

The Alignment of Innovation Policy and Social Welfare: Evidence from Pharmaceuticals

Margaret K. Kyle*

March 27, 2019

1 Introduction

Health care spending accounts for 10-18% of gross domestic product in most of Europe, Japan, and the United States. While pharmaceuticals typically are less than a fifth of that outlay, their share has been increasing over time.¹ The pricing of many products, from anti-overdose treatments to insulin to recent advances in gene therapy, has provoked public outcry as well as investigations by competition authorities. The industry defends high prices and spending as necessary rewards for innovation, but with aging populations and strained government budgets, now faces more resistance from payers and questions about current innovation policy is sustainable.

This chapter provides an overview of different innovation policies and their performance in the pharmaceutical sector. The output of drug research and the benefits of pharmaceutical products are relatively easy to observe and measure, which facilitates empirical study. While

*MINES Paristech and PSL Research University, 60 boulevard Saint Michel, 75006 Paris, France; margaret.kyle@mines-paristech.fr

¹Source: OECD Health Statistics.

pharmaceuticals differ from many other innovative products along some dimensions – in particular, the extent of regulation and the involvement of governments in markets – the drug industry is one of the most research intensive, and thus where innovation policy is especially pertinent. This chapter also highlights the interaction of innovation policy with other policies as well as with policies in other countries.

1.1 The role of pharmaceuticals in health outcomes

Life expectancy in the United States in 2015 was near 78 years, compared to only 49 in 1900.² Global life expectancy has increased by 5.5 years since 2000 alone, and by more than 10 years in Africa.³ Pharmaceutical treatments are responsible for much of these improvements, as infectious diseases were once the leading cause of death worldwide. For example, the discovery of penicillin in 1928 and new classes of antibiotics from the 1950s-70s provided the means to cure many diseases, including smallpox, plague, and syphilis. The sulfa drugs of the 1930s alone are credited with reducing overall mortality by 2-3% and increasing life expectancy by between .4 and .7 years ([Jayachandran et al. \(2010\)](#)). Vaccines enabled the eradication of smallpox, and childhood immunization programs in the US are estimated to have prevented 1.4 million hospitalizations and more than 56,000 early deaths ([Whitney et al. \(2014\)](#)).

More recent innovations in treating HIV/AIDS and hepatitis C have also had enormous impacts on population health. The use of antiretroviral drugs in Africa is associated with 10-20% declines in mortality each year ([et al. \(2014\)](#)), despite only 53% of those infected having access to treatment ([World Health Organization \(2009\)](#)). The introduction of direct-acting antiretrovirals targeting hepatitis C prompted the World Health Organization to establish elimination targets by 2030, and could prevent more than 600,000 deaths from cirrhosis and

²See [Centers for Disease Control and Prevention \(2015\)](#).

³See [World Health Organization \(2018\)](#).

liver cancer ([Heffernan et al. \(2019\)](#)).

Progress treating non-communicable diseases has been less dramatic, but nevertheless significant. While cancer remains the leading cause of death in the US, new cancer drugs contributed to large gains in life expectancy from 1996-2011 ([Howard et al. \(2016\)](#)). [Cutler et al. \(2017\)](#) suggest that pharmaceutical treatments for cardiovascular disease and vision problems account for an important share of the improvement in healthy life expectancy from 1992-2008 in the US.

The examples cited here are not an exhaustive list: big picture, pharmaceuticals are responsible for significant health improvements. While surgical techniques require skills in short supply and often involve learning-by-doing, drugs can usually be adopted at low costs (aside from price), with low labor needs. Diagnostic machines such as magnetic resonance imaging (MRIs) are more costly to manufacture and service. In contrast to other health technologies, pharmaceuticals are relatively easy to distribute and produce. These features make their diffusion rapid (at least in theory), enabling the realization of social benefits.

1.2 Is innovation policy working?

The success stories cited above suggest that innovation policies – at least those relevant to pharmaceuticals – are having their intended effect. However, the health gains associated with drugs often come with high price tags. Pharmaceutical spending in the US was about \$1200 per capita in 2015, more than double its level in 2000. In many OECD countries, drugs account for more than one-fifth of total health care spending.⁴

In addition, the costs of drug development continue to climb. In 2003, [DiMasi et al. \(2003\)](#) estimated the average development cost to be \$802 million; in 2016, the same researchers pegged this at \$2558 million, with capitalized costs growing at 8.5% per year ([DiMasi et al. \(2016\)](#)). While the number of new drugs approved has ticked up in recent years, worries

⁴Source: OECD Health Statistics.

about a productivity crisis have persisted for some time (Cockburn (2006)).

Some critics dispute both the cost estimates as well as the claim of an innovation crisis (Light & Lexchin (2012)); others contend that most pharmaceutical innovation has its origins in academic research, rather than industry (Angell (2004)). In the US, prominent politicians from both ends of the political spectrum have targeted pharmaceutical prices. Senator Bernie Sanders (D-VT) complains that “[f]irst we pay to create these lifesaving drugs, then we pay high prices to buy those drugs.”⁵ President Donald Trump similarly gripes that “Americans pay more so that other countries can pay less.”⁶

It is vital that innovation policies direct spending where the social returns are highest. I address two broad questions. First, is innovative effort – in the private as well as public sector – directed at the right targets? The social benefits of curing diseases vary depending on their severity and prevalence, and the costs of finding a treatment may also differ. Within a disease, some drugs may have more therapeutic value than others. Second, is research conducted by the appropriate institutions or people? Not all labs are created equal, or have identical production functions. The appropriate choice of innovation policy depends on the importance of different types of market frictions and information problems.

2 Innovation policies

Economists have long held that investment in innovation is below what is socially optimal. Because innovation often generates spillovers, inventors (or investors) fail to account for the externality resulting from their efforts. In addition, inventors may have private information about their quality. The inability of outside investors to distinguish between “good” inventors and lemons; the risk of financing the latter causes underinvestment. Broadly, innovation

⁵New York Times op-ed, March 10, 2017.

⁶“Trump Proposes to Lower Drug Prices by Basing Them on Other Countries’ Costs,” New York Times, October 25, 2018.

policy addresses this market failure either by increasing the expected (private) rewards or by subsidizing the cost of investment in innovation.

2.1 “Pull” approaches

“Pull” policies address an inventor’s expected revenues. In the presence of spillovers, an inventor’s private rewards can be significantly lower than the social benefits. In the case of pharmaceutical research, this gap between private and social rewards can be very large. Once a safe and effective molecule has been discovered, imitation is relatively easy, and the marginal costs of production are low relative to the fixed costs of development. Consequently, a cure for cancer is unlikely to be privately profitable in the absence of a policy intervention. The most important pull policies in the pharmaceutical sector are patent protection, which allows an inventor to block competitors from manufacturing the same product for the duration of the patent, and data exclusivity, which prevents competitors from relying on the clinical evidence provided by the drug’s originator to a regulatory authority for a fixed period of time. Both patents and exclusivity terms trade off static costs, in the form of higher prices and/or reduced output as a consequence of the market power they grant, with dynamic benefits from increased incentives to innovate.

2.1.1 Underlying assumptions

A number of important assumptions underpin these pull policies. First, product markets must work well, so that private benefits align with social benefits. That is, treating diseases with important burdens should be more profitable than treating minor ailments, and the most effective treatment for a particular condition should generate higher profits than those that add little therapeutic value. As [Murphy & Topel \(2007\)](#) explain, distortions in health care markets have the potential to reduce the benefits of medical innovation.

