Pharmaceutical Profits and the Social Value of Innovation *

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June 2015

Abstract

Prior research has shown that demand shocks for medical products spur additional product development. These studies do not distinguish between innovative products and those that largely duplicate existing options. We explore the impact of the introduction of Medicare Part D on the development of new biotechnology products. The law spurred research into products targeting illnesses affecting the elderly, but the effect is concentrated among diseases with multiple existing treatments. Moreover, we find no increase in products with regulatory indicators of novelty. This suggests that marginal demand changes may have little effect on the development of products with large welfare benefits.

* We thank Ernst Berndt, Jen Brown, Amitabh Chandra, Rena Conti, Amy Finkelstein, Matthew Notowidigdo, Jon Skinner, Ariel Dora Stern, and Heidi Williams for helpful suggestions. All errors remain our own.

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1. INTRODUCTION

The profits of pharmaceutical firms receive a large amount of attention and have caused many in the popular press and policymaking community to propose various policies to limit them (e.g. Rome, 2013). Critics claim that firms selling branded drugs under patent protection set prices at many multiples of marginal costs, excessively exploiting both their monopoly power and the inelastic demand for these often life-saving products. Industry defenders counter that high prices are necessary to offset expensive and uncertain research and development, and that if profits were to fall, incentives for future innovation would suffer. Danzon (2000) provides the quintessential defense of the industry: "[a]ny form of price regulation, including the setting of uniform prices within the United States or cross-nationally, would discourage innovation." Similarly, discussing the re-importation of low-price pharmaceuticals to the United States, Bast (2004) wrote "increasing importation means cutting off the stream of investment that makes this system sustainable. It means fewer new lifesaving drugs."

Many studies bolster the arguments of pharmaceutical industry supporters by documenting a causal relationship between expected profitability, primarily from changes in market size, and new products. Some of these studies find a link between demand and research activity (Ward and Dranove, 1997; Kyle and McGahan, 2012; Blume-Kohut and Sood, 2013; Finkelstein, 2004) while others find that higher expected profits result in a greater number of products actually reaching market (Acemoglu and Linn, 2004; Finkelstein, 2004; Cerda 2007; Dubois et al., 2014).

Industry critics counter that most recently approved new drugs are little more than slightly modified versions of existing products whose development costs far outstrip any benefits (e.g. Spector, 2005; Angell, 2012). Marcia Angell, former editor of the *New England Journal of Medicine*, has been an outspoken critic stating "[i]n fact, the big drug companies now concentrate mainly on … producing *variations of top-selling drugs already on the market* (emphasis added) —called 'me-too' drugs. There is very little innovative research in the modern pharmaceutical industry, despite its claims to the contrary"

(Angell, 2010). According to Angell and other industry critics, restrictions on industry prices and profits will not harm welfare even if they deter new product development, because they will largely affect this "me-too" innovation.

Prior research connecting demand and research investments does little to address the concerns of these industry critics because the studies generally fail to determine whether the marginal products are actually "innovative," i.e. they make positive contributions to social value, or simply represent rent-seeking by private firms. For example, Acemoglu and Linn (2004) found an increase in *new molecular entities* targeting conditions with growing patient populations which they suggest represents new innovation. However, they do not distinguish between new molecular entities that represent genuine welfare-improving therapeutic breakthroughs and those that are simply "variations of top-selling drugs already on the market." As an illustration of this point, consider the first anti-cholesterol statin drug Lovostatin. This product uses a radically different biochemical pathway which makes it far more effective than prior cholesterol reducing drugs. Therefore, it might be considered more innovative, i.e. offer a larger increase in welfare, than the subsequent ten statin drugs to reach the market, all of which were new molecular entities that effectively use the same pathway as Lovostatin.[1] Since each subsequent statin was a new chemical entity, Acemoglu and Linn's classification would broadly consider each to be equally innovative.

We contribute to this debate by examining how biotechnology firms responded to the creation of Medicare Part D (hereafter Part D) – a large expansion of pharmaceutical insurance coverage for elderly Americans. Blume-Kohut and Sood (BKS; 2013) found that Part D increased research investments in the overall pharmaceutical sector. However, much like the previous literature, BKS did not distinguish between the type of firm (i.e. traditional pharmaceutical or biotechnology), the type of

[1] These drugs inhibit the enzyme HMG-CoA reductase, which is a key building block for cholesterol. We recognize that several early statin drugs were in development at the same time; it is difficult to say that any one of these was more innovative than the others. But the ongoing "patent racing" may have involved greater expenditures in drug development than was socially optimal. New statin drugs more closely fit the model of research described by Angell.

pharmaceutical (i.e. small molecule or biologic), or any other measure of the potential welfare contributions of the new products. Without these distinctions, it is possible that most of the research activity identified in BKS provides little social value because it involves the me-too products frequently cited by critics of pharmaceutical firms. We expand the existing literature by classifying research activity using several measures of the novelty of the innovation.

This classification is not merely an exercise in taxonomy. At the broadest level, new pharmaceutical products can improve health and/or decrease prices, both of which provide value to consumers but have far different welfare consequences. If research investments in the pharmaceutical sector are aimed at "me-too" products then they primarily represent business stealing. If the demand in the product category is inelastic, as is the case with many pharmaceuticals, this business stealing may lower prices without meaningfully increasing welfare. However, if investments result in novel products that improve health, they will increase welfare – though much of the increase may initially be captured by pharmaceutical firms through monopoly prices charged while the product is under patent.[2] Partly as a result of this distinction, Weyl and Tirole (2012) suggested that monopoly rights granted under intellectual property law should, to some extent, be a function of the social value of the product rather than simply its chemical composition.

It is not surprising that previous work has failed to systematically classify individual products based on their contribution to social value.[3] Trusheim, Aitken and Berndt (2010) state, "[i]t is difficult if not impossible to quantify reliably, objectively and unambiguously the extent to which new biopharmaceuticals embody significant innovation and address unmet medical needs." This difficulty

[2] Some studies have found evidence of health benefits from aggregate research and development spending on pharmaceuticals (e.g.,Budish, Roin and Williams, 2013). However, there is little evidence of the benefits from the change in investment activity following a *marginal* increase in demand.

[3] One partial exception is Finkelstein (2004), which considers the effect on research activity from expanded public health vaccination policies – a setting that by definition involves the creation of products for which there are already treatments. Even in this more limited setting, Finkelstein can concentrate on the question of the innovative nature of new products and finds no evidence of new pre-clinical studies or patent filings for vaccines. This provides some of the first suggestive evidence that the new clinical trials do not necessarily reflect large technological advances or improvements in therapy.

stems, at least in part, from the fact that drugs can be novel across two broad attributes, both of which are difficult to systematically quantify. First, a product could be a true innovation in molecular development and therefore represent *scientific advancement*. Products in this category are by definition not simply variations of existing treatments. Second, new products could expand treatment applications by targeting conditions that previously had few or no existing options. Products exhibiting such *therapeutic innovation* likely have the most immediate effect on welfare. However, scientific advancements may also contribute to welfare for conditions with existing treatments by offering novel pathways for patients that do not respond to available options. In addition, progress in basic science could facilitate the future development of products that target untreated conditions. New products that are neither meaningful scientific advancements nor an expansion of treatment applications primarily represent business stealing with little welfare improvement.

Of course, each new product represents varying degrees of scientific advancement and therapeutic innovation, which makes classifying them on a product by product basis quite difficult. This is particularly true for products that are relatively early in development process. In our analysis, we take two steps in that direction. First, we concentrate on products developed by biotechnology firms. The firms in our sample distinguish themselves from traditional pharmaceutical firms by primarily using biological technologies and/or targeting conditions that have an unmet medical need (Thompson Reuters, 2014). As we explain in Section 3, biological products (biologics) are, almost by definition, scientific advancements to some degree. They certainly are not "variations of top selling" small molecule drugs already on the market and, by the nature of the science, they are not even simple variations of each other – i.e. one cannot easily create a new biologic through a simple manipulation of an existing one.[4] In addition to biologics, many biotechnology firms also research and produce a limited number

[4] The exception is "biosimilars," which are equivalent to generics for small molecules and are a new and emerging market. Unlike generic drugs, biosimilars are not exact copies of the branded product but instead represent a close approximation. The degree of similarity is a source of great debate (Schellekens, 2004). However, in our time period it should be noted that there was no process for approving bio-similar products for sale which limits their influence on our estimates.

of small molecule products targeting unmet medical needs such as hepatitis C (Gilead's Sovaldi) and multiple sclerosis (Biogen Idec's Tecfidera). We are unable to separately identify all small molecule products in our sample, but note that they are in the minority.

By demonstrating a specific link between demand and research in the biotech sector, we can provide initial evidence that profitability drives the development of products that are more likely to be scientifically innovative. We also consider whether profitability drives the development of therapeutically innovative products. First we note that as a product category, biologics have historically represented therapeutic innovations. For example, these products are more likely than small molecule products to target orphan diseases which are designated by the FDA as relatively rare diseases that lack existing treatments (Trusheim, Aitken, and Berndt, 2010). However, this historical description of the average biologic product may not apply to the new research activity after a marginal demand shock and, as we noted above, some biotech products in our data are small molecules. This is particularly true given that the increase in clinical trials that we identify often involve secondary indications which are replications of existing products rather than the development of new products. Therefore, we next distinguish between those biotech products that are "first to treat" a condition (henceforth FTTs) and those that augment the arsenal (henceforth AAs).

Though there will be exceptions, it is likely that FTT drugs provide greater welfare benefits than AAs. For example, contrast Gilead's small molecule product Sovaldi with Sanofi's biologic product Zaltrap. Sovaldi provides the first cure for hepatitis C and represents a large welfare increase, which Gilead is set to capture through very high prices that are unlikely to greatly limit demand. In contrast, Zaltrap treats metastatic colon cancer, which is treated to a similar degree by several existing products such as Avastin, Erbitux, Stivarga, and Vectibix. Perhaps as an indication of its relatively small welfare contribution, Sanofi's revenues from Zaltrap put it far short of blockbuster status.[5]

[5] Zaltrap's first year sales were well below $50 million (Hall, 2013). In contrast, Sovaldi is on track to be the highest grossing pharmaceutical in the first year after approval (Rockoff, 2014b).

We acknowledge that the FTT versus AA distinction may fail to capture some important aspects of therapeutic innovation. Therefore, we also consider whether marginal demand shocks encourage socially valuable products as indicated by three designations awarded by the FDA during the development and review process: orphan drug designation, fast track status, and priority review. As mentioned earlier, orphan drugs treat rare conditions lacking existing cures. The FDA grants fast track status to drugs undergoing clinical trials that promise to provide treatment for conditions for which no other drug works as well. Similarly, the FDA grants priority review to promising drugs that have completed clinical trials and await final approval. A common thread across these designations is that they represent attempts by policymakers to provide incentives for the development of new products through either explicit support or reduced regulatory hurdles.

We find that following the passage of Part D there was a relative increase in clinical trial activity for biotech products aimed at diseases that have a higher Medicare market share (MMS), i.e. diseases that are more prevalent among elderly Americans. Figure 1 shows the number of clinical trials by whether a disease has an above or below median MMS. Prior to the passage of Part D, clinical trial activity was very similar in level and trend across these two categories. However, after the passage there is a marked increase in clinical trials for products aimed at drugs with a higher MMS. The number of clinical trials for above-median MMS drugs peaks in 2008 and then declines. A similar decline is seen for below-median MMS drugs suggesting that this was primarily a secular change, perhaps as a result of the broad decline in the macroeconomy. These results are generally similar to the pattern for the more traditional pharmaceutical sector contained in the data used by BKS. However, as discussed earlier, the biologics that represent the major component of the product portfolio for the biotech firms in our sample, are historically more scientifically and therapeutically innovative than small molecule products. Therefore, our results suggest the increase in expected profits did more than simply spur the development of "me-too" products and instead encouraged some degree of scientific advancement.

As we discuss in Section 2, the extent to which expansions in market size can spur therapeutic innovation is unclear, as pre-existing scientific barriers may outweigh any marginal increases in profitability. Figures 2 and 3 preview the results of these analyses. Figure 2 contains the number of indications entering clinical trials by year based on MMS status for diseases with five or more existing treatments (i.e. AAs). Prior to the passage of Part D there was little difference in the level or trends in clinical trial activity based on MMS. Beginning immediately after the insurance expansion there was a marked increase in the number of clinical trials for products aimed at diseases with an above median MMS. This suggests that the increase in demand owing to the passage of Part D spurred development of drugs that were not particularly innovative.

