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Considering Returns on Federal Investment in the Negotiated "Maximum Fair Price" of Drugs Under the Inflation Reduction Act: an Analysis

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Working Paper No. 219

February 28th, 2024

ABSTRACT

The Inflation Reduction Act (IRA) of 2022 contained landmark provisions authorizing government to negotiate a "maximum fair price" for selected Medicare Part D drugs considering the manufacturer's research and development costs, federal support for discovery and development, the extent to which the drugs address unmet medical needs, and other factors. This working paper describes federal investment in the discovery and development of the ten drugs selected for price negotiation in the first year of the IRA as well as the health value created through Medicare Part D spending on these drugs. We identified $11.7 billion in NIH funding

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The Institute for New Economic Thinking provided funding for foundational studies on NIH funding for pharmaceutical innovation through a grant to Bentley University. The National Biomedical Research Foundation provides core funding for the Center for Integration of Science and Industry through a grant to Bentley University. We want to thank our colleagues at the Center for Integration of Science and Industry and Bentley University as well as our Executives in Residence Dr. Michael Boss, Dr. Nancy Hsiung, and Brice Leicher, Esq. whose critical perspectives contributed to our work. We also thank Juliana Harrison, MBA, for her essential assistance with this manuscript and Dr. Thomas Ferguson for providing a venue for dissemination of these studies.

for basic or applied research leading to approval of these drugs with median investment costs of $895.4 million/drug. This early public investment provided a median cost savings to industry of $1,485 million/drug, comparable to reported levels of investment by industry. From 2017-2021, Medicare Part D spent $126.4 billion (median $10.7 billion) for these products before rebates. Excluding two products for diabetes, Medicare Part D spending was $97.4 billion and the total health value created was 650,940 QALYs or $67.7 billion (WTP/QALY=$104K) representing a negative residual health value of -$29.7 billion (before rebates). We argue that a negotiated fair price should provide returns on both private and public investments in these products commensurate with the scale and risk of these investments, with the principal return on public sector investments being the residual health value (net price) accruing to those using the product. These empirical data provide a cost basis for negotiating a fair price that rewards early government investments in innovation and provides social value for the public.

https://doi.org/10.36687/inetwp219

JEL codes: H43, H51, I10, I18,

Keywords: Inflation Reduction Act, drug pricing, Medicare, federal funding, biomedical research, health value, social return on investment

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1. INTRODUCTION

The US government has been considering measures to moderate the price of pharmaceutical products since the late 1950s when Senator Estes Kefauver convened Senate hearings on monopolistic practices in the pharmaceutical industry (Kefauver and Till 1965, Greene and Podolsky 2012, Mattingly, Seo et al. 2021). Sixty years after passage of the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, which established the modern drug approval process, and amidst continuing public concern about high drug prices (Mattingly, Seo et al. 2021, Kirzinger, Montero et al. 2023), Congress passed the Inflation Reduction Act (IRA) of 2022 (USCongress 2022). This Act contains landmark provisions enabling the Centers for Medicare and Medicaid Services (CMS) to negotiate the price of selected drugs covered by Medicare Part D (Sarpatwari 2022).

The IRA defines a stepwise process for identifying drugs subject to price negotiation, the negotiating process itself, and factors the government can consider in the negotiations. Among these factors are "Prior Federal financial support for novel therapeutic discovery and development with respect to the drug" and "The extent to which such drug and therapeutic alternatives to such drug address unmet medical needs for a condition for which treatment or diagnosis is not addressed adequately by available therapy" (USCongress 2022).

These two issues are related in that the federal government, through the National Institutes of Health (NIH), makes substantial investments in biomedical research for the express purpose of improving health outcomes and reducing the burden of disease.[1] As such, the health benefits that accrue from drugs discovered or developed with federal support represent the expected return on government investment in these products (Cleary, Jackson and Ledley 2020, Galkina Cleary, Jackson et al. 2023).

This working paper quantifies the federal investment in the discovery and development of the ten drugs selected for price negotiation in the first year of the IRA as well as the health benefit accruing to the public from the Medicare Part D payment for these drugs. The federal investment in these drugs is estimated from the NIH project (grant) support for publications describing the

[1] The NIH Mission Statement reads "NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability." https://www.nih.gov/about-nih/what-we-do/mission-goals.

results of basic and applied research leading to drug approval. This total is then used to estimate the federal investment cost relative to reported levels of industry investments in new drug approvals as well as the cost savings to industry represented by this federal investment. We separately estimate the total health value created by Medicare Part D spending on these drugs and the residual health value to consumers after consideration of the drug price. These empirical results should be useful to CMS in negotiating the price of drugs selected for price negotiation in the first year of the IRA.

These empirical results are discussed in the context of the government's role as a lead investor in pharmaceutical innovation (Mazzucato 2013, Cleary, Jackson and Ledley 2020) and the principle that public rewards from public sector investments in early innovation should be commensurate with the risk of these investments (Lazonick and Mazzucato 2013, Laplane and Mazzucato 2020). By authorizing CMS to consider "…federal financial support…" in negotiating drug prices, we argue that the IRA empowers government to negotiate drug prices that provide an equitable balance of public and private returns on those investments. This work provides a cost basis for such negotiations while also describing the health value created for Medicare Part D beneficiaries through use of these products.

Outline of this research

Section 2, Background and Literature, provides background on provisions of the IRA related to Medicare price negotiations and describes the ten drugs selected for negotiation in the first year of the IRA. We then describe our previous studies on NIH funding for basic or applied research leading to drug approvals and methods used for that analysis. Six of the ten drugs selected for price negotiation were included in our previous study of drugs approved from 2010-2019, and the methods used in this analysis are an adaptation of those described previously (Cleary, Jackson and Ledley 2020). We then describe our preliminary studies aimed at assessing the multivariate elements of value generated through commercialization of novel pharmaceutical products (Chaves da Silva, Conti and Ledley submitted). The present work applies the methods for estimating health value creation and the health benefit accruing to individuals who use specific medicines developed in those studies.

Section 3, Results and Discussion, describes the results of this analysis including NIH funding for basic or applied research (including development) leading to first approval of these ten drugs,

the NIH investment costs relative to reported investment in new drug approvals by industry, and the cost savings to industry provided by this public sector funding. We then describe the total health value created through Medicare Part D spending on these ten drugs and the health value accruing to patients after consideration of the price paid by Medicare.

Section 4, Conclusions, discusses these empirical findings in the context of the drug price negotiations anticipated under the IRA and the concept of "fair" pricing, which recognizes a central role for considerations of investment and return. We argue that any consideration of a maximum fair price for drugs under Medicare Part D should aim to achieve an equitable balance between the economic returns on private investment in these products and the social returns on the enabling public investment by the NIH.