If willingness-to-pay for treating high burden diseases (cancer, cardiovascular problems) is

higher than that for less serious conditions, and this willingness-to-pay is reflected in higher prices and profits, then we should expect to see R&D directed appropriately. However, the absence of insurers or an important role for government purchases in some countries, particularly poorer countries, often implies that there is no market for innovative drugs: without insurance or the ability to borrow money to finance health care, most patients are unable to pay for these treatments (sometimes even at prices close to marginal costs). The “neglected” diseases, so called because there is little private interest in developing treatments for them, are examples of where pull policies fail due to problems in product markets. Relatedly, diseases with very small markets – orphan diseases – may fail to attract R&D because of low profit expectations.

In order for profits to be correlated with therapeutic value, a product’s quality should be easy to observe. Prices should reflect differences in quality, so that consumption choices are optimal. These conditions may hold for some products, but are not obvious for novel pharmaceutical treatments. Drugs are generally experience or credence goods: their quality is impossible to assess from the physical appearance alone. The Food and Drug Administration (FDA) and its equivalents in other countries regulate entry precisely because of this information asymmetry between the producer of a medication and consumers. Access to most new drugs requires a doctor’s prescription, as regulators and medical professionals consider most patients inadequately informed about appropriate treatments. Even in the presence of entry regulation and intermediation by medical experts, however, some uncertainty about a drug’s quality and side effects remains. Researchers continue to find new uses for old drugs, and we learn about adverse effects over time.

Asymmetric information of a different nature – namely between consumers with heterogeneous needs for treatments, which can be private information – can contribute to the undersupply of preventative products like vaccines. As [Kremer & Snyder \(2003\)](#) show, drugs sold to patients who have already contracted a disease have less asymmetric information,

which allows the producer to extract more surplus. In addition, by preventing the spread of a disease, vaccines reduce demand. These two factors imply that drug treatments are more profitable than vaccines, despite potentially greater social value from the latter.

Pharmaceutical markets also have several potential agency problems. For prescription drugs, doctors first choose the substance deemed best for the patient. In the United States and Europe, doctors do not generally sell the drugs they prescribe. The separation of prescribing and dispensing reduces the risk that a doctor prescribes for profit, rather than in the patient's best interest. However, the choices of prescribers may nevertheless be influenced by other factors; marketing, in particular, and payments by drug companies to doctors for meals or lectures have raised concerns about conflicts of interest that lead to overuse (e.g., of antibiotics) or inappropriate use (e.g., of opioids).

The presence of insurance coverage also contributes to agency problems. Overconsumption of (particularly expensive) drugs is a risk due to moral hazard: prescribers may not be sensitive to the prices of the treatments they recommend, and consumers do not always pay the full price either. The combination of producer market power – often stemming from patents – and price-insensitive prescribers and consumers is a recipe for high drug prices. Consequently, payers and insurers use countervailing policies to rein in these prices. For example, some countries, such as the United Kingdom and Germany, use physician drug budgets to induce doctors to favor less expensive treatment options. Some payers may refuse to cover some treatments that are not deemed cost-effective. There is a risk that patient and payer interests are imperfectly aligned, however. An individual patient may weight differently the criteria used to assess cost-effectiveness, especially those that have difficult-to-measure clinical impact, such as convenience or ease of use. Private insurers may be reluctant to cover treatments that are costly in the short run but that provide long run benefits, since if consumers switch insurance companies, those benefits (in the form of reduced spending later) are realized by competitors.

The large role that many governments play in health care markets, including price-setting, may affect the efficiency of the product market. Governments are monopsony buyers in most developed countries and do not act as price-takers. In a single-payer system, the payer has more incentive to internalize long-run benefits from prevention. However, the increased bargaining power a single payer enjoys can create other problems. As drug development costs have already been sunk at the time of price negotiations, producers should be willing to sell at any price that covers their marginal costs. Governments are therefore in a position to hold up producers, even those with market power, and producers may pare back investment in response. While a forward-looking government should recognize the long-run consequences of a reduction in innovative effort, those consequences may be difficult to observe or measure, especially in comparison to the current budget outlays that result from rewarding innovation with higher prices. As with many other policies, the temptation to defer the pain may be too great.

Governments may also be tempted to free ride on the innovation incentives created by other countries. Rewarding innovation through higher prices or quantities makes sense only if producers respond to the increased profits. In global markets, like those for most innovative drugs, most countries account for only a small share of worldwide profits. Consequently, unilateral changes to innovation policy are unlikely to shift profits enough to induce a change in investment.

Pull policies leave investment to the private sector. Research and development are generally high-risk activities: only a small fraction of new drug development projects result in approved treatments. Development times are long, often ten years or more, and significant levels of investment are required. The efficacy of pull policies depends very much on the willingness of capital markets to finance these risky investments.

Asymmetric information is present throughout the process of drug development. That is, the scientists and researchers working with a drug development candidate are likely to

be better informed about its qualities than a firm's management, a venture capitalist, or a shareholder. As noted previously, this asymmetric information, and the risk of buying a lemon, is likely to result in suboptimal investment.

The degree of information asymmetry may be smaller inside a firm than between a firm and outside investors, as managers inside can use organization design to improve information flows and align incentives. For this reason, internal finance through current cash flows is often cheaper than external, as outsiders require a premium to compensate for their information disadvantage. Pull policies may therefore favor large, established firms over small start-ups: large firms can rely more on internal finance, while start-ups without any revenues have no choice but to seek external sources of finance.

There are two main sources of external finance in pharmaceuticals. The existence of robust venture capital markets is essential for the entry and survival of small firms. Venture capital firms often hire scientists with the necessary expertise to help them weed out the lemons or reduce information asymmetries, and are able to hedge risks through building portfolios of investments. However, the availability of venture capital varies significantly by geography, both within and across countries.

The other source of financing for many young firms is licensing revenues, or more generally the use of "markets for technology." Shepherding a drug candidate through all stages of development, and then navigating the complex regulatory approval process, requires skills that are costly for small, new firms to obtain. Large and established firms benefit from experience and economies of scale or scope in many of these activities, and can amortize these costs over a large portfolio of products. There are often gains from trade from licensing promising drug candidates from small start-ups to larger, established firms. The licensing revenues enable continued investment by smaller firms, and drug candidates may be developed at lower costs by larger firms.

Markets for technology can enhance the effectiveness of pull policies, but are themselves

characterized by many frictions. In addition to information asymmetry, there is increasing concern that some licensing and acquisition of start-ups may have anticompetitive consequences. Increased market power on the buyer side, perhaps as a result of the waves of merger activity observed over recent decades, may also depress licensing prices and therefore incentives for start-ups to invest.

2.1.2 Patents

Few sectors rely on patents as much as the pharmaceutical industry. Not only is imitation easy in comparison to many other technologies, but safety regulations preclude the use of trade secrets.

The “one-size-fits-all” patent term, which is a minimum of 20 years for members of the World Trade Organization, is a limitation: patents are blunt policy tools. Technologies vary considerably in their development times: 20 years may be a reasonable term of protection for pharmaceuticals, which take an average of 10-12 years to bring to market. For other sectors, a technology may be obsolescent after only a few years. An additional complication is the use of multiple patents: a single drug may be protected by a primary patent as well as many secondary patents with much smaller inventive steps, but each adding a full 20 years of protection. While some may embody clinically valuable incremental innovation, the fact that the patent system does not distinguish between breakthroughs and minor extensions may create incentives for firms to focus too much on the latter.

Historically, pharmaceutical patents have had few of the problems observed in industries such as telecom, where overlapping claims make property rights unclear and difficult to navigate.⁷ In contrast to information and communication technology, in which litigation often concerns firms with large patent portfolios and in which cross-licensing is common, most patent disputes in pharma occur between patent owners (innovator or originator firms) and

⁷However, recent disputes over patents in biotechnology and genomics suggest that these problems may become more important over time.

their generic competitors, which do little patenting. The increased use of secondary patents worries competition authorities, which are concerned that they delay generic competition. Secondary patents tend to be weaker, in the sense that they are more likely to be invalidated or can be invented around, but their presence creates legal uncertainty for both innovators and generic entrants. Thus, probabilistic patents and all the associated problems are an issue in pharma too.