Figure 3 contains the number of indications entered to clinical trials by above or below median MMS status for diseases with at most one existing treatment (i.e. FTTs).[6] Both categories have a large and similar number of clinical trials each year before Part D – suggesting that this was a relatively active area of research that was not driven by the average age of the patient population. There is no change in this pattern following the passage of Part D. This suggests that scientific rather than market barriers are the constraint on investments in FTTs, inasmuch as the increase in demand is not associated with an increase in clinical trials for FTTs. Taken together, figures 2 and 3 suggest that research activity for AAs is far more sensitive to demand shocks than for diseases with FTTs. We find thematically similar results when we look at FDA designations of a product's innovativeness—i.e. there was no increase in innovative products targeting the elderly after the passage of Part D.

Overall, our results provide a far more nuanced view of innovation in the pharmaceutical sector than is offered by either the industry's supporters or critics. In the biotech sector, a category dominated by firms believed to be creating a greater proportion of scientifically innovative products, we see a clear

[6] In our data, each observation is a unique targeted condition and clinical trial pair. Thus each clinical trial can have more than one observation in our data. For readability, throughout this paper we will describe this unique pairing as a "clinical trial."

response in research activity following a demand shock. This demonstrates that, at the broadest level, financial incentives do more than simply reward pure copy-cat firms. However, our results also suggest that, at least over the first decade, marginal changes in demand do not appear to spur new clinical trial activity for diseases that currently have few to no treatment options. It is possible that it takes longer than a decade to generate the science necessary to develop truly innovative products that are ready for clinical trials. However, it is important to note that our indicator of research investments, the first clinical trials for human subjects, is fairly early in the drug development process. If Part D did spur the new science necessary for FTT drugs, it will take a long time for consumers to realize the benefits.

In the rest of this paper we describe the innovative process for pharmaceuticals and how responses to demand shocks could reasonably differ based on the number of existing treatments. We then provide a summary of the biotechnology sector and the Medicare Part D program. In Section 5 we describe our data and in Section 6 we present our evidence on the change in clinical trial activity following the passage of Medicare Part D. In Section 7 we conclude.

2. The Innovative Process for Pharmaceuticals

There are many paths to the development of new pharmaceutical products. The traditional model of "big pharma" firms is to employ scientists across a range of disciplines who may work on projects based on areas of science (e.g., cell biology) or application (e.g., cardiovascular disease.) Many of these firms give their scientists some freedom to pursue their own projects (Stern, 2004).[7] Smaller firms, including many biotech companies, are often either spun off by bigger companies or started by academics whose research is usually initially funded by government grants.

[7] In more recent years, large pharmaceutical firms have increasingly relied on purchasing drugs developed at other, often smaller, firms. In 2012, 33 percent of the drugs under development at the top 10 pharmaceutical firms were originally developed at another firm. This was an increase from 16 percent in 2002 (Rockoff, 2014a).

Traditionally, large pharmaceutical firms have committees that allocate resources to projects that score well on both scientific merit and expected profits. Small firms may or may not be primarily driven by pure scientific merit, but must eventually secure tens of millions of dollars if they are to push their discoveries through the drug approval process. Most small firms achieve this outcome by either selling their patents to bigger companies, partnering with more established firms to navigate the regulatory process, or obtaining private equity funding. We conclude that regardless of the size or the type of firm and whether research is outsourced or performed in-house, the expected profits of a product help determine whether it makes its way to the market. These profits can be obtained either through a large price-cost margin and/or high sales volume. The margin is determined by a number of factors including the efficacy of the product compared to the next most effective treatment. The volume is determined by the size of the target patient population and the number and similarity of substitute products.

While potential profits are a clear driver of overall research spending, a more subtle question is whether, at the margin, changes in potential profits equally affect research investments for all types of products. Broadly speaking, firms allocate their research and development dollars to two product types: (1) "breakthrough" therapeutic innovations that offer a dramatically different treatment compared to existing products and (2) "me-too" products that largely mimic existing treatments or offer only incremental improvements in outcomes.[8] As we now explain, a firm's investment decisions for these two product types should not necessarily react similarly to marginal changes in expected profits.

We first consider the investment decision for breakthrough products. There is a case to be made that top scientists producing breakthrough research are motivated by more than just potential profits. Academic scientists, as well as leading corporate scientists given free time to pursue their own ventures, may be attracted by the nature of the underlying scientific question and not just market prospects.[9] At

[8] In reality, firms face a continuum of products across these two extremes but for the purposes of this example considering these two extremes best illustrates the differences in the investment decision facing firms.

[9] Stern (2004) shows that corporate scientists give up wages to enjoy the freedom to pursue their own research objectives. Presumably, they would not have to sacrifice wages if their own objectives were aligned with their company's objectives.

the same time, the applied research performed by profit seeking companies often relies on the insights gained from government-funded basic research, which Ward and Dranove (1997) show is more responsive to medical need than market potential.

Even if all researchers only attempt to maximize profits, there are other reasons why the responsiveness of research spending to market demand could be different for FTTs and AAs. Consider that most research programs are very lumpy – firms must often commit tens of millions of dollars to a specific project. At the same time, scientific "know-how" is also lumpy. Whether through experience, patents, or other resources and capabilities, some firms are likely well positioned to develop breakthrough products in specific areas, while the existing resources and capabilities of other firms leave them with little or no hope of succeeding in the same area regardless of market potential. Given that the profit potential for products that address untreatable conditions is often very large, it is likely that those firms with the necessary scientific know-how have already committed to these projects, and small increases in market size do little to spur additional investment either by those already engaged in research or by those on the sidelines. And even if prior treatments exist, a new treatment that represents a truly novel pathway could be sufficiently differentiated so as to be highly profitable for firms with the necessary resources and capabilities.

Of course, there are always disease categories where a small increase in market size is sufficient to encourage additional research, but it may be that most untreated or undertreated disease categories are inframarginal so that the barrier to breakthrough innovation is not market size, but technical feasibility, which may take considerable time to overcome.[10] If this is the case we might expect to see a

[10] For truly marginal disease categories, absent a particular policy intervention, there should be no meaningful research activity before or after the demand shock. For very small disease categories, additional government policies such as the Orphan Drug Act attempt to stimulate investment through offering Tax Credits. Yin (2008) found that these credits did increase investment activity for the largest categories of orphan diseases but not for those with limited revenue potential. However, it should be noted that the recent high prices for new innovations for oncology and other conditions have demonstrated that even very small markets can be profitable. Consider the case of Pfizer's targeted pharmaceutical Xalkori. This drug is targeted at a sub-population that comprises only 5 percent of lung cancer patients. While the targeted patient population is quite small, the annual cost of this drug is $115,000.

delayed response in research activity for FTT innovations. In the limit, however, scientific barriers may be so high that marginal changes in demand are not sufficient to generate the necessary breakthrough research.[11] To address this point, in the results below we examine the evolution of the change in research activity over time. Finding an immediate change in clinical trials suggests that the new products did not result from newly developed basic science but likely came from existing science which was not sufficiently profitable before Part D. We also examine whether the clinical trial is for a primary or secondary indication.

Now consider the investment decision for "me-too" products, which target large markets with low scientific barriers and many existing treatments. The decision to develop a new product in such markets can be considered in the same light as the traditional decision by firms to incur fixed costs so as to enter competitive markets. In this case, the fixed costs represent the costs of developing a sufficiently different product to avoid patent concerns and obtaining regulatory approval. In addition, releasing new products requires relatively large fixed marketing costs. An increase in market size here would create a roughly proportional increase in profits. We should therefore see a near proportional increase in firm investments in the development of AAs, with the only limitation being expectations of future price reductions that accompany additional entry, a limitation that diminishes in magnitude with each successive entrant.

We examine both aspects of innovativeness defined earlier (i.e. scientific advancement and therapeutic availability) by first considering all biotech products in the research pipeline. We then classify these products based on the number of available alternative treatments for the targeted diseases. We define FTT innovations as those aimed at conditions with at most one existing treatment. While this is a fairly restrictive definition, it is one where the outside pharmaceutical option for treatment is clearly

[11] It should be noted that we are investigating a relatively early period in drug development and not finalized products reaching market. Therefore, attempts at new treatments that are unsuccessful in human clinical trials will be included in our data.

quite limited. We classify AA innovations as those aimed at categories with five or more existing treatments. While it is true that there could still be large welfare gains from products in these categories, the incremental gains are likely tempered by the availability of alternative treatments.

While we believe that this approach captures important dimensions of innovativeness not examined in BKS and other prior studies, we acknowledge Trusheim, Aitken, and Berndt's (2010) proviso about the difficulty of measuring the social value of new products. We recognize that our disease based measures are far from perfect, but note that any of the drugs that target conditions for which there are almost no existing treatments, are likely to be innovative to at least some degree. However, some of the products that we label as AA may actually be highly innovative and offer great welfare gains. To address this point, we also consider that the FDA has a process that is "intended to facilitate and expedite development and review of new drugs to address *unmet medical need in the treatment of a serious or life threatening condition* (emphasis added)" (FDA, 2013). These products qualify for either fast track or priority review (among other programs) which we argue serves as a regulatory marker for socially valuable innovation. This is true even for products targeting conditions that with existing treatments if these products represent a meaningful improvement in efficacy. Therefore, in our empirical analysis we exploit these designations as indicators of socially valuable products in our empirical analysis.

3. THE BIOTECHNOLOGY SECTOR

There is no agreed upon definition of a biotechnology firm. Broadly, they are firms that have emerged after a series of scientific innovations in the late 1970s. One of the first and most well-known biotechnology firms is Genentech, which was formed after a scientific breakthrough in the production of insulin and as of 2009 is a wholly owned subsidiary of the global pharmaceutical firm Roche (Revers and Furczon, 2010). Since that time a large and robust industry has evolved with a common denominator across the firms being both a far more extensive use of biological technologies rather than traditional chemical synthesis methods and a greater focus on unmet medical needs for both small molecule and biologic products.

A primary distinction between traditional pharmaceutical and biotechnology firms is the latter disproportionately produces biologic rather than small molecule products. While often linked under the heading of biopharmaceuticals, small molecule products and biological products are actually quite different in both their development and composition. Discussing the difference, Trusheim, Aitken, and Berndt (2010) note that "[b]iologics and small molecules are usually considered substantially different types of products—perhaps as dissimilar from each other as they themselves are from medical devices." At a scientific level, biologic products are far larger in size and more complex than traditional small molecule products and cannot reasonably be fully chemically synthesized. Instead, biologics are effectively grown from living organisms and therefore are almost certainly not likely to be copies or minor modifications of existing small molecule products.[12]

The biologics market remains relatively new with its first product introduction occurring in the 1980s. Since that time, biologics have tended to demonstrate properties associated with innovative products such are targeting conditions for which there are currently few existing treatments. Grabowski (2008) said, "[o]ne of the key indicators of drug quality or novelty was first-in-class introductions, and NBEs [new biological entity] had a significantly higher likelihood of being a first-in-class or novel therapy compared with NCEs [new chemical entity]." Similarly, Grabowski, Cockburn, and Long (2006) said, "[i]t is also relevant that many biologics have been 'niche drugs' targeting rare conditions and small numbers of patients." It's important to recognize that some of the novel therapies offer new treatment

[12] Evidence of this fact can be seen in the difficulty in creating even biosimilars, or generic biologics, that match the efficacy and performance of the branded product. Belsey et al. (2006) commented, "[a]s protein drugs are produced by cells in culture or whole organisms, which are inherently more variable than chemical synthesis methods, establishing bioequivalence of a protein produced by another manufacturer requires a rigorous assessment of quality, safety and efficacy. In light of the difficulties with establishing bioequivalence, generic biologics are termed 'biosimilars.'" Hirsch and Lyman (2011) state, "the production process of each biologic is proprietary, and therefore cannot be perfectly replicated; even if the process was duplicated, it would be unlikely to result in an identical product because of variations in areas such as vectors, cell line development, and bioreactor conditions."

options for individual suffering from diseases with treatments to which they do not currently respond. These products would create social value. We also note, however, that many biotechnology firms no longer exclusively manufacture biologics. Indeed, some of the biotech products in our data, such as Zavesca for Gaucher's disease and Racivir for HIV/AIDS, are small molecule products. Even so, growth in the pipeline of biotech firms is likely indicative of new products with scientific novelty.

4. MEDICARE PART D

Medicare is the United States social insurance program that primarily covers individuals over the age of 65. First created in 1965, this program originally covered some portion of the costs for physician and hospital services, but offered very limited coverage for pharmaceuticals. As pharmaceutical spending grew so did political pressure to extend Medicare to cover these products. This resulted in the passage of Medicare Part D as part of the Medicare Modernization Act of 2003. Prior to this point, it was unclear whether there would be a prescription drug benefit added to Medicare and certainly little information about its eventual form. Part D became effective in 2006. In our analysis, we consider 2004 as the date where firms would first change their investment decisions. However, we are cognizant of the uncertainty about the impact of Part D on the industry prior to its implementation and therefore present results where we allow the change in the firm's investments evolve over time.