2. BACKGROUND AND LITERATURE

Negotiating drug prices under the Inflation Reduction Act

The Inflation Reduction Act of 2022 (P.L. 117-169) (IRA) included a "Price negotiation program to lower prices for certain high-priced, single source drugs" (Cubanski, Neuman and Freed 2022, USCongress 2022, HHS 2023). This program was designed to rectify provisions of the "Medicare Prescription Drug, Improvement, and Modernization Act of 2003" (P.L. 108-173) (USCongress 2003), which created the Medicare prescription drug benefit for seniors, known as Medicare Part D, but explicitly prohibited the Center for Medicare and Medicaid Services (CMS) from directly negotiating the price of these drugs with manufacturers (Lee, Gluck and Curfman 2016). In 2021, Medicare Part D provided coverage for >3,500 drugs with spending totaling $215 billion (Cubanski and Neuman 2022). Of this amount, Medicare Part D spending was >$130 billion for the top 100 drugs and $48 billion for the top ten drugs (Cubanski and Neuman 2022). Medicare Part D has significantly impacted pharmaceutical innovation (Blume-Kohout and Sood 2013), utilization (Lichtenberg and Sun 2007, Park and Martin 2017), drug spending (Ketcham and Simon 2008, Yin, Basu et al. 2008), and outcomes (Afendulis, He et al. 2011, Lichtenberg 2024).

The IRA authorizes CMS to negotiate a "maximum fair price" for a number of drugs each year, including 10 in year 1 (2023) for implementation in 2026, 15 in years two and three (2024-2025) for implementation in 2027 and 2028, and 20/year thereafter. The Act also establishes criteria for selecting these drugs, which include being covered by Medicare Part D (or Medicare Part B after

2025), a single-source brand name product without generic or biosimilar alternatives, and on the market for at least 7 years for small molecule drugs or 11 years for biologics. The price is then negotiated taking into account a number of specific factors related to the cost of developing, producing, or distributing the drug, the manufacturer's return on investment, federal financial support for discovery and development, generic or biosimilar competition, market data, and alternative therapies.[2] The negotiation then proceeds through a scripted process that includes limits on the offer amount and a ceiling on the negotiated price (Cubanski, Neuman and Freed 2022, USCongress 2022, Sullivan 2023, CMS 2023a, CMS 2023b).

Several studies have tried to model the cost savings that may be achieved through price negotiation. One study simulated how the IRA would have impacted drug prices from 2018-2020, estimating that the negotiation program could have reduced CMS spending by $26.5 billion or approximately 5% (Rome, Nagar et al. 2023). Another study projected ten drugs that could be designated for price negotiation and that the price negotiation process would provide a cost savings of $1.8 billion in the first year (2026) (Hernandez, Gabriel and Dickson 2023). The Congressional Budget Office developed a model for simulated drug price negotiations (Adams and Herrnstadt 2021) estimating that, when the Act is fully implemented in 2031, it could reduce

[2] From: 42 USC 1320F-3 negotiation and renegotiation process. https://www.congress.gov/bill/117th-congress/house-bill/5376/text

"(e) Factors.--For purposes of negotiating the maximum fair price of a selected drug under this part with the manufacturer of the drug, the Secretary shall consider the following factors, as applicable to the drug, as the basis for determining the offers and counteroffers under subsection (b) for the drug:

(1) Manufacturer-specific data. …
- (A) Research and development costs of the manufacturer for the drug and the extent to which the manufacturer has recouped research and development costs.
- (B) Current unit costs of production and distribution of the drug.
- (C) Prior Federal financial support for novel therapeutic discovery and development with respect to the drug.
- (D) Data on pending and approved patent applications, exclusivities recognized by the Food and Drug Administration, and applications and approvals under section 505(c) of the Federal Food, Drug, and Cosmetic Act or section 351(a) of the Public Health Service Act for the drug.
- (E) Market data and revenue and sales volume data for the drug in the United States.

(2) Evidence about alternative treatments. …
- (A) The extent to which such drug represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of such existing therapeutic alternatives.
- (B) Prescribing information approved by the Food and Drug Administration for such drug and therapeutic alternatives to such drug.
- (C) Comparative effectiveness of such drug and therapeutic alternatives to such drug, taking into consideration the effects of such drug and therapeutic alternatives to such drug on specific populations, such as individuals with disabilities, the elderly, the terminally ill, children, and other patient populations.
- (D) The extent to which such drug and therapeutic alternatives to such drug address unmet medical needs for a condition for which treatment or diagnosis is not addressed adequately by available therapy."

Medicare Part D spending by $14 billion/year and Medicare Part B spending by $9 billion/year (CBO 2023) or $102 billion from 2026-2031 (CBO 2022). In general, these models predict that the price negotiation provisions of the IRA will have only moderate impact.

Drugs selected for Medicare price negotiation in the first year of the IRA

In August 2023, CMS announced its selection of ten drugs covered by Medicare Part D for price negotiation in the first year of the IRA (CMS 2023). These drugs are:

- Enbrel (etanercept) – a hybrid recombinant DNA-derived protein combining portions of the tumor necrosis factor (TNF) receptor and a human monoclonal antibody. The product binds to the inflammatory cytokine TNF, preventing activation of immune cells and inhibiting inflammatory processes leading to autoimmune diseases like rheumatoid arthritis.
- NovoLog (insulin aspart) – a synthetic rapid short-acting insulin. NovoLog is designed for as-needed dosing to manage short-term blood glucose elevations after meals. A mixture of short- and long-acting insulin is the standard of care for insulin replacement therapy in both type 1 and 2 diabetes care.
- Januvia (sitagliptin) – a small molecule that binds to and inhibits enzyme DPP-4 and prolongs the activity of the hormone GLP-1 in patients with type 2 diabetes. This leads to increased production of natural insulin and a reduction in digestion speed and appetite, lowering insulin need and slowing disease progression from insulin desensitization.
- Stelara (ustekinumab) – a human monoclonal antibody. It binds to and inhibits pro-inflammatory cytokines like interleukin (IL-12 and IL-23) by selectively targeting and binding to their shared p40 subunit chemical backbone. This lowers inflammation inducing cytokines in the blood and reduces the immune response in patients with autoimmune disease, preventing further damage and providing symptom relief.
- Xarelto (rivaroxaban) and Eliquis (apixaban) – small molecules that selectively bind to and block clotting factor Xa. Disabling factor Xa limits the conversion of prothrombin to thrombin, a critical step in blood clotting, thus preventing thrombosis that can cause stroke or heart attacks in individuals at risk due to surgery or irregular heart rhythms. In addition, these drugs have significant safety advantages over current therapy with warfarin.