Patents serve another crucial purpose that is not directly related to innovation incentives, but rather to the functioning of markets for technology. In the absence of patents, markets for knowledge goods – which drug candidates are – may fail due to Arrow’s information paradox. Also known as the disclosure problem, this results from the seller of an idea having private information about its quality. Buyers, naturally, seek some proof or evidence before agreeing to transact. But doing so often discloses so much about the idea that the buyer no longer has need to pay for it, and so trade never occurs. By providing the right to block the use of an invention by others, patents enable the seller to disclose it.

The pharma industry has persistently – and successfully – argued for the strengthening of patent rights in developing countries, especially through their inclusion in trade agreements. One justification for their inclusion, however, is that by committing all countries to a pull policy, free-riding between countries is reduced. This view is far from universal; a key objection to the use of patents as an innovation policy instrument is the difficulty in finding the appropriate balance between static costs and dynamic benefits, which may differ from country to country.

2.1.3 Data and market exclusivity

An alternative pull policy is the use of data or market exclusivity terms. In practice, these forms of regulatory protection are used in addition to and run concurrently with, rather than in place of, patents. The economic logic is similar, as the producer of an innovative

treatment enjoys a (legally limited) period of market exclusivity, during which the producer has the opportunity to recover R&D costs. In the US, a new chemical entity (NCE) has five years of exclusivity and biologics have 12; in Canada, both NCEs and biologics have eight years; and in the European Union, the term is ten years. Most countries also provide extensions to exclusivity for pediatric trials and orphan drugs.

While the patent clock begins at the date of application, generally early in the drug development process, the exclusivity clock only starts when the product receives marketing authorization. Thus, drugs that require more time in development are not penalized by shorter protection terms. In addition, if a drug cannot be protected by patents – for example, if it is not a new molecule – data exclusivity provides an incentive to develop it for potentially valuable new uses. Legal clarity is also greater for exclusivity terms, in contrast to protection from multiple secondary patents with uncertain validity or strength.

The TRIPS Agreement requires a minimum of 20 year patent term, as noted previously, which limits the ability to link patent terms to the value of innovation, and the value of innovation is difficult to assess early in the development process when patent applications are filed. In contrast, exclusivity terms provide more flexibility. No massive multilateral trade agreement applies, and far more information about the value of new treatment is available once it has completed clinical trials. For now, however, countries have made limited use of the possibility to tie exclusivity more closely to the importance of a new treatment.⁸

2.1.4 Prizes

Both patents and data exclusivity link R&D to market rewards. As described above, product markets may not function perfectly in pharmaceuticals, limiting the usefulness of these incentive mechanisms – but not their static costs. This is especially problematic for developing countries. Often, insurance is limited, as is the ability to pay out-of-pocket. For

⁸In the EU, an originator can request one additional year of exclusivity if a new use is discovered.

diseases with a sufficiently large impact in wealthy countries, firms have incentive to develop treatments; for diseases whose burden falls mainly on poor countries, however, there is no pull created by patents or exclusivity.

[Kremer & Glennerster \(2004\)](#), [Love \(2011\)](#), and others have proposed the use of innovation prizes or advanced market commitments as a solution to situations where problems in the product market make patents and exclusivity ineffective. Instead of chasing profits that are a function of uncertain patent terms, prices, and quantities, firms invest with the guarantee of some minimum payoff – the prize, or advanced market commitment to purchasing a certain number of units at a pre-determined price. Note, however, that prizes still require capital markets to work well.

In delinking profits from innovation incentives, a prize policy cannot rely on the decentralized aggregation of information that markets provide (though prizes are most needed precisely where markets don't perform this function well). Instead, somehow the value of a prize must be determined by experts and agreed to by funders. In this sense, the informational requirements for a prize policy are similar to those for government grants. And as with grants, the potential for free-riding is important, if the innovation that results from a prize policy is available to countries that did not contribute to its financing.

2.1.5 Empirical evidence

There is ample evidence that pharmaceutical firms respond to changes in expected profits by adjusting their investment in innovation across disease areas. [Acemoglu & Linn \(2004\)](#) and [de Mouzon et al. \(2015\)](#), for example, find that the number of new drugs launched increases with market size, using variation in the age distribution of different diseases as an instrument. Indeed, the lack of a large market is the problem of orphan diseases ([Lichtenberg & Waldfogel \(2009\)](#)). Government policy can create demand in some cases: mandating or recommending the use of vaccines, for example, led to a dramatic increase in the number of

vaccines developed in the US (Finkelstein (2004)). Blume-Kohout & Sood (2013) find that the introduction of Medicare Part D, which represented an increase in the elderly population with access to insurance coverage for pharmaceuticals, led to an increase in drugs developed. However, the *value* of the induced innovation is often difficult to assess: Dranove et al. (2014) claim that innovative effort responding to the expansion of PartD was focused on diseases where treatments already existed, and therefore may not have generated substantial social benefits.

More generally, demand for pharmaceuticals is not merely a function of disease incidence. Patients and physicians need to be informed of the benefits and costs of new treatments, and insurers must be willing to pay. In a summary of the empirical evidence on the value of pharmaceutical innovation, Garthwaite & Duggan (2012) conclude that there are substantial health benefits overall, although not necessarily cost offsetting effects. Duggan (2005) shows that spending on antipsychotic drugs did not reduce spending on other health care services, while the opposite was true for antiretrovirals (Duggan & Evans (2008)). They argue that non-health benefits, such as improved productivity or quality of life, should also be considered in evaluating the benefits of new drugs. For example, Garthwaite (2012) finds that Cox-2 inhibitors significantly increased labor force participation. This is a difficult issue for health technology agencies or insurers charged with estimating cost-effectiveness: while there is (mostly) agreement on how to measure clinical benefits, the consensus for measuring these other benefits is weaker; in the US, private insurers may not internalize the economic benefits. Cutler et al. (2007) contend that hypertensive drugs have a benefit to cost ratio of more than six, and indeed should be used more widely. They suggest that this underutilization stems from inefficiencies in the product market related to other aspects of the health care system, noting “private insurance plans are unlikely to bear the costs of the underuse of effective medicines today.”

Despite the enormous cost-effectiveness literature that exists to guide medical decision-

making, we know little about the rewards to innovation within diseases. That is, are clinically superior products rewarded with higher profits? And does this vary across countries with more market-oriented pricing, such as the US, and those with more extensive government involvement in pricing? Using a measure of therapeutic value from the French health ministry, [Kyle \(2018\)](#) compares outcomes for products with large added value from those that are considered only minor improvements over existing treatments. Globally, products with better scores have higher revenues because they are launched in more countries, and locally, these products tend to have higher market shares. However, prices and revenues bore little relationship to therapeutic value in any of the five large markets examined. [Kyle et al. \(2017\)](#) also show that the adoption of the most therapeutically valuable products is slower in the US than in other markets. This suggests that information about quality is slow to diffuse, or ignored by payers when negotiating price.

Relatedly, agency problems in the doctor-patient relationship can distort demand, and therefore incentives. The separation of prescribing and dispensing activities is common in the US and Europe, which gives physicians less incentive to be informed about or respond to prices. In markets where doctors can profit from prescribing, there is clear evidence that they shift demand to products that give them high margins. [Iizuka \(2007\)](#) and [Iizuka \(2012\)](#) demonstrate these tendencies in Japan, with consequences not only for the patient's well-being but also government spending. In the US context, where doctors who administer drugs in-office can realize higher revenues by shifting to high margin drugs, [Jacobson et al. \(2010\)](#) show that both the likelihood of prescribing chemotherapy and the type of chemotherapy used change with the payment rates set by Medicare. While none of these studies focuses on the response of innovative effort, based on the evidence that pharmaceutical research responds to expected profits, we can reasonably expect these distortions to have some effect on investment behavior.