The implementation of Part D caused an immediate increase in pharmaceutical insurance coverage for seniors. In 2006 there were nearly 26 million elderly individuals covered by the expansion. This number grew to over 30 million by 2011, the end of our sample period. Perhaps more importantly for the investment decisions of pharmaceutical firms, this broader insurance coverage also caused an increase in pharmaceutical use among this population (Ketcham and Simon, 2008; Yin et al., 2008).

One concern for pharmaceutical firms may be that the higher utilization might be accompanied by a decrease in prices resulting from government monopsony power. However, the structure of Part D made this unlikely. Unlike other government programs such as the Veterans Administration, Part D is run by a series of private insurance programs (similar to the health insurance exchanges under the Affordable Care Act). In addition, the law explicitly prohibits the Center for Medicare and Medicaid Services (CMS) from directly bargaining with pharmaceutical firms. Duggan and Scott Morton (2010) found that enrollees in Part D paid higher prices and increased their utilization of prescription drugs compared to when they were uninsured. This suggests that Part D represents a substantial positive profit shock for pharmaceuticals targeted at conditions with a large number of elderly patients. This shock may be even more apparent for the biologic products in our database. Beyond the technical difficulties inherent in creating a copy-cat biologic product, at the time period of the passage of Part D (and for over a decade after) there was no regulatory process for a firm to introduce biosimilars, i.e. a generic biologic product. As a result, firms introducing new biologic products could expect near monopoly status for a longer time horizon than the length of their patent.

While Part D represented the first broadly available pharmaceutical benefit for Medicare beneficiaries, Medicare has always offered limited pharmaceutical coverage through the Medicare Part B medical benefit. The Part B program is complex and has many exceptions, but as a general rule Part B applies to drugs that are administered as part of a physician office visit if the drug is purchased and administered by the physician. Drugs purchased at retail pharmacies are generally not covered under this benefit. There could be a concern that the many of the biologics in our data are more likely to be administered by a physician and therefore coverage for these products may have been unaffected by the passage of Part D. However, many biologics are covered under both Part B and Part D depending upon the treatment application and the source of purchase. For example, we identified the top 5 highest selling biologic drugs from 2009 to 2012 and found that all 5 were covered to some degree under Part D.[13]

[13] *Nature Biotechnology* publishes annual top ten lists of biotechnology drugs. The 2010-2012 lists may be accessed at http://www.nature.com/nbt/journal/v29/n7/fig_tab/nbt.1913_T5.html, http://www.nature.com/nbt/journal/v30/n8/fig_tab/nbt.2320_T5.html and http://www.nature.com/nbt/journal/v31/n8/fig_tab/nbt.2653_T7.html respectively. A list of the top five biologics in 2009 can be found at http://www.kaiserhealthnews.org/charts/2009/drug-sales.aspx.

Similarly, there were 14 drugs over this time period that were in the top 10 in at least one year, and 13 of those 14 had some Part D coverage.[14] This included oncology products such as Avastin and Rituxan. The vast majority of these products were *also* covered by Part B, however, with Part B covering the majority of claims.

What is important for our analysis is when and how firms determine which insurance program will cover their product. Once products have completed the FDA review process and are ready for market, firms have a generally good sense of whether they will be primarily covered by Part B or Part D. However, it is important to draw a distinction between this *ex post* knowledge and what firms know *ex ante,* i.e. when they are first making their investment decisions. The passage of Part D increased certainty for firms regarding the potential insurance coverage of new products aimed at conditions with a large potential elderly population. Following the passage of Part D biotech firms had a much greater expectation that any product they developed for conditions with a high Medicare market share would have a larger number of fully insured elderly patients than before the passage of Part D.[15] It should also be noted that in recent years a growing proportion of oncology product have been small molecule products and not biologics (IMS, 2014). This shift in product type could itself be a result of this increased certainty from the passage of Part D.

[14] Some of this coverage comes through "brown bagging" where patients purchase biologics at a retail specialty pharmacy using Part D and then have these drugs immediately administered in an outpatient setting. Given the differences in cost sharing between the two programs, this strategy can limit the out of pocket costs for patients and therefore might increase demand for individuals who could not afford out of pocket costs for these drugs under only Part B.

[15]There could be a concern that products more likely to be covered by Medicare Part B are also more likely to be the first to treat in their category. This could explain why Part D did not spur FTT innovations. However, this does not appear to be the case. Using data from the MEPS we created a variable for the percentage of products for an indication that are prescribed in an inpatient setting. A regression of this variable on a set of therapeutic fixed effects and an indicator variable for whether the disease has 5 or more existing treatments had a coefficient (standard error) on the indicator variable 0.011 (0.015). This suggests that there is no relationship between the number of existing treatments and the coverage of Medicare Part B.

5. DATA

Examining the role of demand shocks on investments in innovation in the biotechnology sector requires data from a variety of sources. In this section we detail our data sources for describing clinical trial activity, the change in the market size as a result of Medicare Part D, and the number of available alternative treatments.

5.A. The Biotech Pipeline

While some studies such as Acemoglu and Linn (2004) and Dubois et al. (2014) consider new drugs reaching the market, given the timing and nature of biotech research, there are several reasons why we believe in our setting it is more appropriate to follow BKS and examine the research pipeline. First, the decision to move forward with clinical trials is based on the current and future investment climate. In contrast, as a result of the length of clinical trials, the actual introduction of new products represents decisions based on mainly on past economic environments.[16] Given that Part D was enacted only a decade ago, many of the biotech products that reached the market in the "post" period would have been funded in the "pre" period, making it difficult to identify the effect of the law. Second, examining only new products would generate a survivor bias in our estimates of innovative activity, i.e. we would only see successful innovation. This would be a particular concern if the effect of the demand shock was for truly innovative products which might be riskier. Third, only small number of biotech products have been approved by the FDA subsequent to the passage of Part D. Restricting our study to approved products would limit our statistical power.

We examine the research pipelines of biotech firms that have pursued FDA approval for their biomedical drug candidates. We obtained data on 251 self-identified biotech firms from Deloitte RECAP

[16] Obviously firms retain the right to not market products that have completed clinical trials but are no longer economically profitable because of other changes. However, the ability to bring a product to market requires a decision to invest in the candidate over a decade prior.

IQ (now called Thompson Reuters RECAP), a consulting firm specializing in biotech business intelligence. The firms that are included in the data are described by Thompson Reuters (2014) as:

> "self identified as biotechnology firms from their inception, were largely financed through venture capital and public equity in their early years, tended to focus on pursuit of new, untested technologies (i.e., recombinant DNA, monoclonal antibodies, and novel molecular targets) and unmet medical needs (rather than developing 'me-too' or second generation drugs) to a greater degree than 'traditional' pharmaceutical companies."

The sample includes very large biotech firms such as Genentech, Amgen, and Gilead, as well as many young, single-compound firms such as Alba Therapeutics and Osteologix. Importantly, these historical data include pipelines of firms that have exited the market through bankruptcy, as well as those that have been acquired by traditional pharmaceutical firms such as the small biotech firm Pharmasset which developed Sovaldi and was subsequently purchased by Gilead. Thus, our data provide a broad picture of biomedical innovation, pursued both by independent companies and subsidiaries of large pharmaceutical companies. The dataset includes information such as the start date of clinical trial activity, the disease targeted by the drug candidate, whether the drug was granted an Orphan Drug Designation (ODD), fast track status, or priority review.

Our data contains 1,466 biotech-originated drug candidates that began clinical testing on humans between the industry's birth in the 1970's and 2012. It is reasonable to assume that the clinical trial stage (as opposed to approved products) is where we are most likely to detect a change in firm behavior during the relatively short time period after the passage of Medicare Part D. This is particularly true given that clinical trials for biologics have been found to take longer on average than those for small molecule products (DiMasi and Grabowski, 2007).

During the development process for new products every drug candidate has a single primary indication, which is the targeted disease that was designated when the candidate first entered Phase I clinical testing. Drug candidates can also designate a secondary indication for a different disease. This could be done at any time during clinical trials. As an illustrative example considered the case of

Tiagabine, which is marketed under the brand name Gabitril. This candidate was originally introduced to our sample with a Phase I trial in 2002 targeting anxiety. Having successfully completed this stage, a secondary indication for insomnia was directly introduced to Phase II trials in 2005. Another example would be Rilonacept, which is marketed under the brand name Arcalyst. This drug has a primary indication targeting rheumatoid arthritis in 2001, but then received secondary indicators for cryopyrin-associated periodic syndromes in 2004 and gout in 2007. RECAP data contain both primary and secondary disease indications. Figure 4 presents the distribution of clinical development starts within 1998-2011.[17]

We limit the scope of candidate introductions in the RECAP data to 1998-2011. This restriction results in 1,211 drug candidates with a total of 2,026 indications (approximately 60% of which are primary) targeting 488 different diseases across 20 broad therapeutic areas. Our primary RECAP dataset is at the indication level, with each observation representing a unique candidate-targeted disease interaction. The distribution of targeted diseases is presented in Figure 5 and has remarkable resemblance to that reported by the independent research of Ernst & Young (2012), which is also presented in the figure and aims to describe the overall state of the industry.

As can be seen in Figure 5, while each therapeutic area has some clinical trial activity, approximately half of our indications target cancer. There are 99 different cancer conditions in the data, but 5 of these cancers (solid tumors, lung, prostate, breast, and colorectal cancer) account for approximately 40 percent of all cancer products. At the other extreme, 48 of the 99 cancer conditions are targeted by a single candidate (e.g., islet cell carcinoma, mesothelioma, medullary thyroid cancer and

[17] Comparing the RECAP data to publicly available information, we found some degree of error in these dates. In some cases the RECAP dates for the introduction of new indications were actually the dates for alternative events such as the date of in-licensing, IND filing, or even just the acquisition of the original developing firm by another entity. Where necessary we correct these dates using data from www.clinicaltrials.gov and, in some cases, on the phase-specific average lengths reported by DiMasi et al. (2003). This was accomplished in the following manner. First, we replaced the project start date in the RECAP file with data from clinicaltrials.gov when these data were available and indicated an earlier start date. Second, when data were not available on clinicaltrials.gov we used the average clinical trial lengths reported in DiMasi et al. (2003) and that the trial process was carried out sequentially.

gastrointestinal adenocarcinoma). Given the large presence of cancer conditions in our clinical trial data, we also present results excluding this therapeutic area. Finding similar results among the non-cancer sample suggests that our results are not driven by a confounding shock such as a scientific development in the process of developing cancer treatments.

Given that our measure of the demand shock from the passage of Part D is at the ICD-9 level, we match our 488 diseases in the RECAP data to the 241 corresponding ICD-9 codes. This allows us to link each indicator to a measure of the Medicare orientation for the targeted disease, the construction of which we now describe. Following this process our final dataset is at the condition-year level.

5.B. Medicare Market Share

We account for the differential market effects of the passage of Medicare Part D by estimating the percentage of patients with a particular disease who are covered by Medicare. We create the variable Medicare Market Share (MMS) using data from the Medical Expenditure Panel Survey (MEPS), a large, representative sample describing the utilization of prescription drugs, medical services, and insurance.

We use the MEPS yearly conditions and insurance files from 1998-2003 to construct the MMS variable. The first of these reports the conditions suffered by each respondent in each year of the sample. The second reports the type of insurance coverage held by the respondent throughout the year. Between these two datasets we generate the share of Medicare covered individuals for each ICD-9 code. We then averaged across these 6 years to get the MMS variable used in our analysis.[18] Therefore, our measure of MMS represents the information available to biotech firms in the year that Part D was passed.

The distribution of MMS that we obtain from the MEPS makes intuitive sense with respect to the epidemiological characteristics of Medicare enrollees. That is, those diseases that are commonly

[18] Our measure of MMS is similar in spirit to Duggan and Scott-Morton (2010). One key difference is that their analysis focused on prices at the brand name drug level and therefore their measure of MMS was based on the percentage of Medicare patients using the drug prior to the passage of Part D. Given that our analysis is at the condition level, we instead use the MEPS conditions file. This allows us to account for individuals with a condition that did not purchase a prescription medication due to their lack of prescription insurance coverage.

associated with older people tend have a higher values of MMS. For example, MMS equals zero for indications such as infertility, smallpox, and Japanese encephalitis. Around the median of MMS are indications such as ischemic stroke, bronchiectasis, pain management, and spinal chord injury. Finally, at the top of the distribution there are indications such as lung cancer, Parkinson's disease, heart failure, and (with the highest MMS) Alzheimer's disease. Figure 6 displays the (Kernel) distribution of MMS scores of the indications in our sample.