- Imbruvica (ibrutinib) – a small molecule that binds to and inhibits Bruton's tyrosine kinase, a protein regulating cell division and death. This drug is used to reduce the proliferation and survival of cancer cells.
- Jardiance (empagliflozin) and Farxiga (dapagliflozin) – small molecules that inhibit the function of SGLT2 channels, thus controlling the amount of glucose in the blood. In patients with type 2 diabetes, this can help maintain lower blood glucose levels and treat kidney and heart disease associated with diabetes.
- Entresto (sacubitril/valsartan) – a small molecule that combines two different drugs to manage heart failure. The newly approved component of Entresto is sacubitril, a small molecule that inhibits neprilysin. This reduces the workload on the heart by dilating blood vessels and increasing excretion of sodium and water. The second drug, valsartan, is an older hypertension medication that blocks the action of angiotensin, which incidentally increases in response to sacubitril and could raise blood pressure.

Table 1 shows Medicare Part D spending on these drugs for the five years 2017-2021 and the number of beneficiaries.

Table 1. Drugs identified for Medicare price negotiation in first year of the Inflation Reduction Act, the first approved indication, and Medicare Part D spending and number of beneficiaries from 2017-2021

Brand Name (Generic Name)	Initial Indication	Part D Spending[a] (millions)	Number of Beneficiaries[b]
Enbrel (etanercept)	Rheumatoid arthritis	$9,985	239,511
NovoLog[c] (insulin aspart)	Diabetes mellitus (Type 1, 2)	$11,965	4,292,206
Januvia (sitagliptin)	Diabetes mellitus (Type 2)	$17,066	4,619,191
Stelara (ustekinumab)	plaque psoriasis	$4,306	58,569
Xarelto (rivaroxaban)	prophylaxis deep vein thrombosis, pulmonary embolism	$19,442	5,579,404
Eliquis (apixaban)	nonvalvular atrial fibrillation	$36,614	10,724,482
Imbruvica (ibrutinib)	mantle cell lymphoma	$11,459	119,019
Jardiance (empagliflozin)	Diabetes mellitus (Type 2)	$8,187	2,252,196
Farxiga (dapagliflozin)	Diabetes mellitus (Type 2)	$3,085	908,804
Entresto (sacubitril/valsartan)	chronic heart failure	$4,271	1,141,574
TOTAL		$126,381	29,934,956

Part D spending values are inflation-adjusted to 2018. [a] Part D spending includes amounts paid by the Medicare Part D plan sponsors and beneficiaries but not manufacturers' discounts or rebates. [b] Number of beneficiaries = number of Part D beneficiaries utilizing the drug. [c] Includes multiple forms/types of the drug. NovoLog includes Fiasp; Fiasp FlexTouch; Fiasp PenFill; NovoLog; NovoLog FlexPen; NovoLog PenFill. Enbrel includes Enbrel Mini and Enbrel Sureclick.

Source: Center for Medicare & Medicaid Services data (https://data.cms.gov).

Estimating federal funding and investment related to the discovery and development of new drugs

Federal funding for biomedical science plays a central role in pharmaceutical innovation. Studies have demonstrated that federal funding contributes to discovery or development of many new products (Comroe Jr and Dripps 1976, Sampat and Lichtenberg 2011, Stevens, Jensen et al. 2011, Toole 2012, Chakravarthy, Cotter et al. 2016, Nayak, Avorn and Kesselheim 2019, Cleary, Jackson and Ledley 2020, Galkina Cleary, Jackson et al. 2023, Zhou, Jackson and Ledley 2023), product-related patents that provide market exclusivity (Sampat and Lichtenberg 2011, Stevens, Jensen et al. 2011, Li, Azoulay and Sampat 2017, Azoulay, Graff Zivin et al. 2019, Ledley and

Cleary 2023), and the efficiency of product development (Beierlein, McNamee et al. 2017, McNamee and Ledley 2017, McNamee, Walsh and Ledley 2017, Cleary, Jackson and Ledley 2020).

This present work builds on a 2020 INET working paper "Government as the first investor in biopharmaceutical innovation: Evidence from new drug approvals 2010–2019" (Cleary, Jackson and Ledley 2020) and a series of related papers (Cleary, Beierlein et al. 2018, Galkina Cleary, Jackson et al. 2023, Ledley and Cleary 2023, Zhou, Jackson and Ledley 2023). The 2020 study reviewed evidence for the foundational role of government funding for biomedical research in pharmaceutical innovation and identified NIH funding for basic or applied research leading to approval associated with 354/356 drugs approved by the FDA from 2010-2019 (excluding antimicrobials). Inasmuch as the NIH provides more than 80% of the federal support for life science research (Boroush and Guci 2022), estimates of NIH funding represent a reasonable proxy for the "financial support for discovery and development of these drugs" that may be considered by CMS in price negotiations.

The studies by Cleary et al. identified $187 billion in NIH funding leading to drug approval, with 83% of the NIH funding representing basic research on the drug target and 17% representing applied (translational) research on the drug, including development (Cleary, Jackson and Ledley 2020, Galkina Cleary, Jackson et al. 2023). Follow-on studies on a larger dataset demonstrated that 3.3% of the total NIH funding contributed to the phased clinical trials required for FDA approval (Zhou, Jackson and Ledley 2023).

The 2020 working paper also used an analytical model for the maturation of basic research (McNamee, Walsh and Ledley 2017) to demonstrate that successful product development was associated with a mature foundation of basic research. No drugs in the 2010-2019 dataset were approved before published research on the drug target (basic research) passed an analytically-defined "established point," consistent with observations in previous studies on drugs for cancer (McNamee and Ledley 2017), cardiovascular disease (Beierlein, McNamee et al. 2017), Alzheimer's Disease (Beierlein, McNamee et al. 2017), and classes of pharmaceutical agents (Ledley, McNamee et al. 2014, Beierlein, McNamee and Ledley 2017, Cleary, Jackson et al.

2020).[3] The study also confirmed previous observations that the timeline of phased development was significantly shorter for products that entered clinical trials after the "established point" than for those that entered clinical trials before this point (Beierlein, McNamee et al. 2017, McNamee, Walsh and Ledley 2017, Cleary, Jackson and Ledley 2020). These studies illustrate that a mature body of basic research is requisite for successful product development. Evidence shows that more than half of this critical basic research is performed at academic institutions in the US with the largest fraction of funding coming from the federal government, principally through the NIH (Trapani 2021).

Many studies of the NIH contribution to pharmaceutical innovation consider the total NIH budget allocations (Lazonick and Tulum 2011, Moses, Matheson et al. 2015, Sekar 2020) or categories of funding included in the Research, Condition, and Disease Categories (RCDC) and Research Portfolio Online Reporting Tools (RePORT) (Sampat, Buterbaugh and Perl 2013, Torrey, Knable et al. 2020, Ballreich, Gross et al. 2021). These methods are not applicable to estimating the NIH funding related to specific pharmaceutical products.