The possibility that pharmaceutical firms can exploit these agency problems through

their marketing and promotion efforts is an important concern. Many studies document that physicians may be imperfectly informed and that their prescribing habits are “sticky” (Azoulay (2002), Janakiraman et al. (2008), and Epstein & Ketcham (2014), among others) – which raises barriers to entry for new (and better) treatments, as substantial investments may be required to persuade doctors to switch. The opioid crisis in the US has prompted a closer look at payments by manufacturers to prescribers. Fernandez & Zejcirovic (2018) show that doctors who received payments from opioid manufacturers tended to prescribe more of these drugs, for example. While the causal effect of marketing is notoriously difficult to pin down, there are two potential implications for innovation. Market-expanding promotion creates more demand for a class of products, pulling in more R&D directed at that disease. If incentives for marketing are closely tied to social value, this can be good for welfare; of course, if the marketing is misleading or physicians are insufficiently informed about risks, the opposite may be true. Similarly, marketing that is business-stealing can also have either positive or negative effects, depending on whether demand shifts towards drugs that have better clinical performance.

As described above, several characteristics of pharmaceuticals – large sunk costs of development and low imitation costs in particular – imply an important role for patents, and a large body of empirical work has confirmed that innovative efforts in pharma are tied to intellectual property rights. Williams (2016) describes the challenges of empirical work in this area, but most studies find that increased exclusivity, whether through patents or other exclusivity terms granted by regulators, is associated with increased innovative efforts. For example, Kyle & McGahan (2012) find that drug firms initiated more clinical trials in diseases whose patent-protected market size changed as countries gradually complied with the TRIPS Agreement. The 1983 US Orphan Drug Act, which included an extension to market exclusivity for drugs treating rare diseases, also spurred innovative activities toward those targets (Yin (2008)). At a very micro level, Gaessler & Wagner (2018) show that drug firms’

willingness to pursue a drug development project is sensitive to their expected period of market exclusivity. The fixed term of protection can distort incentives. [Budish et al. \(2015\)](#) show that firms favor drugs with shorter development times with a longer period of patent protection remaining once the product reaches the market.

Despite the importance of patents and other forms of exclusivity in pharmaceuticals, they are far from perfect policy tools. The problem is not restricted to pharmaceuticals: aligning the private value of patents with their social benefits is a challenge in other sectors (for example, see [Scott Morton & Shapiro \(2016\)](#) and their chapter in this volume). However, this is one of the few sectors where proxies for social value are available, namely in assessments of therapeutic value or clinical benefits. Unfortunately, the news is not great. [Abrams & Sampat \(2017\)](#) estimate the link between a common measure of patent value, citations, to measures of therapeutic value of the drugs they protect, and find only a weak relationship. Similarly, the number of patents associated with a drug is not correlated with its therapeutic value ([Kyle \(2018\)](#)). Since relatively little information about a drug's clinical value is known at the time of patent application, and clinical value is not a criterion for patentability in most countries,⁹ these findings should be unsurprising.

A more subtle issue that has received less attention in the health economics literature on pharmaceuticals is how firm size and markets for technology affect innovation. Some authors find that size is an advantage in pharmaceutical R&D, due to economies of scale and/or scope ([Cockburn & Henderson \(2001\)](#)). Others isolate any advantage to later stages of development, where access to a global network of clinical trial sites may be more important ([Grabowski & Kyle \(2012\)](#)). For smaller firms, [Guedj & Scharfstein \(2004\)](#) argue that internal agency issues may make managers reluctant to end unpromising drug development projects, reducing productivity. Resolving these issues is critical for merger policy, as competition authorities have increasingly focused on the consequences of mergers for innovation in

⁹India is an exception in requiring proof of added therapeutic value for secondary pharmaceutical patents.

addition to consumer welfare. Two recent empirical papers are particularly critical. [Haucap & Stiebale \(2016\)](#) find a decline in R&D output following European pharmaceutical mergers, and [Cunningham et al. \(2018\)](#) show that firms tend to kill off drug development projects that compete with their own internal projects when acquiring smaller firms.

As an alternative to mergers (or a precursor), licensing is used extensively in the pharmaceutical sector. To the extent that firm size is related to productivity advantages at different stages of development, this use of markets for technology should enhance overall industry efficiency. However, frictions clearly remain. While information asymmetries can be partially overcome through experience ([Danzon et al. \(2005\)](#)), they may affect when technology transfer occurs in ways that offset some of the efficiency gains ([Allain et al. \(2015\)](#)).

Small and new firms rely not only on licensing revenues to finance their R&D, of course, but first on venture capital. [Krieger et al. \(2018\)](#) show that financing frictions affect the willingness of pharmaceutical firms to invest in novel, risky projects. However, these findings are somewhat at odds with [Kaplan \(2018\)](#), who argues that despite concerns that firms are too short-termist (and therefore less likely to invest in risky R&D), patterns of VC funding and returns over time are not consistent with too little investment.

2.2 “Push” approaches

“Push” policies intervene to lower the costs of innovation. These include the direct provision of research through government laboratories such as the National Institutes of Health (NIH), in the hopes of generating spillovers that benefit the private sector; directed grants and subsidies to academic researchers; and more generally, tax credits for R&D spending by the private sector. [David et al. \(2000\)](#) describes in more detail the case for government support of R&D through such policies.

2.2.1 Underlying assumptions

As described above, inefficiencies in product markets or capital markets may affect the usefulness of pull policies. Push policies may be more appropriate in such circumstances. For example, where the private value of developing a novel treatment is well below that of its social value, government-funded research could play an important role. Or, if capital markets underinvest in early stage research – which may not be patentable – support from government grants may be essential. However, push policies too require several critical assumptions. While pull policies rely on market signals to allocate R&D efforts, government plays a more direct role in implementing push policies. Consequently, government must function well. In addition, information costs should be relatively low: the cost of identifying areas where innovation is needed, the cost of finding the most productive researchers to work in those areas, and the cost of ensuring the money is spent efficiently.

How should government money be allocated across diseases? [Lichtenberg \(2001\)](#) proposes a model in which the social planner's spending is a function of the burden and the scientific understanding of each disease. OTHER CITATIONS HERE Other approaches account for the possibility of crowding out private research; if there is sufficient profitability from curing cancer, government spending may merely replace what the private sector would willingly invest, or even reduce it (through driving up wages of scientists, for example). Others argue that government support is most important in basic and early stage research, which generates the largest spillovers and attracts lower levels of private investment.

In practice, assessing both need and the productivity of science in a particular disease is challenging, and not always the responsibility of well-informed experts. In the US, for example, the budget for the NIH and some aspects of how it is spent are determined by Congress, and therefore subject to influence by lobbyists or other interests. NIH committees that allocate budgets to grant applicants may not be free from bias. The efficiency of push funding, therefore, depends critically on the alignment of these interests with those of society.

Push funding can finance either research conducted by government laboratories or external researchers. At the NIH, which is by far the largest funder of medical research globally, about 80% of funding is external.¹⁰ Like venture capitalists, government funding agencies must contend with both hidden information (the quality of firms or applicants may be difficult to observe, or the most qualified may not be easily located) as well as hidden actions (the effort of funding recipients may also be hard to monitor). The use of expert committees to evaluate applicants mitigates the former to some extent, as do audits and clearly defined milestones for the latter. Both come at some cost, however. The administrative burden is non-negligible; in the presence of asymmetric information about the true productivity of potential grant recipients, funders may rely on reputation, leading to inefficient concentration of funding to high-status institutions (Fraja (2016)). Expert committees may be biased. In addition, grant recipients may not have the incentive to disclose information that reduces their funding, even if the money is more productively spent elsewhere.