5.C. The Novelty of New Drug Candidates

As discussed above, one potential measure of the social value of new products is whether they represent a therapeutic innovation. One way to capture this is by identifying the clinical indications for each new product and then counting the number of existing biologic and non-biologic products that have received FDA approval for treating each indication. To determine the number of available treatments we obtained drug approval dates from the FDA "Orange Book" and the Center for Biologic Evaluation and Research (CBER). From specialized websites we then obtained data describing each drug's approved indications and usages.[19] We obtained approval dates for the primary indication and we assign this date to all indications for the product.[20]

Figure 7 gives the distribution of existing alternative treatments for our disease categories in 1998, 2003, 2008 and 2011. In each of the years, the vast majority of diseases have either zero or one alternative treatment. It should be noted that this is not a patient weighted measure and the diseases with larger caseloads are more likely to have a large number of existing treatments. As would be expected given the progress of technology over time, the number of conditions with 2 or fewer existing treatments declines from 1998 to 2011. Similarly, there is an increase in the number of diseases that have five or more

[19] We relied on three government-sponsored webstites: DailyMed (dailymed.nlm.nih.gov), MedlinePlus (http://www.nlm.nih.gov/) and Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda)
[20] This creates a small upward bias in the recorded number of competitors at any point in time. Given that we classify diseases based on the maximum number of treatments available at the close of our sample this does not affect our results.

existing treatments. We classify the number of existing alternative treatments based on the maximum number of treatments available during our sample. We do this because all or nearly all of the firms in our sample would have had access to data similar or better than ours, and therefore would have knowledge of the entire industry research pipeline. Thus, each firm knows reasonably well whether its candidate is a FTT or an AA. While there are exceptions (e.g., the first firm to start clinical trials may reasonably believe it is FTT), we have no systematic way of parsing the data to deal with these exceptions. As would be expected, the number of alternatives is positively correlated with both the number of patients reporting the conditions in the MEPS and in the total amount of pharmaceutical spending.

As an alternative to defining the potential social value of new products based on the number of existing treatments for the targeted condition, we also consider various regulatory markers of innovation. First, we consider whether a candidate received an orphan drug designation. Passed in 1983, the Orphan Drug Act (ODA) provides financial resources to support clinical trials and an expanded market exclusivity period for drugs targeting rare conditions. The intention of this legislation was to provide incentives for firms to develop products targeting rare conditions for which there were no existing treatments (Yin, 2008). In our data there are 214 candidate products that receive this designation.

We also examine two FDA indicators of innovation – fast track and priority review. Concerned that the approval process for new drugs was causing long delays for socially valuable products, the FDA created several designations to provide a shorter review times for particular types of drugs. Fast track status provides firms with greater opportunities for working with the FDA to craft an application. This status is granted to candidates that are intended for the "the treatment of a serious or life-threatening disease or condition, and it [the drug] demonstrates the potential to address unmet medical needs for such a disease or condition" (FDA, 2014). Drugs can also be granted priority review, which shortens the FDA review time. This status is granted to "a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness" (FDA, 2014). Prior research links biological research to these FDA indicators of innovativeness. Grabowski et al. (2006) found that during 1983–

2001, "biotech firms accounted for two-thirds of the research on orphan drugs…although they represented fewer than half of FDA approvals." Trusheim, Aitken, and Berndt (2010) find evidence that biologics are more innovative across all three of these metrics but the strongest support comes for targeting orphan disease categories.

In our data, 136 candidates are classified as receiving fast track status and 62 received a priority review designation.[21] In our data below, we consider a composite category that indicates whether any of these three designations was granted to a candidate. We obtain qualitatively similar (though statistically less powerful) results when we separately consider each designation.

6. EFFECT OF MEDICARE PART D ON RESEARCH AND DEVELOPMENT EFFORTS IN THE BIOTECHNOLOGY SECTOR

We begin by considering the overall impact of Part D on the development of products targeting diseases of the elderly. Our initial analysis of this aggregate response follows in the general spirit of BKS's earlier work.

Figure 8 shows the Kernel distributions of the MMS of new candidates by time period. Over our sample, there is a meaningful shift towards candidates with a higher MMS – the pattern we would expect if Part D caused firms to shift their investment activity towards newly covered drugs. To quantify the magnitude of these graphical relationships, we turn to a regression analysis where we estimate a poisson quasi-maximum likelihood model of the following form:

$$NewIndications_{it} = f(\alpha + \beta_1 MMS_i + \beta_2 PostPartD_t + \beta_3 PostPartD_t \cdot MMS_i + \lambda_t + \eta_d) \quad (1)$$

where MMS_i is the Medicare Marketshare of condition i, $PostPartD_t$ is an indicator variable equal to 1 in the years after the passage of Medicare Part D (i.e. 2004-2011), λ_t is a year fixed effect, and η_d is a disease or therapeutic area fixed effect depending on the specification. We will also evaluate the pattern of

[21] These designations are sometimes granted later in the drug development process. As a result, it should not be surprising that we observe a lower rate of designations for drugs that have more recently entered clinical trials on humans.

changes after Part D by estimating specifications of equation (1) which break this time period into three sub-periods. Standard errors allow for arbitrary correlation between observations in the same therapeutic area. One concern with our data is that there are a large number of conditions that have no clinical trial activity in any one year. Therefore, we also provide estimates from a zero-inflated negative binomial model.

The coefficient of interest is β_3, which represents the change in the clinical trial activity for drugs after the passage of Medicare Part D based on their MMS. Under the assumption that there was no relationship between MMS and investment activity prior to 2003, this represents the causal effect of Medicare Part D on firm investment activity. In addition to the graphical evidence of the pre-trends in Figure 1, we will also test the validity of this identifying assumption by estimating a placebo regression using data prior to the passage of Part D.

Table 2 contains the estimated coefficients for equation (1). Column (1) contains our estimates when we include therapeutic area fixed effects. Our results suggest that following the passage of Part D in 2004, there is a statistically significant increase in the number of drugs targeting conditions with high levels of MMS, relative to those targeting conditions with low levels of MMS. To provide some context of the magnitude, consider the average drug in our sample has a MMS of 0.33 percentage points and that the mean number of clinical trials per condition per year is 0.3. Therefore, the marginal effect at the mean for this coefficient is an approximately 0.044 increase in the number of indications per condition per year. While this may appear small in magnitude, recall that many conditions have only one product in trials throughout our entire sample. Column (2) contains the estimates controlling for disease rather than therapeutic area fixed effects. The estimated coefficient is larger than, but not statistically different from, those from the model containing therapeutic area fixed effects and the marginal effect at the mean is 0.054. Finally, column (3) contains the zero-inflated negative binomial model. These estimates are slightly larger than the estimates in columns (1) and (2) with a marginal effect at the mean of 0.065.

While the graphical relationships and regression estimates suggest a change in research activity following 2003, there could be a concern that this is simply the continuation of a secular trend towards drugs targeting conditions of the elderly – perhaps because of a demographic shift as a result of the aging baby boomer population. To address this issue, we revisit Figure 1, which shows the number of clinical trials per year based on whether the indication targets a disease that has an MMS above or below the median level from 1998-2011. If the estimates in Table 2 were driven by secular pre-trends, then we should see this in the data prior to 2003. However, that is not the case. Prior to the passage of Medicare Part D (demarcated by the dashed vertical line), there was very little difference in level or trend between these clinical trial activities for these two products. After the passage of Part D there is a marked increase in the number of clinical trials for drugs with higher MMS values. In every year after 2004, there are more clinical trials for indications targeting diseases with MMS scores that are above the median.

To further address this concern, we estimate a placebo specification of equation (1) where the indicator variable for $PostPartD_t$ is equal to 1 for the years 2001-2003. All observations after the 2003 are removed from the data. Table 3 shows the results. The coefficient on the interaction term measures the change in research activity between 2001 and 2003 compared to earlier time periods. Given that there was little clear evidence that Congress would develop and pass a prescription drug benefit, we do not expect any pre-passage anticipatory behavior. However, if our main estimates are simply the result of a gradual shift in the market, we should find generally similar results from this specification. Across all of the columns the estimates on the interaction term are negative, small, and statistically insignificant. This supports a causal interpretation of our main estimates in Table 2.

Recall that cancer treatments represent a large percentage of our sample. One might be concerned that a change in the science of developing cancer drugs that was coincident with the passage of Part D, or that cancer drugs are mostly covered under Part B and therefore the creation of Part D may not represent a substantial profit shock. (Though it should be noted that many biotech companies manufacture oral oncology treatments that would be expected during the development process to be covered under Part D.) To allay these concerns, we re-estimate our main regressions excluding cancer drugs.

We present both graphical and regression evidence for the non-cancer products. Figure 9 contains the same information as Figure 1 for a sample containing no cancer treatments. Prior to the passage of Part D, products in this sample with an above-median MMS had fewer clinical trials in each year than those with a below-median MMS. These products groups followed very similar trends in each year, and in all but one year there are more trials for below-median MMS drugs. Following the passage of Part D, products with an above-median MMS saw an increase in clinical trials and in all but one year had more clinical trials than products with a below-median MMS. To examine the magnitude of these graphical responses, Table 4 contains estimates from equation (1) for a sample that does not contain cancer treatments. The results are remarkably similar in magnitude to those obtained from the full sample but due to the smaller sample are less precisely estimated.

The above results and the previous literature provide strong evidence of pharmaceutical firms expanding their research efforts in response to the demand shock from Medicare Part D. However, it is unclear whether these research efforts are aimed at innovative products that will create large amounts of social value or simply represent rent seeking on behalf of biopharmaceutical firms producing less innovative products. We now examine whether the treatments represent innovations. We begin by examining the timing of the change in clinical trial activity. We then classify new clinical trial activity by three measures: (1) whether the trial is for a primary or secondary indication, (2) the number of existing products targeting the indications and (3) various regulatory measures of innovation involved in the FDA approval process.

7.A. Primary vs. Secondary Indications

We have demonstrated a meaningful change in the research activities of biotech firms in the years after the passage of Part D. We now examine the dynamics of this change in more detail. Columns (4) – (6) of Table 2 contain a specification of equation (1) that breaks the post-Part D period into three time periods. The estimated coefficients in columns (4) and (5) show a jump in investment activity in 2006 and a further increase in the subsequent years. This is generally consistent with the graphical evidence in Figure 1. The zero inflated negative binomial results suggests a more immediate increase in clinical trials that remains elevated throughout the remaining years.

The timing of the change in clinical trial activity provides some information on the scientific innovativeness of the new products. The immediate increase in the first three years is consistent with the previous estimates of BKS, who suggest that pharmaceutical companies have already developed scientific knowledge that was not sufficiently profitable prior to the passage of Part D. In other words, firms have products "on their shelves" and will perform the necessary clinical trials only when market demand has grown. As we discussed above, these types of marginal technologies are likely less socially valuable than truly innovative technologies which would likely have been sufficiently profitable before and after Part D. When we consider that physicians are free to prescribe FDA approved products for any purpose, including "off-label" prescribing for secondary indications, we conclude that the social value of obtaining approval for secondary indications can be quite small. However, firms are not allowed to encourage physicians to use the product in this manner.[23]

One manifestation of products "moving off the shelf" is when firms seek FDA approval for new indications for existing drugs. Importantly, even if the firm does not seek (or receive) approval for the secondary indication, We explore this issue by re-estimating our models using a sample split into whether the clinical trial is for a primary or secondary indication. Figures TK and TK depicts the change in clinical trial activity for primary and secondary indications respectively. In each figure the solid line represent trials targeting indications with an above median MMS and the dashed line represents

[23] Firms are not allowed to encourage physicians to use the product in this manner and firms marketing products for off-label usage can receive large fines. For example, in 2009 Pfizer settled with the Department of Justice and agreed to pay a $2.3 billion fine for marketing four of its products for off label use (Rubin, 2009).

indications with a below median MMS. Both figures show a marked increase in research activity for drugs with an above median MMS.

Table TK contains estimates from a specification of equation (1) for samples based on whether the trial is for a primary or a secondary indication. For reference, we reprint the results for the full sample in columns (1) – (3). These estimates demonstrate that the change in research activity that we identify is not solely driven by a re-application of existing products to new indications. While the smaller sample sizes decrease precision, the estimated magnitude of the response is remarkably similar for the change in clinical trials for primary and secondary indications.