Other studies identify the NIH funding for applied research related to patents, prior art, or clinical trials associated with specific products (Sampat and Lichtenberg 2011, Azoulay, Graff Zivin et al. 2019, Nayak, Avorn and Kesselheim 2019, Wimmer and Keestra 2022), but may fail to identify funding for the basic science that is requisite for drug approvals. In contrast, the methods used in this work identify NIH funding for both basic and applied science.

Many previous studies of NIH funding are further predicated on a model of scientific and technical progress that identifies progress as a series of salient insights, inventions, or milestones. In contrast, our method posits that progress arises from a comprehensive body of scientific knowledge that includes not only selected advances, but also the studies necessary to replicate, refute, or refine these advances without which clinical investigations are less likely to succeed (Bretz, Maurer and Xi 2019, NAS 2019).

[3] The analytical model for assessing the maturation of basic science is described in McNamee et al. (2017). The "Technology Innovation Maturation Evaluation" (TIME) model fits the accumulation of publications to the log logistic function characteristic of technology maturation in other fields (Christensen 1997) and identifies the "initiation point," or point of maximum acceleration into a period of exponential growth, and "established point," or point of maximum slowing towards a limit (McNamee et al. 2017).

The present analysis of the federal contribution to discovery and development of the drugs selected for Medicare price negotiations uses a modification of the method described by Cleary (Cleary, Beierlein et al. 2018, Cleary, Jackson and Ledley 2020, Galkina Cleary, Jackson et al. 2023) which has been updated for Python code (Zhou, Jackson and Ledley 2023, Zhou and Ledley submitted).[4] Briefly, the method involves identifying publications (PMIDs) in the PubMed database related to the drug or the drug target using the search parameters described in Attachment A. Drug searches included 12 years before first drug approval. Target searches included 12 years before approval of a first-in-class drug against that target. Publications identified in drug searches are designated applied research. Those identified in target searches only are designated basic research. Basic research totals are estimated only through the year of approval of a first-in-class product associated with that target.[5] NIH funding contributing to these publications is then identified via the NIH-funded projects (grants) associated with the PMIDs from the PubMed search. These projects were identified in the NIH Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER) from 1985-2020. The NIH costs are estimated from one year of project funding corresponding to the publication year, eliminating PMIDs with publication dates before the first year of project funding and accounting for lags of 1-4 years after the end year of project funding. Duplicate project years and NIH funding are eliminated for each data point shown.

The NIH investment costs account for the estimated costs of basic research on the target through year of first-in-class drug approval, applied research on the drug through FDA approval, the estimated NIH costs of failed clinical trials[6] and a 3% discount rate reflecting the historical cost of government borrowing (OMB 1992, Advisers 2017).

This estimate of NIH investment costs is theoretically comparable to reported industry investment costs, which typically include the costs of clinical trials, preclinical studies, and clinical failures as well as a 10.5% cost of capital (DiMasi, Grabowski and Hansen 2016,

[4] This method is described in detail in Galkina Cleary et al. (2023) eMethods available online at https://jamanetwork.com/journals/jama-health-forum/fullarticle/2804378 or http://tinyurl.com/ClearyMethod. Python Code (version 3.9.7) is freely available at https://github.com/BentleySciIndustry/NIH-funding-for-first-round-inflation-reduction-act-drugs-approvals.

[5] A first-in-class product is defined as the first New Molecular Entity targeted to a specific biological target. For this study, research on the target is considered mature when it enables development of a first-in-class product. First-in-class products are identified by the FDA (Lanthier et al. 2013) or using the method of Eder et al. (2014).

[6] This analysis uses the phase-specific clinical failure rates reported by Dimasi et al. (2016) and phase-specific NIH costs described by Zhou et al. (2023).

Wouters, McKee and Luyten 2020, Rennane, Baker and Mulcahy 2021).[7] While estimates of industry investment in economic theory typically include the cost of capital (namely the minimum return on investment that a company would expect in making the investment), there is no theoretical justification for considering a cost of capital for public sector investments.[8] Using the 3% discount rate for NIH costs and the 10.5% cost of capital for industry costs, Galkina Cleary et al. (2023) showed that the average NIH investment cost in the first-in-class drugs approved from 2010-2019 was not less than the average industry investment costs for 63 products reported by Wouters et al. (2020).

Galkina Cleary et al. (2023) also estimated the per drug investment cost taking into account spillovers of the basic science that enables development of the first-in-class drug associated with that target to other products that may share that target. It has been estimated that an average of 2.85 products are approved for each biological target (Santos, Ursu et al. 2017, Galkina Cleary, Jackson et al. 2023), enabling the NIH investment cost in basic science to be distributed across multiple products. This lower estimate of the per drug NIH investment recognizes the efficiencies gained by government investments in basic research that is typically made available in the public domain for use in drug discovery or development by multiple pharmaceutical companies.

It should be emphasized that estimating cost savings to industry provided by NIH funding for basic research and spillover effects requires the assumption that NIH-funded basic research is available to multiple companies in the public domain. Academic investigators are expected to disseminate their research through publication or presentation of the results and are increasingly required to post data inputs, methods, and code for public access (NIH 1999, Merrill and Mazza 2006, NRC 2011).[9] Research is also made available to industry through education and workforce

[7] This analysis compares the NIH investment costs for the drugs selected for Medicare price negotiations with industry investment costs reported for 63 drugs by Wouters et al. (2020).

[8] The Office of Management and Budget (OMB) also recommends estimating the cost of federal investments with a 7% discount rate to account for the "opportunity cost" based on the theory that public sector investments can reduce ("crowd out") private investments and, thus, fail to generate the returns that would be expected from such investments (David, Hall and Toole 2000, OMB 2017). This argument is contradicted by evidence that NIH funding for biomedical research significantly stimulates, rather than reduces, private sector investment (Toole 2007). Therefore, this analysis uses only the 3% discount rate in estimating NIH investment costs.

[9] The NIH released its "Final NIH Policy for Data Management and Sharing" – (Notice Number:

training that enables them to bring research knowledge or skills to industry and by faculty who converse, collaborate, or consult with companies (Link, Siegel and Bozeman 2007). While academic institutions may exclusively license inventions made with government funding to companies, only a small fraction of government-funded research results in patents subject to such licenses (Ledley and Cleary 2023).