Government funders may of course have a different objective function than venture capitalists – maximizing spillovers rather than profits, for example – and they may have a different time horizon or tolerance for risk. They also may face different constraints. Most government grants are reserved for residents of the country financing the research, which limits the pool of potential applicants. Other considerations, such as gender, racial, or geographic representation, may be factors driving the allocation of grants.

Another important difference is that the market punishes venture capitalists who fail to manage problems of hidden information and hidden actions. The accountability of government funders is less obvious, and is likely to vary across countries and over time. Push and pull policies differ in the allocation of risk. Pharmaceutical R&D, like many other high-tech sectors, has high failure rates. In the case of pull policies, the private sector bears most of this risk; government pays only for successful outcomes through higher prices or prizes. With

¹⁰See “[Extramural and Intramural Research Programs](#)” from the NIH.

push policies, the government must pay for failure. The benefits of basic science can take years to realize, and may be difficult to attribute to a specific source of funding. Pressure on governments to show a return on investment may change their willingness to make risky bets, as [David et al. \(2000\)](#) warns. In particular, they may focus on short-run measures of economic performance, and fund of projects that are already close to success (and less in need of money) rather than those that generate the greatest social benefits.

Finally, effective push funding depends critically on the transfer of technology and ideas between institutions, and in particular between academia (or recipients of public funds) and industry (for later stages of development, manufacture, and marketing). There is a large literature on the “valley of death” and the difficulties of moving knowledge from the university into commercialized products. Pharmaceuticals may be easier than many other technologies to transfer due to fairly well-defined patent rights and commercial applications that are easy to identify. Legislation such as the Bayh-Dole Act as well as university-level policies have an important effect on the incentives of researchers to seek opportunities for technology transfer and commercialization.

2.2.2 Empirical evidence

How is push funding for medical research allocated in practice? [U.S. Government Accountability Office \(2014\)](#) describes how the NIH makes budget decisions. In addition to setting the total NIH budget, Congress mandates spending for specific diseases. NIH directors then choose funding levels according to scientific needs and opportunities, the burden of disease, and public health need. Expert committees select recipients based on peer review of applications. Of course, private sector investment may use similar criteria, depending on many of the factors discussed in the previous section on pull policies. There is some evidence that public and private money has different aims, however. [Ward & Dranove \(1995\)](#) find that public research funding targets diseases that affect fewer people, but more serious, than

those favored by private investment – though this study pre-dates the Orphan Drug Act that increased private returns to developing treatments for small market diseases.

Unfortunately, the allocation of funding may be determined by factors that are less consistent with the idea that government is maximizing social welfare. [Lichtenberg \(2001\)](#) confirms that disease burden explains much of NIH funding allocations, but also finds evidence that public R&D is more responsive to the needs of males and whites. In a study examining the role of Congress in directing research, [Hegde \(2009\)](#) shows that Congressional representatives earmark funds for research fields that are most likely to benefit their constituents, and these benefits are largest for state universities and small businesses. This finding has two implications. First, research fields are not just a function of need, and second, recipients are not selected only on merit. Thus, even with peer review, the allocation of funding across institutions is unlikely to be perfectly efficient.

The question of how the NIH and other funders select grant recipients is the focus of several recent studies on the “science of science.” [Jones \(2011\)](#) documents a shift in funding towards older, more senior researchers and towards teams. These trends potentially affect the productivity of push funding through several channels. Faced with the difficulty of raising funds, younger researchers may be discouraged and exit scientific research or academia, with consequences for the number and quality of scientists in decades to come. As evaluators’ expertise narrows, the evaluation of grants by committees may suffer. Finally, teams of researchers must contend with moral hazard problems, which can be costly. The return on push funding, therefore, may fall.

[Azoulay et al. \(2013\)](#) focus specifically on the process of peer-review at the NIH. They also cite the tendency to favor older scientists as problematic. An additional worry that the NIH is too risk-averse in its selection of applications. Alternative models of funding allocation, such as those used by the Howard Hughes Medical Institute ([Azoulay et al. \(2011\)](#)) and ARPA ([Azoulay et al. \(2019a\)](#)), may be preferable.

More optimistic results on the behavior of NIH committees can be found in [Li \(2017\)](#). She concludes that NIH committees are biased – they favor their own areas of research – but expertise still dominates: they know those fields better and can select the best projects. Other work ([Li & Agha \(2015\)](#)) shows that NIH peer review scores positively correlated with other measures of research impact.

Studies on the effect of NIH funding generally yield good news. A survey by [Cockburn & Henderson \(2000\)](#) concludes that returns from public investment in medical research are very high, and that public and private efforts are complementary: spillovers occur both from public to private labs as well as in the other direction. [Toole \(2007\)](#) also finds that private pharmaceutical R&D investments complement public spending by the NIH, with the contribution of the latter most important in the early stages of drug development ([Toole \(2012\)](#)). This is consistent with earlier work by [Ward & Dranove \(1995\)](#); [Blume-Kohout \(2012\)](#) finds no significant effect of targeted NIH funding has positive impact on late stage development, but confirms the other studies’ results for early stage research. Most recently, using an identification strategy that exploits the idiosyncracies of the NIH funding process, [Azoulay et al. \(2019b\)](#) show that NIH funding spurs private sector patenting.

Overall, there is little evidence that public funding has crowded out private investment. However, it should be noted that the push funding for pharmaceutical innovation largely serves to boost the efforts of the private sector, rather than to fill the disease gaps overlooked by industry. Since governments rarely finance development through Phase III clinical trials and manufacturing, for example, most drug development efforts initiated by public funding still depend on the transfer of technology to the private sector in order to reach the market. These transitions are not always smooth. The recent case of a Zika vaccine developed by the US Army illustrates some of the issues. The government’s efforts to auction off the rights to produce the vaccine attracted the interest of only one firm, Sanofi. Political pressures to sell the product in the US at a price comparable to that in Latin America probably played a role

in Sanofi’s decision to pull out. Without addressing some of the inefficiencies in the product market discussed above, push funding – even that which funds breakthrough science – may be less effective.

Factors external to the NIH may also bear on the outcomes of its funding. For example, [Hellerstein \(1998\)](#) examines how managed care organizations may affect the allocation and efficiency of push funding. Academic medical centers with a large share of managed-care patients receive fewer NIH grants, either because clinicians have less time to spend on research or because managed care restricts the flow of patients who can be enrolled in clinical trials. The strategic responses of grant recipients are also largely overlooked in the economics literature. [Furman et al. \(2012\)](#) demonstrate that scientists may respond to changes in policy, such as targeted grants, by seeking alternative funding sources. These responses may undermine policy efforts to direct research to (or away from) specific areas.

Most of the empirical work examining push funding in pharmaceutical-related fields concerns the US, and especially the NIH. There may be valuable lessons from experiences in other countries, not only for learning “what works” but also for improving the allocation of funding at a global level. [Kyle et al. \(2017\)](#) explore how non-US funders respond to changes in NIH spending across a subset of infectious diseases. They find patterns that are consistent with either free-riding (if the NIH is willing to cure HIV, why should INSERM in France?) or optimal reallocation (perhaps INSERM can now focus on Ebola). Coordination among global funders in setting disease priorities and finding the best qualified researchers may enhance the effectiveness of push funding from all sources.

2.3 Indirect effects of other policies

(still incomplete)

2.3.1 Entry regulation

The pharmaceutical sector is highly regulated, and through changing expectations about both costs and revenues associated with investments in R&D, regulations also play a role in the level and direction of innovative efforts, and are themselves a response to perceived need for innovation. For example, the FDA created a number of regulatory pathways designed to encourage development of innovative treatments. These include the Breakthrough Therapy designation expedites the review of treatments that treat serious conditions and that provide preliminary evidence of significant clinical benefits. Expedited review, if it results in faster market authorization, should increase the expected period of patent protection and act as an indirect pull policy. Similarly, the FDA's acceptance of surrogate endpoints (such as tumor size rather than survival) can speed clinical development and expected market exclusivity.

