. Estimates of MMS are derived from the 2007-2010 MEPS for individuals in the Northeast, West, and Midwest Census Divisions. Data on clinical trials comes from Cortellis and includes all U.S.-based trials with at least one reported indication.