We recognize that there are limitations to the methods employed here. First, assignment of one fiscal year of funding to each PMID is consistent with the reported average of one PMID/year for NIH grants (Li, Azoulay and Sampat 2017), but the costs may not accurately reflect funding related to any one PMID. This is especially problematic for applied research related to multi-year experiments and trials where several years of federal funding might reflect one year of funding data for this analysis if only one publication exists on these works. Second, the analysis is limited by the sensitivity and specificity of PubMed searches as well as incomplete data and false positive or negative associations in NIH RePORTER (Boyack and Jordan 2011). These limitations of NIH RePORTER may be more pronounced before 2000. Third, RePORTER may not account for federal funding from sources other than the NIH, such as Department of Defense or NSF (Boroush and Guci 2022). Each of these limitations lead mostly to underestimation of federal spending and thus our results should be considered lower bounds for federal spending on discovery and development of the drugs included in this analysis. Fourth, while we include an estimate of the spillover effects resulting from application of NIH-funded basic research placed in the public domain to develop multiple products, there are likely other spillover effects from NIH funding related to establishing laboratory infrastructure, training, and improved technologies that contribute to product development that are not reflected in this analysis. This may lead to underestimations of the impact and efficiency gained through public sector investments on biomedical science and the cost savings to industry.

Estimating total health value and the health benefit to individuals

There is longstanding concern that industry practices fail to balance the value accruing to society and the value accruing to corporations and their shareholders (Leopold, Chambers and Wagner

NOT-OD-21-013 policy) in January 2023 https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html, which states in part "Sharing scientific data accelerates biomedical research discovery, in part, by enabling validation of research results, providing accessibility to high-value datasets, and promoting data reuse for future research studies.[1] As a steward of the nation's investment in biomedical research, NIH has long championed policies that make research available to the public to achieve these goals."

2016, Mazzucato 2016, Mattingly, Seo et al. 2021, GAO 2022, Angelis, Polyakov et al. 2023). Public opinion surveys demonstrate that <20% of respondents believe pharmaceutical companies "price their products fairly" and 83% believe that the "profits made by pharmaceutical companies … are a major factor contributing to prescription drug costs" (Montero, Sparks et al. KFF Health Tracking Poll July 2023). This concern contributed to passage of the drug price negotiation provisions of the IRA, recent guidance regarding the march-in provisions of the Bayh-Dole Act and the meaning of "reasonable terms" for products arising from government-funded inventions (NIST 2023), and recent hearings of the Senate Committee on Health, Education, Labor, and Pensions in which the CEOs of major pharmaceutical companies were asked to testify on "Why Does the United States Pay, by Far, the Highest Prices in the World for Prescription Drugs?" It is also embodied in the concept of value-based pricing, which posits that there should be a balance between the health benefit a product provides to patients and the price of that product (Neumann and Cohen 2015, Neumann, Cohen and Ollendorf 2021).

We have developed a model for the value created through pharmaceutical innovation (Chaves da Silva, Conti and Ledley submitted) based on the concept of estimating "total stakeholder value" as the sum of value accruing to different stakeholders (Lingane and Olsen 2004, Mitchell, Van Buren III et al. 2015). This model posits that the total value created through commercialization of a new pharmaceutical product is the "total health value" accruing to those who use the products. A portion of this value is then distributed among different stakeholders from the price paid for the drug and how this revenue is expensed or invested by the pharmaceutical manufacturer (Chaves da Silva, Conti and Ledley submitted), with the "residual health value" representing the value retained by the patient or consumer.[10]

This total health value associated with use of a pharmaceutical product can be estimated using metrics developed for studies of value-based pricing that represent proxies for the amount of health gained by an individual taking a product measured in Quality-Adjusted Life Years (QALYs) (Weinstein, Torrance and McGuire 2009, Neumann, Cohen and Weinstein 2014, ICER 2020, Cohen, Neumann and Ollendorf 2023), the number of people to use the product, and the

[10] This is analogous to the consumer surplus in which a consumer's gain from an exchange is the value of the product to the consumer net of the price paid. The consumer surplus has been used as a measure of the health received by patients across the lifetime of a product relative to the producer surplus or value retained by industry (Philipson and Jena 2006, Camejo, McGrath et al. 2014).

individuals' willingness to pay (WTP), specifically their WTP/QALY. WTP/QALY is the amount a person is willing to spend to obtain a level of health benefit through medication or health services (Martín-Fernández, Polentinos-Castro et al. 2014) and is used as a measure of perceived value of health.

While this model incorporates QALY metrics that are most commonly used for Health Technology Assessment (HTA) or cost-effectiveness studies (Weinstein, Torrance and McGuire 2009, Neumann, Cohen and Weinstein 2014, ICER 2020), there are important differences in how these metrics are applied. First, this analysis considers QALYs gained compared to standard/usual care or untreated controls as a measure of total health value created by a product. Second, while some cost-effectiveness studies report QALYs relative to placebo or no treatment, most cost-effectiveness studies are concerned with the QALYs gained relative to alternative therapies (Neumann, Ganiats et al. 2016).

In this model, the most appropriate measure of the health benefit to those who use the drug is not the "total health value," but rather the "residual health value," net price paid. This is analogous to the use of the consumer surplus as a measure of the social benefits of drugs relative to the producer surplus as a measure of the value retained by industry (Philipson and Jena 2006, Camejo, McGrath et al. 2014)). More importantly, this reflects clinical evidence that high drug prices are associated with economic insecurity, poor adherence to treatment regimens, food insecurity, and poor housing, all of which represent social determinants of health that impact health outcomes and can lower the net benefit of being prescribed expensive products (Blanchard, Madden et al. 2013, Berkowitz, Seligman and Choudhry 2014, Afulani, Herman et al. 2015, Berkowitz, Meigs et al. 2015, Herman, Afulani et al. 2015, Berkowitz, Seligman et al. 2018, Caouette, Boss and Lynn 2020, IQVIA 2020, XCENDA 2020). With respect to Medicare Part D beneficiaries, it has been estimated that from 2006-2011, the proportion of disabled Medicare beneficiaries with cost-related medical nonadherence was 31.6%-35.6% while 17.7%-21.8% reported reducing spending on basic needs (Naci, Soumerai et al. 2014). A 2020 report from IQVIA notes: "the cost exposure of Medicare Part D patients represents a potentially significant cost barrier to adherence" (IQVIA 2020).

We would note that this calculation could result in negative residual health value if the price paid for the drug is greater than the total health value created. In a recent case study of the products

commercialized by Gilead Sciences, for example, we found that US or global sales of Gilead's products for hepatitis C generated considerable positive residual health value, while sales of products for HIV therapy or pre-exposure prophylaxis (PrEP) generated negative residual health value (Chaves da Silva, Conti and Ledley submitted). Although the negative residual health value for HIV drugs was in part due to drug pricing, it was more largely due to the fact that it is necessary to treat a large number of individuals at risk for HIV for each new case averted (number needed to treat, NNT=58.1 (Reyes-Urueña, Campbell et al. 2018)).