Regulation may discourage innovation as well. Novel science that is harder for regulators to understand may face a more difficult path to approval, for example. In some cases, the lack of a regulatory pathway might be an impediment, as was arguably the case for biosimilar drugs in the US before the BCPI Act of 2009. Indeed, some have argued that entry regulation should be significantly relaxed. In a multisector study of OECD countries, [Alesina et al. \(2005\)](#) suggest that such liberalization would increase investment. In 2018, the US passed "right-to-try" legislation to facilitate patient access to experimental treatments. Though increased access was the primary motivation behind the law, it may reduce the time or expense of bringing some treatments to market. Of course, entry regulation exists in part because of large information asymmetries. Removing or reducing this regulation would likely have other effects on both demand (as doctors, pharmacists and patients might have to exert more effort to assess the quality of a product) and supply (as producers might invest large sums in developing brand name reputations or other means of signalling quality).

The effects of regulation may differ across firms. In contrast to the early-mover advantages estimated for pharmaceuticals in earlier studies, recent work by [Stern \(2017\)](#) finds that first

movers in medical devices spend more time in regulatory review than do followers, and that small firms are less likely enter new device markets than is observed in pharmaceuticals. Depending on what type of organization is best positioned to innovate, these differences can therefore have implications for the overall rate of progress.

2.3.2 Product liability

As noted previously, we generally have incomplete information about a drug's quality when it arrives on the market. Entry regulation reduces some, but not all, of the information asymmetry between a producer and consumers, but even the producers don't know everything. Clinical trials are limited in size, and conducted under conditions that may differ in important ways from how a drug is ultimately used in practice.

The optimal risk level is difficult to determine and likely to vary across drugs. While entry regulation takes an *ex ante* approach to risk, product liability addresses problems *ex post*. Product liability policies, which govern the financial risk associated with marketing a product that turns out to have unexpected negative effects, can therefore be a factor in innovative investment. Vaccines are an important example of treatments where product liability risk drove many firms out of the market, a problem at least partially rectified by the establishment of the Vaccine Compensation Program in 1987 ([Manning \(1994\)](#)). [Viscusi & Moore \(1993\)](#) find an inverted U-shaped relationship between product liability costs and new product introductions in manufacturing firms. However, in a review of the economic literature on product liability and pharmaceutical innovation, [Garber \(2013\)](#) concludes that empirical evidence on the relationship is limited.

2.3.3 Price regulation

In most developed (and now many developing) countries, the government plays an important role in setting pharmaceutical prices. As these prices serve as a signal for investment in

innovation, it is vital that they reflect social value. While governments may have more reason to explicitly consider society’s priorities when negotiating price than would a for-profit insurance company, there are nevertheless potential problems.

Governments face budget constraints that may render paying high prices impossible, even for socially valuable innovations. In addition, politicians may favor short-run political “wins” – such as reducing expenditures – over the provision of long-run innovation incentives, particularly when the benefits of such incentives could be claimed by political rivals that have power in the future. Finally, most governments represent only a small share of the total global market for pharmaceuticals. Consequently, knowing that their own prices are unlikely to shift innovation incentives, they may be tempted to let other countries pay high prices and negotiate for very low domestic prices. These issues are not isolated to pharmaceuticals, of course, and thus present challenges for innovation policy more generally.

3 Conclusion

There is little doubt that innovation policy, both pull (especially patents) and push (especially NIH funding), has contributed to the development of pharmaceutical treatments with enormous social benefits. Broadly speaking, innovative efforts in both the public and private sectors have targeted diseases with large burdens. On average, medical research funding in the US generates positive benefits, even if peer review is imperfect. That said, fixing problems in product and capital markets may increase the efficacy of pull policies. Refinements to how grants and subsidies are allocated are also likely to improve innovative performance.

However, there are areas where policies have failed, and others where they may have gone too far. Some policymakers and others worry that pharmaceuticals sometimes enjoy too much protection. “Evergreening” – the attempt to extend a product’s exclusivity by patenting minor improvements – is especially criticized ([Hemphill & Sampat \(2012\)](#)) and

DG Competition (2009)). Bagley et al. (2019) argue that the Orphan Drug Act may have gone too far, and that the legislation disproportionately rewards producers of inframarginal products. In some cases, the protection generates no innovation benefits. Kyle & McGahan (2012) demonstrate that the extension of patent protection to developing countries is not associated with an increase in private R&D on neglected diseases, only to those that are also prevalent in richer countries. Chaudhuri et al. (2006) highlighted the large potential static losses that could result from the introduction of patents in developing countries (though subsequent studies, such as Duggan et al. (2016) and Kyle & Qian (2014), find less worrisome outcomes), and it is concerning if there is no offsetting dynamic gain from increased innovation.

The lack of novel antibiotics illustrates why the usual innovation policies can fail for other reasons. Resistance to antibiotics develops over time, and ideally, their use today would account for the potential for resistance in the future. Unfortunately, with a limited patent term, the owner of a new antibiotic has an interest in maximizing its use during the period of patent protection; after that, the producer expects generic competitors to take most of the market, and reduced demand from resistance has little effect on its own expected profits. Antibiotic stewardship policies aim to prevent this problem by limiting the use of new drugs, but this also limits the expected profitability from developing such treatments. Thus, the limited patent term distorts incentives downstream, and efforts to address the downstream problems undercut innovation incentives upstream.

In recent years, various policy initiatives have been undertaken to address the looming crisis of antibiotic resistance. The Generating Antibiotic Incentives Now (GAIN) Act of 2012 in the US, for example, adds five years of additional exclusivity for new antibiotics. Between 2012 and 2017, the FDA approved 12 qualifying treatments, but noted that all were already in development when the act was passed, and none employs a novel mechanism of

action.¹¹ This highlights a gap in our understanding of many innovation policies. To judge the efficiency of innovation policy, we need to know much more about the *marginal* benefits generated by either extensions to patents and exclusivity or additional public subsidies. In other words, is the last dollar spent yielding innovations that provide at least one dollar of therapeutic benefit? Perhaps in this case and others, policy has overshot.

Other policy proposals include prizes for antibiotics. For example, the NIH created a \$20 million fund to develop diagnostic tools. In the UK, the Longitude Prize recently created a challenge for the development of a rapid test to determine the appropriate use of antibiotics, worth £8 million. The Longitude Fund also provides seed funding to start-ups of £10-25,000, suggesting a recognition that capital market imperfections could hinder the ability of scientists to pursue this prize. While a direct comparison of diagnostics and drugs is probably inappropriate, these figures are well below the estimated cost of bringing a new drug to market. It is too early to say whether they will successfully pull innovative activity.

The challenges in implementing these efforts are typical of any prize. The benefits of antibiotic innovation are global, but heterogenous and endogenous to other policies. Within Europe, for example, resistance varies greatly. For the *Acinetobacter* species, rates are below 1% in Denmark, Ireland, and Norway, while in Greece, Italy, Portugal, and Spain, they exceed 50%.¹² At least some share of this difference is due to antibiotic stewardship, which entails (often costly) policy changes to alter the incentives of prescribers and patients. These two countries also differ in per capita income and their capacity to contribute to an antibiotic prize. Coordinating these other policies with the implementation of a pull policy like a prize, both within and across countries, is essential.

¹¹See the FDA's 2017 report to Congress on the GAIN Act, available on the [FDA's website](#).

¹²The percentage of invasive isolates with combined resistance to fluoroquinolones, aminoglycosides and carbapenems in 2013 for *Acinetobacter* species. Source: European Centers for Disease Control.