While the aggregate change in research activity appears to be relatively evenly split by primary vs. secondary indications, it is possible that there are differences in the speed with which firms can initiate these different types of trials. To further examine this point, Appendix Table A2 contains the estimates which break to the time period after the passage of Part D into three segments. These estimates suggest that the similar aggregate response appears to results from a nearly immediate increase in trial activity for secondary indications and an increase in trials for primary conditions that only begins after 2009. This pattern is consistent with these firms immediately seeking approval for known off-label uses while also beginning the development of new products which first enter into clinical trials several years later.

7.B. Number of Existing Alternatives

As discussed earlier, we expect that the response to Part D may be concentrated among products that target conditions for which there are already many alternatives. We therefore now contrast how Part D spurred innovation of FTT versus AA products. Recall that we define FTTs to be those products treating conditions for which there is at most one existing alternative, whereas AAs treat conditions for which there are more than five alternatives. These represent starkly different levels of treatment availability. Figures 2 and 3 show that there was a marked increase in research for AAs but little change for FTTs. We now turn to regression analysis to more precisely estimate these relationships.

In Table 5 we report estimates of equation (1) for samples based on the number of alternatives. Column (1) – (3) contain estimates for the FTT sample. The coefficients on the interaction term are near zero and statistically insignificant. This demonstrates that following the passage of Part D there was no detectable change in the pipeline of biotech drugs targeting nearly untreatable conditions that disproportionately affect the elderly. This suggests that research activity for these categories is not sensitive to marginal changes in expected profits. While this does not rule out effects on innovative activity from changes in expected profits, it does demonstrate that the innovation will be unlikely to come in the form of new treatments for diseases without existing pharmaceutical options.

Figure 3 suggests that AAs were most responsible for the increase in research activity following the passage of Part D. The estimates in columns (4) - (6) of Table 5 confirm this graphical relationship; the coefficients on the interaction term are all large, positive, and statistically significant. To gauge the magnitude of the Part D effect on AA innovation, consider the estimate in column (5), which controls for disease specific fixed effects. The average number of clinical trials per condition-year in the AA sample is 0.65. Therefore, the marginal effect at the mean for AAs is 0.18 indications per condition per year.

Table 6 presents results of the previous regressions but breaks the post-Part D period into three sub-periods. Once again, we find no evidence of changes in clinical trial activity for FTT products. However, the investment activity for AA products in the years following the passage of Part D grows in magnitude and is statistically significant at a p-value of 0.01 after 2006. This relatively fast increase for products with many existing treatments provides further evidence that these were likely not based upon significant scientific breakthroughs but instead on already existing technologies.

The lack of an effect for the FTT products might simply reflect the large number of clinical trials that are for secondary instead of primary indications. However, this is not the case. Panel A of Appendix Table A3 contains the estimates of the change in clinical trial activity for FTT products for samples of primary and secondary indications. Panel B contains the same estimates for AA products. These estimates show that the lack of an increase in clinical trial activity for FTT products is consistent across both primary and secondary indications.

7.C. Regulatory Indicators of Innovation

To further examine the innovative nature of the investment response to demand shocks, we turn to FDA designations of innovation. As discussed above, our data contain indicators for whether a product has received orphan drug designation, priority review, or fast track status. Given the relative rarity of these designations, we create a single variable equal to 1 if any drug candidate received one of these designations. We begin with a graphical exploration of this relationship. Figure 10 contains the number of conditions with at least one product receiving an FDA designation of innovation over time. Prior to the passage of Part D, products with an above-median MMS had more of these designations in each year. However, between 1998 and 2003 the difference between these two categories narrowed. Following the passage of Part D, the difference in the number of designations narrowed further and was nearly equal by the end of the sample. This figure suggests that after the passage of Part D there was a decrease in the number of FDA designations for products targeting above-median MMS diseases compared to those targeting below-median MMS diseases. However, it appears that this change represents the continuation, or possibly the acceleration, of a pre-existing downward trend.

We next estimate a logit specification of equation (1) with this indicator variable as the dependent variable. We also include a control for the number of new products introduced that year.[24] Column (1) of Table 7 contains the estimated coefficients from this model. The coefficient on the interaction term suggests that products with a higher MMS were less likely to receive one of the three designations for innovativeness. On its own, this coefficient suggests that the passage of Part D may have shifted firm investments away from innovative products. Such an effect is theoretically possible given that the

[24] Estimated models also include year dummies that control for the fact that our data is more likely to record FDA designations for candidates introduced to clinical trials earlier in the sample.

increase in investment activity following Part D could increase expected competition and decrease expected profits even for novel products. However, it could also be the case that this decline is simply the continuation of pre-existing trends for this outcome. To examine this possibility, column (2) contains the estimate from a falsification test using data prior to the passage of Part D. The estimated coefficient on the interaction term is approximately the same size as in column (1).

Taken together, this evidence suggests that products with a higher MMS had a declining number of FDA indications of innovativeness *before and after* the passage of Part D. As a result, the statistically significant coefficient in column (1) appears to be the continuation of a pre-existing trend. This suggests that Part D did not cause a decrease in investment into products deemed innovative by the FDA or cause a break from this pre-existing trend. In other words, Part D did not differentially spur investment activity for products that received an FDA designation.

8. CONCLUSION

The expansion of pharmaceutical insurance for the elderly in the United States caused an increase in clinical trial activity in the biotechnology sector. This suggests a strong link between expected profits and research investments. To provide some sense of the magnitude of these findings, we consider the estimated change in revenue from Part D suggested by Duggan and Scott-Morton (2010). Based on these estimates, the average product in our sample should expect a revenue increase of approximately 9 percent.[25] Our estimates show that Part D increased clinical trials for the average product by approximately 18 percent. This suggests an elasticity of clinical trials with respect to the expected change in market size of approximately 2. This implied elasticity is less than the earlier estimates in BKS for clinical trials as well as the estimate in Acemoglu and Linn (2004) for new molecular entities. Our smaller

[25] For a drug with a 100 percent Medicare Market Share, Duggan and Scott-Morton predict a 27 percent increase in revenue (though it should be noted that this estimate is statistically insignificant). In our sample, the mean MMS is 33 percent suggesting an expected revenue increase of approximately 9 percent. It should be noted that given the potential for partial Part B coverage for biotech products this may be an overestimate of the effect of Part D on revenue in our sample.

elasticity likely results from the combination of two factors. First, products from biotechnology firms may be more difficult to develop than the average product. Second, these products may be more likely to be partially covered by Part B and therefore the profit shock from Part D for these products may be smaller than for the average small molecule product with a similar MMS.

An open question in the existing literature is whether these new products represent welfare improvements or simply rent seeking by pharmaceutical firms. At the broadest level, the biotechnology sector has been found to be generally innovative and the complexity of the products suggests that it is difficult to make small changes to generate a "me-too" product. In fact, the complexity of these molecules makes it more difficult to even make generic versions of these products. Therefore, new products emerging from this sector are more likely to represent some form of scientific advancement rather than only the me-too products cited by many critics of the pharmaceutical industry.

Our results are quite different when we examine whether the new biotech products spurred by Part D provide innovative treatments as measured by the absence of existing pharmaceutical treatments for the same conditions and by FDA designations of novelty. We find no evidence that the passage of Part D caused the emergence of innovative products across these dimensions. The research activity following a demand shock is primarily for products targeting conditions with five or more treatments. For these products we estimate an implied elasticity of clinical trials to change in revenues of 3.3 – far closer to the estimates of the earlier literature. In addition, we see no evidence of an increase in products receiving FDA designations.

It could be that true breakthroughs take longer to develop than incremental innovations. This is particularly true if biotech firms have a cache of potential products that are marginally unprofitable before a small change in market demand and their immediate response to a shift in demand is to bring these products "off the shelf." While there is no systematic method of calculating the time from basic science to human trials, we do note that we examine a relatively long window after the passage of Part D and that there are prominent examples of compounds being identified and reaching human trials in far less time. For example, the hepatitis C cure Solvaldi discussed earlier was primarily the result of the work of Michael Sofia at Pharmasset. Sofia joined the firm in 2005 and Sovaldi entered clinical trials five years later (Gounder, 2103). Similarly, Merck's insomnia treatment Suvorexant moved from first concept to clinical trials in four to six years (Parker, 2013). While these provide only anecdotal evidence, they do demonstrate that the time period we consider after Part D is sufficient for some socially valuable products to reach market. That being said, we realize that we cannot rule out the possibility that over an even longer horizon more innovative products could enter clinical trials as a result of this marginal demand shock.

As the debate about the rate of growth of health care spending in the United States continues it will almost certainly continue its focus on the profits earned by pharmaceutical firms. For example, the Centers for Medicare and Medicaid Services is currently not allowed to exploit its market power to negotiate lower prices for drugs purchased by Medicare Part D. Examining the prices paid by other government agencies without this restriction, such as the Veterans Administration, suggests that changing this policy would lead to lower prices and profits for pharmaceutical firms. Our results suggest that this would decrease the number of new biotechnology products available for individuals suffering conditions with a large elderly patient share. That being said, it also appears that this would have little effect on the emergence of new products for conditions with few existing treatments or those deemed by the FDA to require a swift approval process. Future work should examine whether the new treatments following Part D that target conditions with many existing options represent a welfare increase on a dimension not recognized by the FDA rather than simply lower prices.

It is also important to note that our estimates represent the causal effect from a *marginal* change in expected profits. We posit that the reason why there is little effect from this change on true scientific breakthroughs is that these products are always profitable and therefore research investments in them are inframarginal with respect to small profit changes. Another possibility is that the scientific barriers are largely impenetrable and firms will not attempt to overcome them without substantially higher profit potential than what was conferred by Part D. Thus, large changes in profits from a single payer health system, a dramatic reduction in patent length, or some form of compulsory licensing would likely have far different effects.

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Figure 1
Number of New Indications by Medicare Market Share

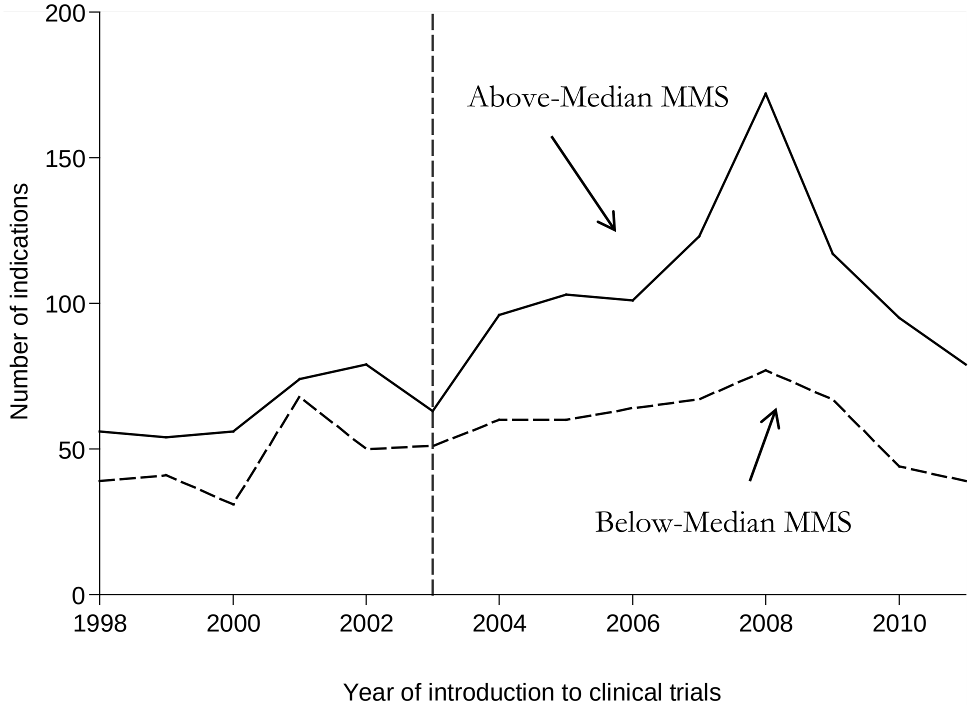


Figure 2
Number of New Indications by Medicare Market Share
More than Five Existing Treatments