The present study describes the total health value created for Medicare Part D beneficiaries prescribed the ten products selected for IRA drug price negotiation. Publications reporting QALYs gained from each drug were identified in The Cost-Effectiveness Analysis (CEA) Registry (www.cearegistry.org, accessed October 2021). The lifetime QALYs provided in this literature were averaged and converted to annual QALYs using the geometric series:

$$\text{Annual QALY} = \text{lifetime QALY} / [(1-(1-r)^{n+1})/(r)]$$

where r=discount rate for future health benefits, and n=number of years (time horizon) for the reported data. Studies lacking information on both the time horizon (or time horizon < 5 years) and the discount rate were excluded due to insufficient data. Pilot projects and HTA reports were excluded. When papers provided populational QALYs and population size data, individual QALYs were manually converted. QALYs gained from each drug was compared with the standard of care or untreated group. For example, QALYs gained from Eliquis were estimated as the sum of lifetime QALYs gained from using Eliquis vs warfarin and the lifetime QALYs gained from using warfarin vs no treatment. The same approach was applied to Xarelto. For Imbruvica, QALYs gained were the sum of lifetime QALYs gained from using Imbruvica vs standard/usual care (obinutuzumab in combination with chlorambucil) and lifetime QALYs gained using obinutuzumab vs chlorambucil.

Medicare Part D spending on individual drugs and the number of beneficiaries were identified in the CMS "Medicare Part D Spending by Drug" dataset (https://data.cms.gov, accessed February 2024). The CMS dataset provides annual data on Medicare Part D spending by drug [variable: Tot_Spndng_"year"] defined[11] as "aggregate drug spending for the Medicare Part D program

[11] Medicare Part D Spending by Drug Data Dictionary (last updated December 13, 2023) https://data.cms.gov/resources/medicare-part-d-spending-by-drug-data-dictionary

during the benefit year." "Drug spending metrics for Part D drugs are based on the gross drug cost, which represents total spending for the prescription claim, including Medicare, plan, and beneficiary payments. The Part D spending metrics do not reflect any manufacturers' rebates or other price concessions." The number of beneficiaries is defined as the number of Part D beneficiaries utilizing the drug during the benefit year.

The total health value in QALYs created by drug "d" in year "y" is calculated as:

$$\text{Health value}_{d,y} = \text{QALYs gained}_{d} * \text{Number individuals benefited}_{d,y}$$

The total health value created by each drug in USD is calculated as:

$$\text{Health value}_{d,y} = \text{QALYs gained}_{d} * \text{Number individuals benefited}_{d,y} * \text{WTP/QALY}$$

using a US-specific WTP threshold of $104,000/QALY (Vanness, Lomas and Ahn 2021).

Residual Health Value is calculated as:

$$\text{Residual Health Value}_{d,y} = \text{Total Health Value}_{d,y} - \text{Medicare Part D spending}_{d,y}$$

The analysis was performed for the years 2017-2021, the most recent year for which Medicare Part D data is currently available. All values are inflation-adjusted to 2018.

Again, we recognize that there are limitations to this approach. First, QALY metrics have been criticized (Neumann and Weinstein 2010) for inconsistent methodologies and biases related to disease severity, chronicity, and age (Rand and Kesselheim 2021), and the present results are subject to the same limitations. It is also recognized that WTP measures vary based on demographic characteristics, economic factors, severity of disease, and methods of ascertainment considerations (Steigenberger, Flatscher-Thoeni et al. 2022). Second, this analysis estimates QALYs from use of a drug as the average published values across varied indications and populations and may not be applicable to any indication or individual. Moreover, the populations studied may not be representative of Medicare Part D beneficiaries who are more likely to be >65 years old or designated with a disability. Third, studies assessing QALYs gained from a drug compared to placebo or no therapy are not available for all drugs in this study. Inference of QALY values from different combinations of therapies introduces potential error in the QALY estimates. Fourth, measures of WTP/QALY are influenced by study design and population demographics (Martín-Fernández, Polentinos-Castro et al. 2014, McDougall, Furnback et al. 2020, Iino, Hashiguchi and Hori 2022). Fifth, Medicare Part D spending includes amounts paid

by the Medicare Part D plan sponsors and beneficiaries but not manufacturers' discounts or rebates. As discussed below, this may increase the Medicare Part D costs and underestimate the residual health value.

3. RESULTS AND DISCUSSION

NIH funding for basic and applied research prior to approval

This analysis identified NIH-funded basic or applied research prior to first approval for each of the ten drugs selected for Medicare price negotiation under the IRA. The ten drugs are listed in Table 2 along with their biological targets.

Table 2. Drugs selected for Medicare price negotiations and their biological targets

Brand Name (Generic Name)	Targets
Enbrel (etanercept)	tumor necrosis factor alpha
NovoLog (insulin aspart)	Insulin receptors
Januvia (sitagliptin)	dipeptidyl peptidase 4
Stelara (ustekinumab)	Interleukin 12 and Interleukin 23
Xarelto (rivaroxaban)	factor Xa
Eliquis (apixaban)	factor Xa
Imbruvica (ibrutinib)	Bruton's tyrosine kinase
Jardiance (empagliflozin)	Sodium-glucose cotransporter-2
Farxiga (dapagliflozin)	Sodium-glucose cotransporter-2
Entresto (sacubitril[a]/valsartan)	neprilysin

[a] Sacubitril is the New Molecular Entity in this combination product. NIH costs for basic research were determined for neprilysin, the target for sacubitril.

Table 3 shows the number of NIH-funded PMIDs, NIH project years (fiscal years) of funding, and the total NIH funding for basic or applied research related to each of these drugs. No data on basic science research related to insulin aspart was available. Insulin aspart is considered a follow-on product to recombinant insulin approved in 1982 and no NIH funding data was available before 1985. Two pairs of products have the same target: Xarelto and Eliquis both target clotting factor Xa, and Jardiance and Farxiga both target sodium-glucose co-transporter-2 (SGLT2).

Table 3. NIH-funded PMIDs, project years of NIH funding, and NIH funding for basic or applied research prior to first approval of drugs selected for price negotiation in year one of the IRA

Brand Name (Generic name)	Approval Year	NIH-funded PMIDs[a]		Project Years		NIH Funding (millions)[b]	
		Basic	Applied	Basic	Applied	Basic	Applied
Enbrel (etanercept)	1998	2,312	1	3,077	1	$2,604.0	$2.3
NovoLog (insulin aspart)	2000	N/A[c]	1	N/A[c]	1	N/A[c]	$4.5
Januvia (sitagliptin)	2006	154	1	213	1	$227.3	$0.2
Stelara (ustekinumab)	2009	3,683	1	5,281	1	$6,467.1	$15.0
Xarelto (rivaroxaban)	2011[d]	575	16	701	16	$745.0[f]	$18.6
Eliquis (apixaban)	2012[d]	577	9	701	15		$45.6
Imbruvica (ibrutinib)	2013	195	53	369	61	$432.5	$133.5
Jardiance (empagliflozin)	2014[e]	256	6	403	16	$423.3[f]	$11.0
Farxiga (dapagliflozin)	2014[e]	252	8	403	18		$14.1
Entresto (sacubitril[g]/valsartan)	2015	383	3	689	6	$894.3	$6.8