References

- Abrams, D., & Sampat, B. (2017). What's the value of patent citations? evidence from pharmaceuticals.
- Acemoglu, D., & Linn, J. (2004). Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry. *Quarterly Journal of Economics*, *119*(3), 1049–1090.
- Alesina, A., Ardagna, S., Nicoletti, G., & Schiantarelli, F. (2005). Regulation and investment. *Journal of the European Economic Association*, *3*, 791–825.
- Allain, M.-L., Henry, E., & Kyle, M. (2015). Competition and the efficiency of markets for technology. *Management Science*, *62*(4), 1000.
- Angell, M. (2004). *The Truth about Drug Companies: How They Deceive Us and What to Do about It*. New York: Random House.
- Azoulay, P. (2002). Do Pharmaceutical Sales Respond to Scientific Evidence? *Journal of Economics & Management Strategy*, *11*(4), 551–594.
- Azoulay, P., Fuchs, E., Goldstein, A. P., & Kearney, M. (2019a). Funding Breakthrough Research: Promises and Challenges of the “ARPA Model”. *Innovation Policy and the Economy*, *19*, 69–96.
URL <https://doi.org/10.1086/699933>
- Azoulay, P., Zivin, J. G., Li, D., & Sampat, B. (2019b). Public R&D investments and private sector patenting: Evidence from NIH funding rules. *Review of Economic Studies*, *86*(1), 117–152.
- Azoulay, P., Zivin, J. S. G., & Manso, G. (2011). Incentives and creativity: evidence from the academic life sciences. *The RAND Journal of Economics*, *42*(3), 527–554.
URL <http://www.jstor.org/stable/23046811>

- Azoulay, P., Zivin, J. S. G., & Manso, G. (2013). National Institutes of Health peer review: Challenges and avenues for reform. *Innovation Policy and the Economy*, 13(1), 1–22.
URL <http://www.jstor.org/stable/10.1086/668237>
- Bagley, N., Berger, B., Chandra, A., Garthwaite, C., & Stern, A. D. (2019). The Orphan Drug Act at 35: Observations and an outlook for the twenty-first century. *Innovation Policy and the Economy*, 19, 97–137.
URL <https://doi.org/10.1086/699934>
- Blume-Kohout, M. E. (2012). Does Targeted, Disease-Specific Public Research Funding Influence Pharmaceutical Innovation? *Journal of Policy Analysis and Management*, 31(6), 641–660.
- Blume-Kohout, M. E., & Sood, N. (2013). The Impact of Medicare Part D on Pharmaceutical R&D. *Journal of Public Economics*, 97, 327–36.
- Budish, E., Roin, B. N., & Williams, H. (2015). Do Fixed Patent Terms Distort Innovation? Evidence from Cancer Clinical Trials. *American Economic Review*, 105(7), 2044–2085.
- Centers for Disease Control and Prevention (2015). National vital statistics reports. Tech. rep., Centers for Disease Control and Prevention.
- Chaudhuri, S., Goldberg, P. K., & Jia, P. (2006). Estimating the Effects of Global Patent Protection in Pharmaceuticals: A Case Study of Quinolones in India. *American Economic Review*, 96(5), 1477–1514.
- Cockburn, I. M. (2006). Is the Pharmaceutical Industry in a Productivity Crisis? *NBER Working Paper*.
- Cockburn, I. M., & Henderson, R. M. (2000). Publicly funded science and the productivity

of the pharmaceutical industry. *Innovation Policy and the Economy*, 1, 1–34.

URL <http://www.jstor.org/stable/25056140>

Cockburn, I. M., & Henderson, R. M. (2001). Scale and Scope in Drug Development: Unpacking the Advantages of Size in Pharmaceutical Research. *Journal of Health Economics*, 20(6), 1033–1057.

Cunningham, C., Ederer, F., & Ma, S. (2018). Killer acquisitions.

Cutler, D. M., Chernow, M., Ghosh, K., & Landrum, M. B. (2017). *Understanding the Improvement in Disability Free Life Expectancy in the U.S. Elderly Population*. Chicago: University of Chicago Press and The National Bureau of Economic Research.

Cutler, D. M., Long, G., Berndt, E. R., Royer, J., Fournier, A.-A., Sasser, A., & Cremieux, P. (2007). The value of antihypertensive drugs: A perspective on medical innovation. *Health Affairs*, 26(1), 97–100.

URL <http://content.healthaffairs.org/cgi/content/abstract/26/1/97>

Danzon, P. M., Nicholson, S., & Pereira, N. S. (2005). Productivity in Pharmaceutical-Biotechnology R&D: The Role of Experience and Alliances. *Journal of Health Economics*, 24(2), 317–339.

David, P. A., Hall, B. H., & Toole, A. A. (2000). Is Public R&D a Complement or Substitute for Private R&D? A Review of the Econometric Evidence. *Research Policy*, 29, 497–529.

de Mouzon, O., Dubois, P., Morton, F. S., & Seabright, P. (2015). Market size and pharmaceutical innovation. *RAND Journal of Economics*, 46(4), 844–871.

DG Competition (2009). Pharmaceutical Sector Inquiry Final Report.

- DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics*, *47*, 20 – 33.
URL <http://www.sciencedirect.com/science/article/pii/S0167629616000291>
- DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*, *22*(2), 151–85.
- Dranove, D., Garthwaite, C., & Hermosilla, M. (2014). Pharmaceutical profits and the social value of innovation.
- Duggan, M. (2005). Do new prescription drugs pay for themselves?: The case of second-generation antipsychotics. *Journal of Health Economics*, *24*(1), 1 – 31.
URL <http://www.sciencedirect.com/science/article/pii/S016762960400102X>
- Duggan, M., & Evans, W. (2008). Estimating the impact of medical innovation: A case study of HIV antiretroviral treatments. *Forum for Health Economics & Policy*, *11*(2), 1–37.
- Duggan, M., Garthwaite, C., & Goyal, A. (2016). The market impacts of pharmaceutical product patents in developing countries: Evidence from india. *American Economic Review*, *106*(1), 99–135.
URL <http://www.aeaweb.org/articles?id=10.1257/aer.20141301>
- Epstein, A. J., & Ketcham, J. D. (2014). Information technology and agency in physicians' prescribing decisions. *RAND Journal of Economics*, *45*(2), 422–448.
- et al., G. R. (2014). Mortality trends in the era of antiretroviral therapy: evidence from the network for analysing longitudinal population based hiv/aids data on africa (alpha). *AIDS*, *28*, S533–S542.

- Fernandez, F., & Zejcirovic, D. (2018). The role of pharmaceutical promotion to physicians in the opioid epidemic.
- Finkelstein, A. (2004). Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry. *The Quarterly Journal of Economics*, (May), 527–564.
- Fraja, G. D. (2016). Optimal public funding for research: a theoretical analysis. *The RAND Journal of Economics*, 47(3), 498–528.
URL <http://www.jstor.org/stable/43895655>
- Furman, J. L., Murray, F., & Stern, S. (2012). Growing Stem Cells: The Impact of Federal Funding Policy on the U.S. Scientific Frontier. *Journal of Policy Analysis and Management*, 31(3), 661–705.
- Gaessler, F., & Wagner, S. (2018). Patents, data exclusivity, and the development of new drugs.
- Garber, S. (2013). Economic effects of product liability and other litigation involving the safety and effectiveness of pharmaceuticals. Tech. rep., RAND Corporation.
- Garthwaite, C., & Duggan, M. (2012). Empirical evidence on the value of pharmaceuticals. In P. M. Danzon, & S. Nicholson (Eds.) *Empirical Evidence on the Value of Pharmaceuticals*. Oxford University Press.
- Garthwaite, C. L. (2012). The economic benefits of pharmaceutical innovations: the case of Cox-2 inhibitors. *American Economic Journal: Applied Economics*, 4(3), 116–137.
- Grabowski, H. G., & Kyle, M. K. (2012). Mergers, Acquisitions and Alliances. In P. M. Danzon, & S. Nicholson (Eds.) *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, chap. 18, (pp. 552–577). Oxford: Oxford University Press.