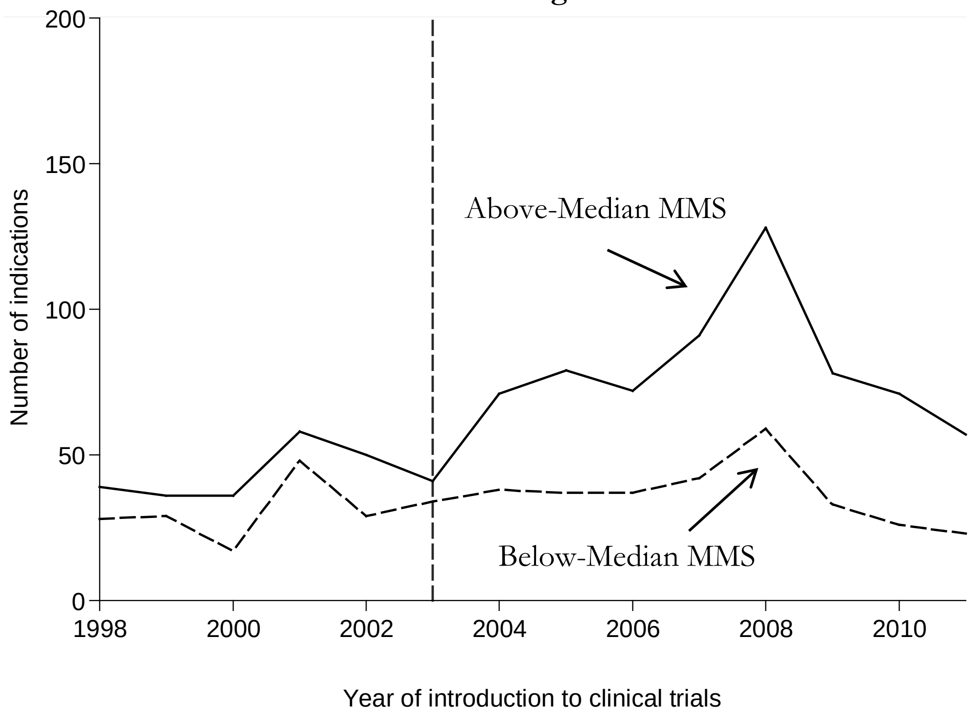


Figure 3
Number of New Indications by Medicare Market Share
Less Than Two Existing Treatments

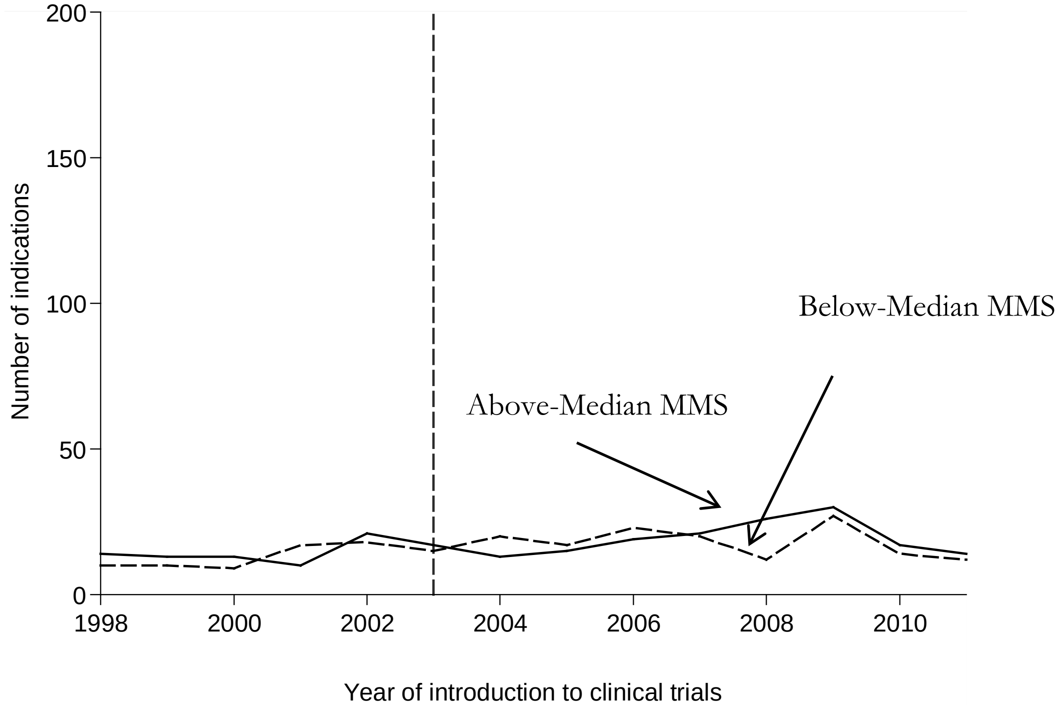


Figure 4
Number of Indications Entering Clinical Trials by Year

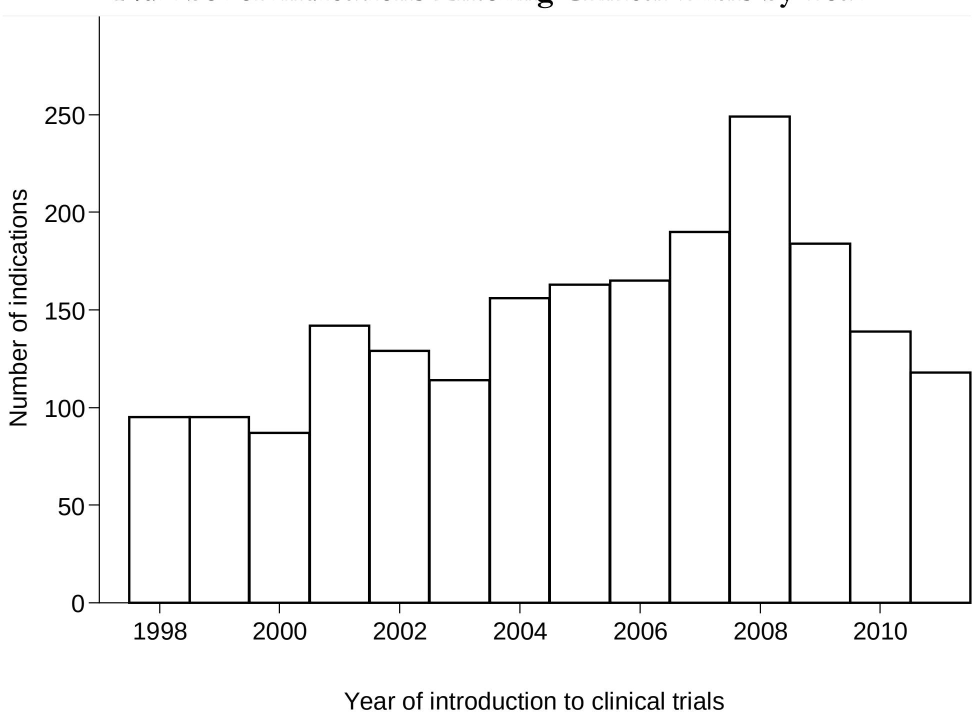


Figure 5
Distribution of Therapeutic Areas
RECAP and Ernst and Young (2012)

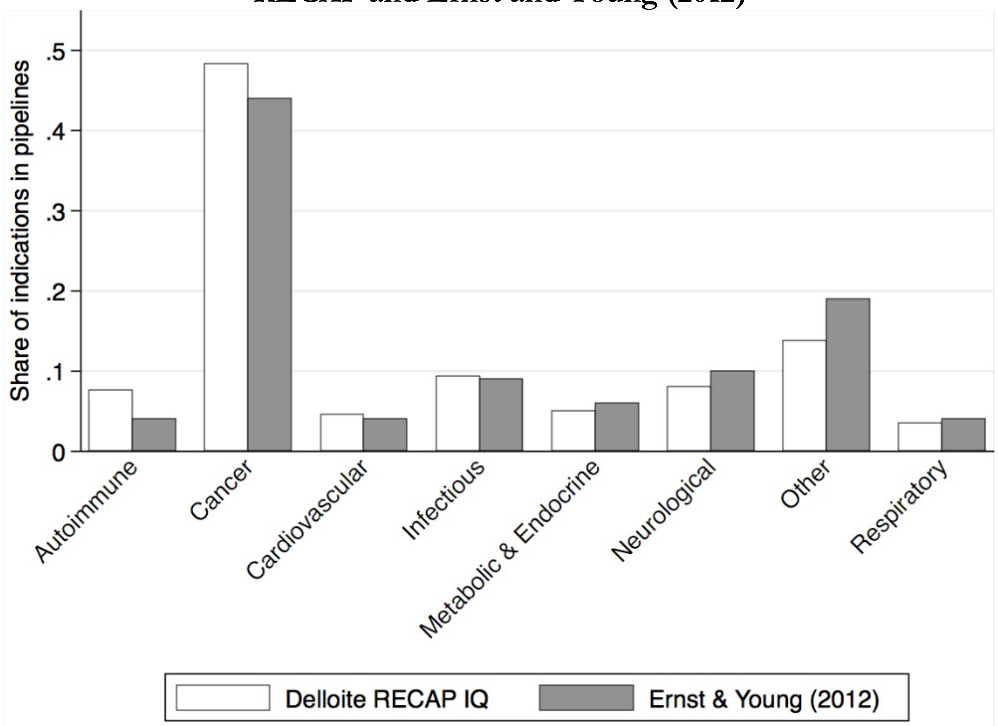


Figure 6
Kernel Density of Medicare Market Share 1998-2011

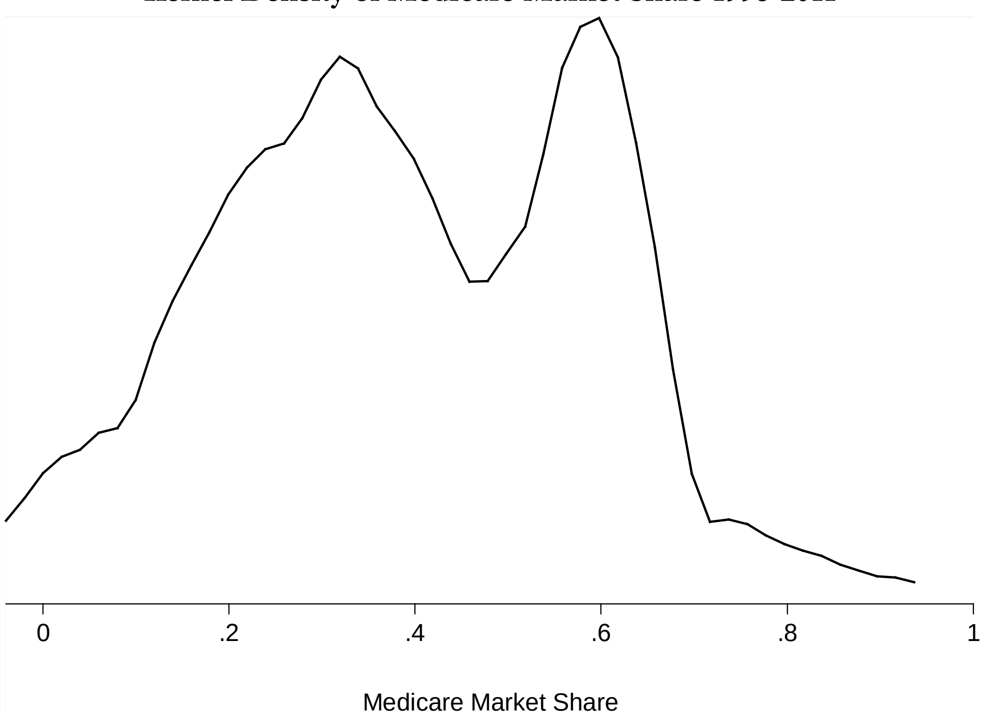


Figure 7
Targeted Diseases by Number of Existing Alternative Treatments

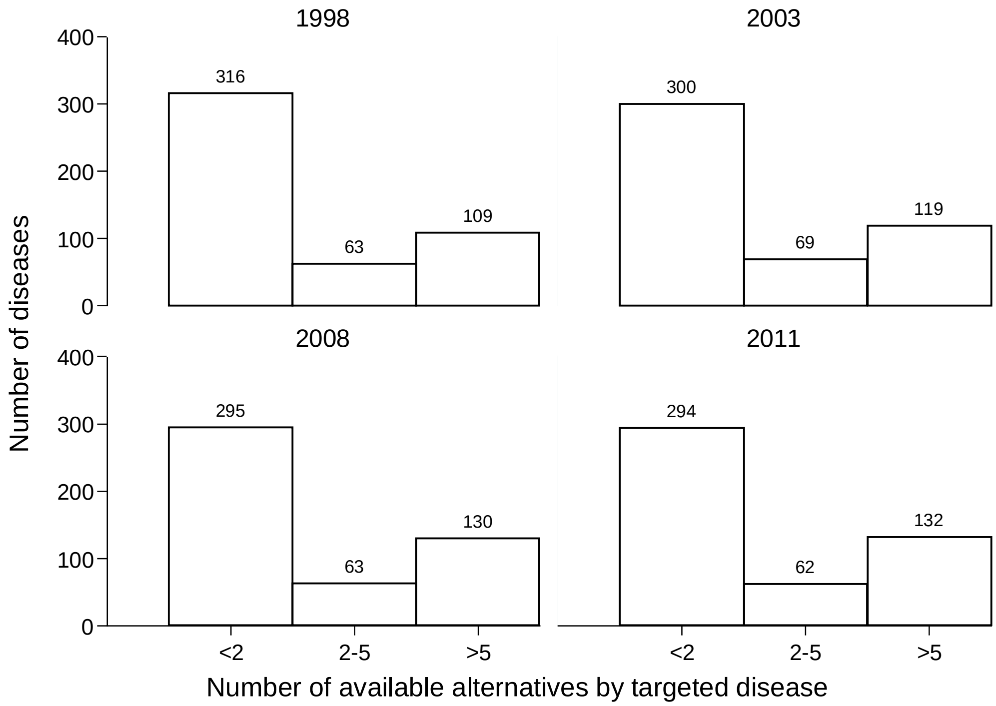


Figure 8
Kernel Density of Medicare Market Share Before and After the Passage of Part D