PMIDs, project years, and NIH funding are shown after eliminating duplicate values. NIH funding is inflation-adjusted to 2018. Rows are not additive, as PMIDs or NIH funding may contribute to more than one product. [a] Publications were identified in PubMed searching for drug targets (basic research) or drugs (applied research) from 1985 through one year after drug approval (first-in-class if available). PMIDs identified in both target and drug searches are classified as applied research. This designation may change on project years for any drugs with the same biological target for the funding analysis. [b] Applied research costs calculated for 12 years before drug approval. Basic research costs calculated for 12 years before approval of first-in-class product associated with target. [c] Not available. First-in-class recombinant insulin was approved in 1982. No data on NIH program funding is available before this date. [d] Basic research and costs estimated for first-in-class drug Xarelto approved 2011. [e] Basic research and costs estimated prior to approval of first-in-class drug Invokana (canagliflozin) in 2013. [f] Basic science funding for drugs with a common biological target is shown only once. PMIDs are classified as applied research if identified with either product. [g] Sacubitril is the New Molecular Entity in this combination product. Neprilysin is the drug target.

NIH funding for basic research ranged from $227.3 to $6,467.1 million/drug, with the highest level of basic research funding associated with the p40 target for Stelara. This protein is a shared

subunit of both IL-12 and IL-23 and has a central role in cellular immunity. Understanding p40 was central to decades of research and many failed clinical trials aimed at developing products related to IL-12. Basic research on the TNF receptor target for Enbrel includes research in oncology, sepsis, and immune disorders, reflecting the complicated development history of TNF-related products in the 1990s. NIH funding for applied research ranged from $0.2 million for Januvia to $133.5 million for Imbruvica.

The total PMIDs, NIH-funded PMIDs, project years, and NIH funding contributing to approval of the ten drugs (without basic science data related to insulin aspart) is shown in Table 4. This body of research comprised 7,603 NIH-funded PMIDs and was supported by 10,667 project years of NIH funding totaling $11.7 billion. Overall, more than 95% of the identified funding was related to basic, rather than applied, research or development, and none of the patents cited in DrugPatentWatch as protecting market exclusivity arose from this funding.[12]

Table 4. Identification of total NIH funding associated with ten drugs selected for price negotiation in year one of the Inflation Reduction Act

Stage of Analysis	Basic Research[a]	Applied Research[b]	Total
PMIDs (all)	46,931	2,649	49,580
NIH-funded PMIDs (all)	9,815	155	9,970
NIH-funded PMIDs (12 years)[c]	7,510	93	7,603
Project Years	10,553	114	10,667
NIH Funding (millions)	$11,439	$263	$11,702[d]

PMIDs were identified by searching PubMed for the ten drugs selected for price negotiation or their biological targets. Duplicate data arising from identification of a PMID or project year in more than one search was eliminated. [a] PMIDs are classified as basic research if they are identified in a target search but not any drug search. Total does not include basic research related to insulin aspart. [b] PMIDs are classified as applied research if they are identified in one or more drug searches. [c] PMIDs 12 years before drug approval for applied research and 12 years before approval of first-in-class product associated with target for basic research. [d] Combined cost of basic and applied research. NIH funding is inflation-adjusted to 2018.

Investment costs

Table 5 shows total NIH funding for basic and applied research related to each drug as well as NIH investments costs also including NIH spending on clinical failures and a 3% discount rate to

[12] DrugPatentWatch™ includes patents listed in Orange Book and Purple Book, or cited in litigation. www.drugpatentwatch.com.

account for government borrowing costs as recommended by the OMB (OMB 1992, Advisers 2017). Total NIH funding without any adjustments ranged from $277.5 million for Januvia to $6,482.1 million for Stelara (median = $763.6 million). With adjustments, NIH investments ranged from $317.5 million for Januvia to $6,951.5 million for Stelara (median = $895.4 million).

Table 5. Estimated federal (NIH) investment costs leading to first approval of drugs selected for price negotiation in year one of the IRA, estimated cost savings to industry, and estimated NIH costs with spillovers of basic science to multiple drug approvals

Brand Name (Generic Name)	Total NIH Funding[a]	NIH Investment Cost (3%)[b]	Cost Savings to Industry (10.5%)[c]	NIH Investment Cost with Spillovers (3%)[d]
Enbrel (etanercept)	$2,606.3	$2,799.5	$4,176.2	$1,036.2
NovoLog (insulin aspart)[e]	N/A	N/A	N/A	N/A
Januvia (sitagliptin)	$227.5	$317.5	$455.8	$163.8
Stelara (ustekinumab)	$6,482.1	$6,951.5	$10,815.4	$2,501.8
Xarelto (rivaroxaban)	$763.6	$895.4	$1,485.8	$379.0
Eliquis (apixaban)	$790.6	$910.9	$1,494.1	$404.8
Imbruvica (ibrutinib)	$566.0	$683.8	$1,001.7	$382.5
Jardiance (empagliflozin)	$434.2	$539.6	$821.3	$249.0
Farxiga (dapagliflozin)	$437.3	$547.9	$832.0	$257.3
Entresto (sacubitril[f]/valsartan)	$901.1	$1,078.6	$1,763.8	$435.4

All values are in millions and inflation-adjusted to 2018. Rows are not additive as NIH funding may contribute to more than one drug. [a] NIH funding for basic research and applied research without adjustments. [b] 3% discount rate recommended for government spending reflects the costs of federal borrowing. [c] 10.5% discount is equivalent to the 10.5% cost of capital commonly used in estimating industry investment costs. NIH investment calculated with 10.5% discount represents the per drug cost savings to industry from NIH funding for basic and applied research. [d] Spillovers represent past observations on publicly funded basic research going towards the development of an average of 2.85 drugs per biological target. [e] The first-in-class recombinant insulin was approved in 1982. No data on NIH program funding is available before this date. [f] Sacubitril is the New Molecular Entity in this combination product. Neprilysin is the drug target.

The cost savings to industry provided by NIH funding was estimated with a 10.5% discount rate for NIH funding, corresponding to the cost of capital most commonly used in reporting industry investments in product development. The premise of this calculation is that, in the absence of NIH funding for research, industry would need to perform the same work to generate an established foundation of basic science and would estimate the cost of this additional investment using the typical 10.5% cost of capital. For the ten drugs selected for price negotiation, the cost

savings to industry provided by NIH funding ranged from $455.8 million for Januvia to $10.8 billion for Stelara (median = $1.5 billion) (Table 5).