- Guedj, I., & Scharfstein, D. (2004). Organizational scope and investment: Evidence from the drug development strategies and performance of biopharmaceutical firms. Working Paper 10933, National Bureau of Economic Research.
- Haucap, J., & Stiebale, J. (2016). How mergers affect innovation: Theory and evidence from the pharmaceutical industry. Tech. Rep. 218, Dusseldorf Institute for Competition Economics.
- Heffernan, A., Cooke, G. S., Nayagam, S., Thursz, M., & Hallett, T. B. (2019). Scaling up prevention and treatment towards the elimination of hepatitis c: a global mathematical model. *The Lancet*.
- Hegde, D. (2009). Political Influence behind the Veil of Peer Review: An Analysis of Public Biomedical Research Funding in the United States. *The Journal of Law and Economics*, 52(4), 665–690.
- Hellerstein, J. K. (1998). Public funds, private funds, and medical innovation: How managed care affects public funds for clinical research. *The American Economic Review*, 88(2), 112–116.
URL <http://www.jstor.org/stable/116903>
- Hemphill, C. S., & Sampat, B. N. (2012). Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals. *Journal of Health Economics*, 31(2), 327–339.
- Howard, D. H., Chernew, M. E., Abdelgawad, T., Smith, G. L., Sollano, J., & Grabowski, D. C. (2016). New anticancer drugs associated with large increases in costs and life expectancy. *Health Affairs*, 35(9), 1581–7.
- Iizuka, T. (2007). Experts' agency problems: Evidence from the prescription drug market in japan. *RAND Journal of Economics*, 38(3), 844–862.

- lizuka, T. (2012). Physician agency and adoption of generic pharmaceuticals. *American Economic Review*, 102(6), 2826–58.
URL <http://www.aeaweb.org/articles?id=10.1257/aer.102.6.2826>
- Jacobson, M., Earle, C. C., Price, M., & Newhouse, J. P. (2010). How Medicare’s Payment Cuts for Cancer Chemotherapy Drugs Changed Patterns of Treatment. *Health Affairs*, 29(7), 1391–1399.
- Janakiraman, R., Dutta, S., Sismeiro, C., & Stern, P. (2008). Physicians’ persistence and its implications for their response to promotion of prescription drugs. *Management Science*, 54(6), 1080–1093.
- Jayachandran, S., Lleras-Muney, A., & Smith, K. V. (2010). Modern medicine and the twentieth century decline in mortality: Evidence on the impact of sulfa drugs. *American Economic Journal: Applied Economics*, 2, 118–146.
- Jones, B. F. (2011). As science evolves, how can science policy? *Innovation Policy and the Economy*, 11(1), 103–131.
URL <http://www.jstor.org/stable/10.1086/655820>
- Kaplan, S. N. (2018). Are us companies too short-term oriented? some thoughts. *Innovation Policy and the Economy*, 18, 107–124.
URL <https://doi.org/10.1086/694409>
- Kremer, M., & Glennerster, R. (2004). *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*. Princeton: Princeton University Press.
- Kremer, M., & Snyder, C. M. (2003). Why Are Drugs More Profitable than Vaccines. *NBER Working Paper Series*.

- Krieger, J. L., Li, D., & Papanikolaou, D. (2018). Missing novelty in drug development. Tech. rep., NBER Working Paper 24595.
- Kyle, M. (2018). Are important innovations rewarded? evidence from pharmaceutical markets. *Review of Industrial Organization*, 53(1), 211–234.
- Kyle, M., & Qian, Y. (2014). Intellectual Property Rights and Access to Innovation: Evidence from TRIPS. *NBER Working Paper 20779*.
- Kyle, M., Ridley, D., & Zhang, S. (2017). Strategic interaction among governments in the provision of a global public good. *Journal of Public Economics*, 156, 185–199.
- Kyle, M. K., & McGahan, A. M. (2012). Investments in Pharmaceuticals Before and After TRIPS. *Review of Economics and Statistics*, 94(4), 1157–1172.
- Li, D. (2017). Expertise versus bias in evaluation: Evidence from the NIH. *American Economic Journal: Applied Economics*, 9(2), 60–92.
- Li, D., & Agha, L. (2015). Big names or big ideas: Do peer review panels select the best science proposals? *Science*, 348(6233), 434–438.
- Lichtenberg, F., & Waldfoegel, J. (2009). Does misery love company - evidence from pharmaceutical markets before and after the orphan drug act. *Michigan Telecommunications and Technology Law Review*, 15(2), 335–357.
- Lichtenberg, F. R. (2001). The Allocation of Publicly Funded Biomedical Research. In D. M. Cutler, & E. R. Berndt (Eds.) *Medical Care Output and Productivity*.
- Light, D. W., & Lexchin, J. R. (2012). Pharmaceutical research and development: what do we get for all that money? *BMJ*, 345.
- URL <https://www.bmj.com/content/345/bmj.e4348>

Love, J. (2011). De - linking r&d costs from product prices.

URL http://www.who.int/phi/news/phi_cewg_1stmeet_10_KEI_submission_en.pdf

Manning, R. L. (1994). Changing rules in tort law and the market for childhood vaccines.

The Journal of Law & Economics, 37(1), 247–275.

URL <http://www.jstor.org/stable/725611>

Murphy, K. M., & Topel, R. H. (2007). Social value and the speed of innovation. *The American Economic Review*, 97(2), 433–437.

URL <http://www.jstor.org/stable/30034490>

Scott Morton, F., & Shapiro, C. (2016). Patent assertions: Are we any closer to aligning reward to contribution? *Innovation Policy and the Economy*, 16, 89–133.

URL <https://doi.org/10.1086/684987>

Stern, A. D. (2017). Innovation under regulatory uncertainty: Evidence from medical technology. *Journal of Public Economics*, 145, 181–200.

Toole, A. (2012). The impact of public basic research on industrial innovation: Evidence from the pharmaceutical industry. *Research Policy*, 41, 1–12.

Toole, A. A. (2007). Does Public Scientific Research Complement Private Investment in Research and Development in the Pharmaceutical Industry? *The Journal of Law and Economics*, 50(1), 81–104.

U.S. Government Accountability Office (2014). Research Priority Setting, and Funding Allocations across Selected Diseases and Conditions. Tech. rep.

URL <http://www.gao.gov/products/GAO-14-246>

Viscusi, W. K., & Moore, M. J. (1993). Product liability, research and development, and innovation. *Journal of Political Economy*, 101(1), 161–184.

- Ward, M. R., & Dranove, D. (1995). The Vertical Chain of Research and Development in the Pharmaceutical Industry. *Economic Inquiry*, 33(1), 70–87.
- Whitney, C. G., Zhou, F., Singleton, J., & Schuchat, A. (2014). Benefits from immunization during the vaccines for children program era — united states, 1994–2013. *Mortality and Morbidity Weekly Report*, 63(16), 352–355.
- Williams, H. L. (2016). Intellectual property rights and innovation: Evidence from health care markets. *Innovation Policy and the Economy*, 16, 53–87.
URL <https://doi.org/10.1086/684986>
- World Health Organization (2009). Towards universal access: Scaling up priority hiv/aids interventions in the health sector. Tech. rep., World Health Organization.
- World Health Organization (2018). World health statistics. Tech. rep., World Health Organization.
- Yin, W. (2008). Market incentives and pharmaceutical innovation. *Journal of Health Economics*, 27(4), 1060–77.