2008-2011

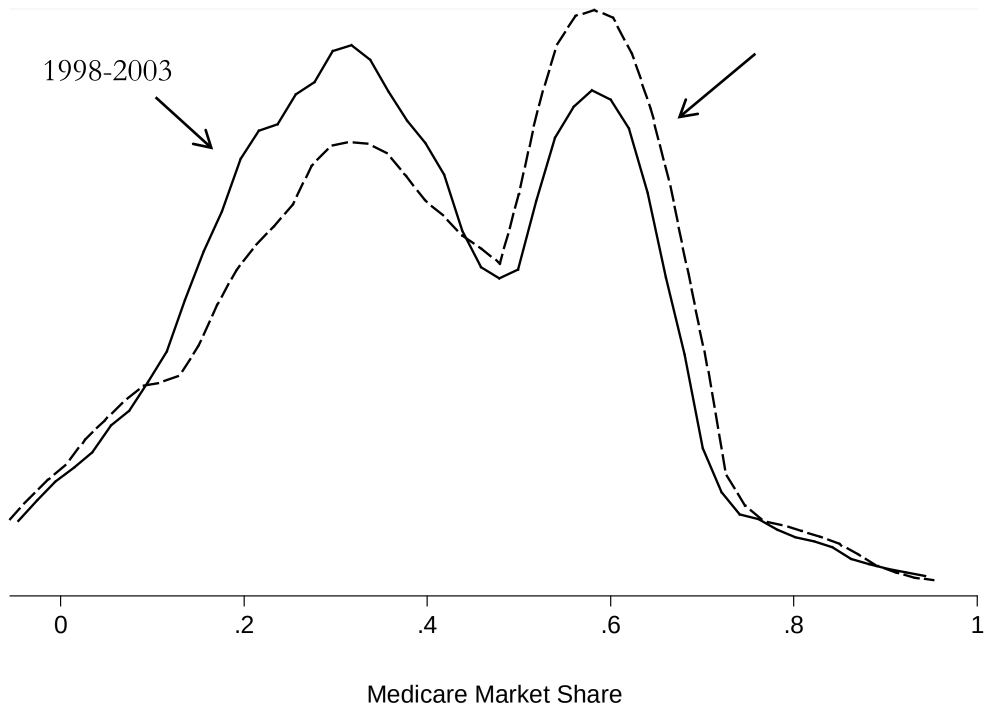


Figure 9
Number of New Indications by Medicare Market Share
No Cancer Indications

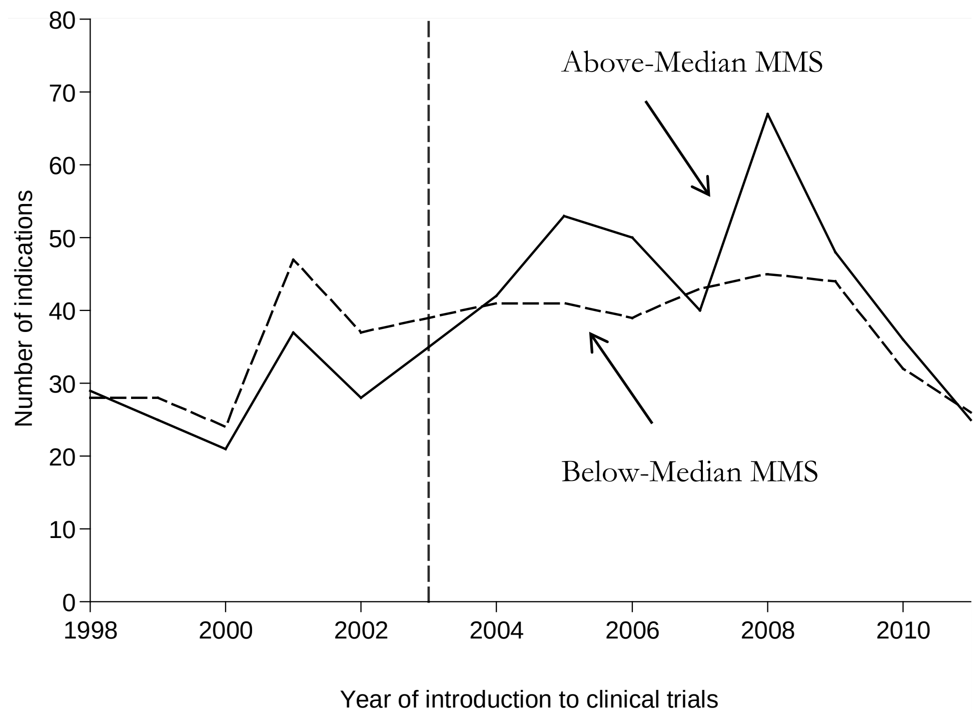


Figure 10
Number of FDA Designations by Medicare Market Share

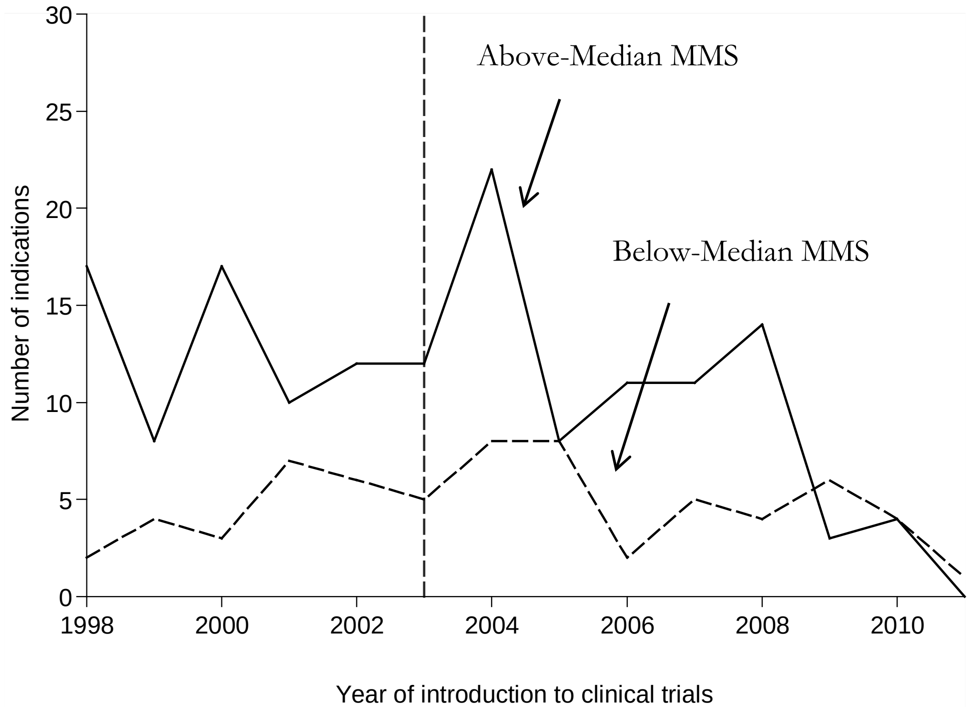


Figure 11
Number of New Primary Indications by Medicare Market Share

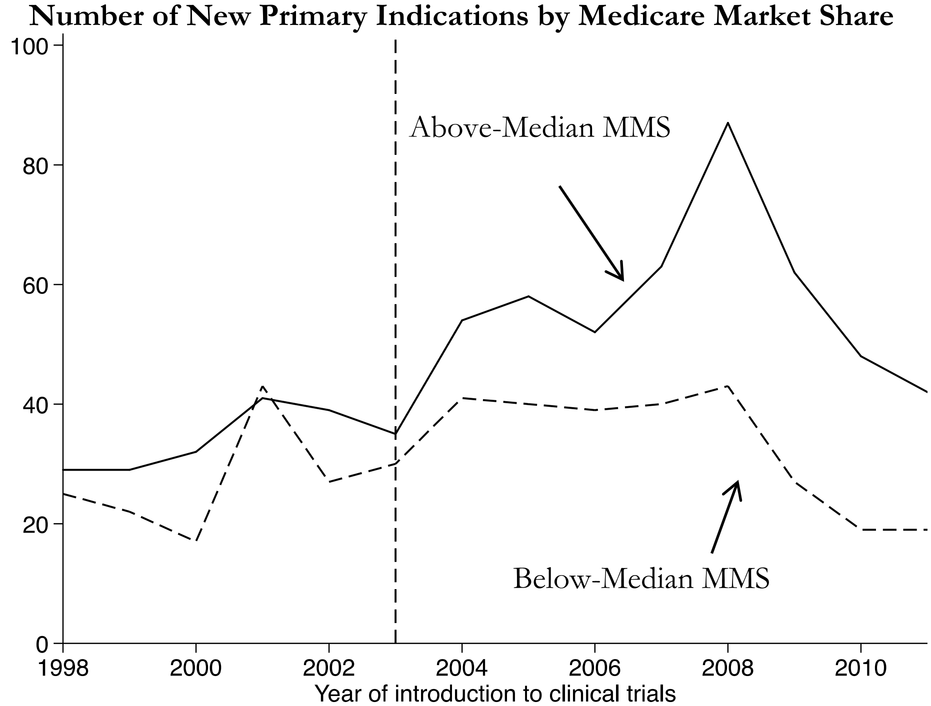
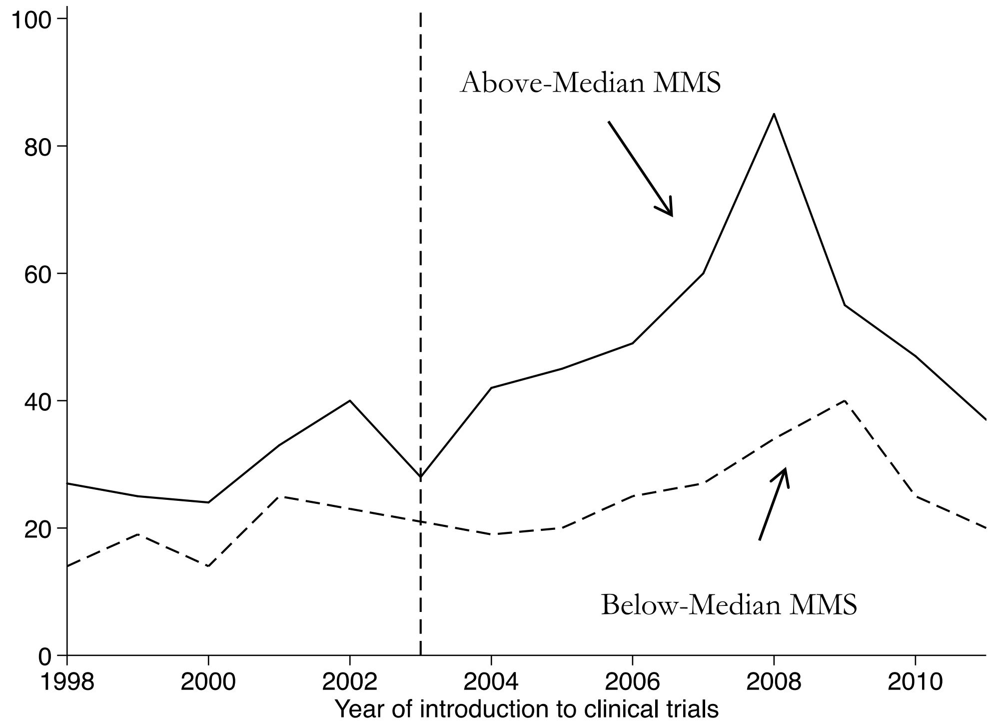


Figure 12
Number of New Primary Indications by Medicare Market Share



Above-Median MMS
Below-Median MMS
100
80
60
40
20
0
1998
2000
2002
2004
2006
2008
2010
Year of introduction to clinical trials

Table 1
Distribution of indications across therapeutic areas

Therapeutic area	# indications	% of total
Allergic	12	0.59%
Autoimmune/inflammatory	154	7.60%
Bone disease	21	1.04%
Cancer	979	48.32%
Cardiovascular	93	4.59%
Central nervous system	121	5.97%
Dental	4	0.20%
Dermatologic	50	2.47%
Endocrinological & Metabolic	101	4.99%
Gastrointestinal	55	2.71%
Genitourinary/gynecologic	20	0.99%
Hematologic	51	2.52%
Infectious-bacterial	58	2.86%
Infectious-viral	129	6.37%
Ophthalmic	22	1.09%
Other	8	0.39%
Psychiatric	42	2.07%
Renal	20	0.99%
Respiratory	71	3.50%
Transplantation	15	0.74%
Total	2,026	100%

Table 2
Estimated Effect of Medicare Part D on Clinical Trials

	(1)	(2)	(3)	(4)	(5)	(6)
MMS	1.02***		0.49	1.02***		0.49
	(0.33)		(0.38)	(0.33)		(0.38)
	[0.00]		[0.20]	[0.00]		[0.20]
D2004-2011 x MMS	0.44***	0.55***	0.66***			
	(0.17)	(0.20)	(0.24)			
	[0.01]	[0.00]	[0.01]			
D2004-2005 x MMS				0.12	0.15	0.63
				(0.38)	(0.47)	(0.39)
				[0.75]	[0.74]	[0.10]
D2006-2008 x MMS				0.43*	0.54*	0.68*
				(0.23)	(0.28)	(0.38)
				[0.06]	[0.05]	[0.08]
D2009-2011 x MMS				0.68***	0.85***	0.64**
				(0.20)	(0.26)	(0.30)
				[0.00]	[0.00]	[0.03]
Therapeutic area F.E.	Yes		Yes	Yes		Yes
Disease F.E.	Yes			Yes		
Zero-Inflated Neg. Bin.			Yes			Yes
N	6832	6832	6832	6832	6832	6832

Columns (3) and (6) contain estimates from a zero-inflated negative binomial regression. Each specification includes year effects and standard errors allow for arbitrary correlations between observations in the same therapeutic area.

Table 3
Placebo Estimates

	(1)	(2)	(3)
MMS	1.30***		0.66*
	(0.31)		(0.34)
	[0.00]		[0.05]
D2001-2003 x MMS	-0.27	-0.33	-0.43
	(0.25)	(0.29)	(0.37)
	[0.28]	[0.26]	[0.24]
Therapeutic area F.E.	Yes		Yes
Disease F.E.		Yes	
Zero-Inflated Neg. Bin.			Yes
N	2928	2928	2928

Columns (3) and (6) contain estimates from a zero-inflated negative binomial regression. Each specification includes year effects and standard errors allow for arbitrary correlations between observations in the same therapeutic area.

Table 4
Estimates of Effect of Medicare Part D on Clinical Trials for Products Not Targeting Cancer

	(1)	(2)	(3)	(4)	(5)	(6)
MMS	0.55		0.06	0.55		0.06
	(0.39)		(0.39)	(0.39)		(0.39)
	[0.16]		[0.88]	[0.16]		[0.88]
D2004-2011 x MMS	0.46*	0.54*	0.66*			
	(0.26)	(0.30)	(0.35)			
	[0.07]	[0.07]	[0.06]			
D2004-2005 x MMS				0.67*	0.78*	0.84**
				(0.36)	(0.41)	(0.35)
				[0.06]	[0.06]	[0.02]
D2006-2008 x MMS				0.38	0.45	0.54
				(0.42)	(0.48)	(0.52)
				[0.36]	[0.35]	[0.30]
D2009-2011 x MMS				0.39	0.46	0.66
				(0.28)	(0.34)	(0.44)
				[0.17]	[0.17]	[0.13]
Therapeutic area F.E.	Yes		Yes	Yes		Yes
Disease F.E.		Yes			Yes	
Zero-Inflated Neg. Bin.			Yes			Yes
N	5474	5474	5474	5474	5474	5474

Columns (3) and (6) contain estimates from a zero-inflated negative binomial regression. Each specification includes year effects and standard errors allow for arbitrary correlations between observations in the same therapeutic area.

Appendix Table A1
Estimates of Effect of Medicare Part D on Clinical Trials by Type of Indication

	All Indications			Primary Indications			Secondary Indi	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
MMS	1.02***		0.49	1.25***		0.49	0.38	
	(0.33)		(0.38)	(0.47)		(0.51)	(0.42)	
	[0.00]		[0.20]	[0.01]		[0.34]	[0.37]	
D2004-2011 x MMS	0.44***	0.55***	0.66***	0.41*	0.49*	0.57	0.47	0.63
	(0.17)	(0.20)	(0.24)	(0.24)	(0.28)	(0.49)	(0.33)	(0.4)
	[0.01]	[0.00]	[0.01]	[0.09]	[0.08]	[0.25]	[0.15]	[0.12]
Therapeutic area F.E.	Yes		Yes	Yes		Yes	Yes	
Disease F.E.		Yes			Yes			Yes
Zero-Inflated Neg. Bin.			Yes			Yes		
N	6,832	6,832	6,832	4284	4284	4284	3,290	3920

Table 5
Estimates of Effect of Medicare Part D on Clinical Trials
by the Number of Alternative Treatments

Sample	<2 total alternatives			>5 alternatives		
	(1)	(2)	(3)	(4)	(5)	(6)
MMS	0.56		0.00	0.57**		-0.53
	(0.39)		(0.65)	(0.22)		(0.42)
	[0.15]		[1.00]	[0.01]		[0.20]
D2004-2011 x MMS	0.14	0.13	0.00	0.64***	0.90***	1.19***
	(0.44)	(0.41)	(0.52)	(0.21)	(0.28)	(0.33)
	[0.75]	[0.75]	[1.00]	[0.00]	[0.00]	[0.00]
Therapeutic area F.E.	Yes		Yes	Yes		Yes
Disease F.E.		Yes			Yes	
Zero-Inflated Neg. Bin.			Yes			Yes
N	4116	4116	4116	1848	1848	1848

Columns (3) and (6) contain estimates from a zero-inflated negative binomial regression. Each specification includes year effects and standard errors allow for arbitrary correlations between observations in the same therapeutic area.

Table 6
Estimates Over Time by Number of Alternative Treatments

Sample	<2 total alternatives			>5 alternatives		
	(1)	(2)	(3)	(4)	(5)	(6)
MMS	0.56		0.00	0.57**		-0.54
	(0.39)		(0.65)	(0.22)		(0.40)
	[0.15]		[1.00]	[0.01]		[0.18]
D2004-2005 x MMS	-0.65	-0.60	-0.00	0.32	0.45	0.75
	(0.75)	(0.70)	(0.78)	(0.41)	(0.58)	(0.70)
	[0.39]	[0.39]	[1.00]	[0.45]	[0.44]	[0.28]
D2006-2008 x MMS	0.27	0.25	0.00	0.50*	0.70**	1.29***
	(0.45)	(0.42)	(0.49)	(0.26)	(0.35)	(0.46)
	[0.55]	[0.56]	[1.00]	[0.05]	[0.05]	[0.01]
D2009-2011 x MMS	0.44	0.40	0.00	1.11***	1.56***	1.32**
	(0.49)	(0.45)	(0.61)	(0.27)	(0.37)	(0.62)
	[0.37]	[0.37]	[1.00]	[0.00]	[0.00]	[0.03]
Therapeutic area F.E.	Yes		Yes	Yes		Yes
Disease F.E.		Yes			Yes	
Zero-Inflated Neg. Bin.			Yes			Yes
Number	4116	4116	4116	1848	1848	1848

Columns (3) and (6) contain estimates from a zero-inflated negative binomial regression. Each specification includes year effects and standard errors allow for arbitrary correlations between observations in the same therapeutic area.

Table 7
Logit Estimates for the Effect of Medicare Part D on FDA Designation of Innovativeness

	(1)	(2)
MMS	0.56	0.93
	(0.51)	(0.73)
	[0.26]	[0.20]
D2004-2011 x MMS	-1.17***	
	(0.41)	
	[0.00]	
D2001-2003 x MMS		-1.95**
		(0.82)
		[0.02]
LNP	-0.30	-0.33
	(0.20)	(0.29)
	[0.13]	[0.26]
NewIndications	0.65***	1.54***
	(0.20)	(0.31)
	[0.00]	[0.00]
N	6,692	2,736

Column (1) contains logit estimates from the full dataset. Column (2) contains logit estimates from a placebo regression using data from 1998-2003. Standard errors allows for arbitrary correlation between observations in the same therapeutic area.

ppendix Table A1
Estimates Over Time by Number of Alternative Treatments

Sample	All Indication			Primary Indications			Secondary Indications		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
MMS	1.02***		0.49	1.25***		0.48	0.38		-0.27
	(0.33)		(0.38)	0.47		0.5	0.42		0.55
	[0.00]		[0.20]	0.01		0.34	0.37		0.62
D2004-2005 x MMS	0.12	0.15	0.63	0.06	0.07	0.52	0.25	0.33	0.77
	(0.38)	(0.47)	(0.39)	0.35	0.42	0.44	0.56	0.72	0.6
	[0.75]	[0.74]	[0.10]	0.87	0.87	0.24	0.65	0.65	0.2
D2006-2008 x MMS	0.43*	0.54*	0.68*	0.33	0.4	0.59	0.54*	0.72*	0.88***
	(0.23)	(0.28)	(0.38)	0.34	0.4	0.76	0.33	0.4	0.3
	[0.06]	[0.05]	[0.08]	0.32	0.31	0.44	0.1	0.07	0
D2009-2011 x MMS	0.68***	0.85***	0.64**	0.83*	0.99*	0.62	0.5	0.67	0.73*
	(0.20)	(0.26)	(0.30)	0.46	0.55	0.53	0.33	0.42	0.44
	[0.00]	[0.00]	[0.03]	0.07	0.07	0.24	0.13	0.11	0.1
Therapeutic area F.E.	Yes		Yes	Yes		Yes	Yes		Yes
Disease F.E.		Yes			Yes			Yes	
Zero-Inflated Neg. Bin.			Yes			Yes			Yes
Number	5474	5474	5474	4284	4284	4284	3,290	3920	3920

Appendix Table A2
Estimates by Number of Alternative Treatments and Indication Status

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	Panel A: FTT Drugs								
	All Indication (n=4,116)			Primary Indications (n=2,212)			Secondary Indications (n=2,282)		
MMS	0.56		0.00	0.77*		0.77*	0.25		0.34
	(0.39)		(0.65)	(0.4)		(0.47)	(0.53)		(1.27)
	[0.15]		[1.00]	[0.06]		[0.1]	[0.64]		[0.79]
D2004-2005 x MMS	0.14	0.13	0.00	0.02	0.02	0.02	0.26	0.25	0.27
	(0.44)	(0.41)	(0.52)	(0.46)	(0.41)	(0.48)	(0.68)	(0.66)	(0.7)
	[0.75]	[0.75]	[1.00]	[0.96]	[0.96]	[0.96]	[0.7]	[0.71]	[0.7]
	Panel B: AA Drugs								
	All Indications (n=1,848)			Primary Indications (n=1,470)			Secondary Indications (n=1,190)		
MMS	0.57**		-0.53	0.8		0.32	-0.26		-1.45***
	(0.22)		(0.42)	(0.58)		(0.97)	(0.34)		(0.28)
	[0.01]		[0.20]	[0.16]		[0.74]	[0.44]		[0.000]
D2004-2005 x MMS	0.64***	0.90***	1.19***	0.66***	0.82***	0.84***	0.67	1.02*	1.07**
	(0.21)	(0.28)	(0.33)	(0.24)	(0.3)	(0.31)	(0.41)	(0.56)	(0.48)
	[0.00]	[0.00]	[0.00]	[0.01]	[0.01]	[0.01]	[0.11]	[0.07]	[0.03]
Therapeutic area F.E.	Yes		Yes	Yes		Yes	Yes		Yes
Disease F.E.		Yes			Yes			Yes	
Zero-Inflated Neg. Bin.			Yes			Yes			Yes