We also estimated the NIH investment costs taking into account the spillover of basic research on a drug target to the approval of an average of 2.85 different products. Considering spillovers, the median per drug investment by the NIH was $380.7 million and ranged from $249 million for drugs targeted to the SGLT2 (i.e., Jardiance) to $2.5 billion for drugs targeted to the p40 subunit shared by IL-12 and IL-23 (i.e., Stelara) (Table 5).

Table 6 shows that the distribution of NIH investment costs for the ten drugs selected for price negotiation estimated with clinical failures and either the 3% or 10.5% was comparable to previously reported data describing all drugs approved 2010-2019 (Galkina Cleary, Jackson et al. 2023) (p=0.65, p=0.67). These data further show that the distribution of NIH investment costs for the ten drugs selected for Medicare price negotiation estimated with clinical failures and the 10.5% discount was not significantly different than that of reported industry investment costs for 63 drugs approved 2009-2018 estimated with the cost of clinical failures, correction for prehuman studies, and the 10.5% cost of capital described by Wouters et al. (p=0.34). The distribution of NIH investment costs estimated with a 3% discount rate was marginally lower than reported industry investment costs and (p=0.04), and NIH investment costs estimated with a 3% discount and spillovers was significantly lower than reported industry costs (p=0.01).

Table 6. Mann-Whitney comparison of NIH investment costs for drugs selected for price negotiation, NIH investment costs for first-in class-drugs approved 2010-2019, and reported industry investment in 63 drugs approved 2009-2018

Comparison	NIH		Comparator		*p*
	Median	(IQR)	Median	(IQR)	
NIH-IRA 3% vs NIH 2010-2019 3%	$895.40	(547.9, 1,078.6)	$1,097.10	(541.5, 2,653.9)	0.65
NIH-IRA 10.5% vs NIH 2010-2019 10.5%	$1,485.80	(832, 1,763.8)	$1,814.00	(797.7, 4,100.9)	0.67
NIH-IRA 3% vs Industry 10.5%	$789.60	(545.8, 1,383)	$1,787.20	(1109.1, 3,364.4)	0.04
NIH-IRA 3%+spillover vs Industry 10.5%	$380.70	(255.2, 562.7)	$1,787.20	(1109.1, 3,364.4)	0.01
NIH-IRA 10.5% vs Industry 10.5%	$1,243.80	(824.5, 2,161.5)	$1,787.20	(1109.1, 3,364.4)	0.34

All costs are in millions and inflation-adjusted to 2018. NIH-IRA refers to the NIH investment cost for the ten drugs selected for price negotiation in year one of the IRA estimated with the cost of clinical failures and either a 3% or 10.5% discount, or 3% discount including spillovers. NIH 2010-2019 refers to the NIH investment cost for first-in-class drugs approved 2010-2019 described in Cleary et al. (2020, 2023), estimated with the cost of clinical failures and either a 3% or 10.5% discount. Industry refers to the reported industry investment costs for the 63 drugs approved 2009-2018 for which data is reported in annual (10-K) filings as described by Wouters et al. (2020) with the cost of clinical failures and correction for prehuman studies based on data from DiMasi et al. (2016) and a 10.5% cost of capital. Two-tailed Mann-Whitney U tests were performed with NIH-IRA, n=9; NIH 2010-2019, n=81, and Industry, n=63.

These data demonstrate that the NIH made substantive investments in basic or applied research underlying each of the ten drugs selected for price negotiation in the first year of the IRA. As noted previously, since NIH funding represents >80% of all federal support for life science research (Boroush and Guci 2022), these estimates of NIH funding represent a reasonable measure of "…Prior Federal financial support for novel therapeutic discovery and development with respect to the drug" and "federal financial support for discovery and development of these drugs" and should be considered by CMS in the ongoing price negotiations.

Health value created for Medicare Part D beneficiaries from products subject to price negotiation

Table 1 shows Medicare Part D spending on the ten drugs selected for Medicare price negotiation and the number of beneficiaries from 2017-2021. Table 7 shows the web-posted prices for each of these drugs. Neither Medicare Part D spending nor the list price includes

rebates and the list prices do not account for discounts or other incentive or assistance programs that may be available.

Table 7. Web-posted prices for ten drugs selected for Medicare price negotiation

Brand Name (Generic Name)	List Price[a]	Unit	Monthly Cost	Average Spending per Beneficiary (2021)[b]
Enbrel (etanercept)[c]	$1,850.5	weekly	$7,402	$42,112
NovoLog (insulin aspart)[d]	$156.6	5 doses	$31.32	$2,971
Januvia (sitagliptin)	$631.0	30 day	$631.0	$3,731
Stelara (ustekinumab)[e]	$25,497.1	every 8 weeks	$12,749	$83,320
Xarelto (rivaroxaban)	$542.0	30 day	$542.0	$3,567
Eliquis (apixaban)	$594.0	30 day	$594.0	$3,456
Imbruvica (ibrutinib)	$16,734.0	28 tablets	$16,734.0	$103,875
Jardiance (empagliflozin)	$570.5	30 day	$570.5	$3,627
Farxiga (dapagliflozin)	$582.3	30 day	$582.2	$3,165
Entresto (sacubitril[f]/valsartan)	$544.8	30 day	$544.8	$3,747

[a] List prices do not include rebates or discounts. Accessed February 20, 2024, without inflation adjustments. [b] Average spending per beneficiary=Total Part D drug spending divided by the number of unique beneficiaries utilizing the drug during the benefit year. Part D spending is inflation-adjusted to 2018 and does not include manufacturers' discounts or rebates. [c] Estimated for four weeks/month. [d] List price for 15 ml (5 x 3 ml). Estimated as one FlexPen (3ml) per month. Average Part D spending refers to Novolog Flexpen.; [e] Estimated as 50% of 8-week price. [f] Sacubitril is the New Molecular Entity in this combination product. Neprilysin is the drug target.

Sources for list prices: https://www.eliquis.bmscustomerconnect.com/afib/price, https://patient.boehringer-ingelheim.com/us/products/jardiance/type-2-diabetes/pricing, https://www.xarelto-us.com/cost, https://www.drugs.com/price-guide/januvia, https://www.farxiga.com/savings-support, https://www.drugs.com/medical-answers/entresto-cost-month-3544065/, https://www.enbrel.com/enbrel-cost, https://www.drugs.com/medical-answers/imbruvica-cost-3539120/, https://www.stelarainfo.com/crohns-disease/cost-support-and-more, https://www.drugs.com/price-guide/novolog-flexpen.

Table 8 shows the QALYs/year per beneficiary for eight of the ten drugs and the total health value created through Medicare Part D coverage of these drugs expressed in both QALYs and USD.

Table 8. Health value created 2017-2021 for Medicare Part D beneficiaries through utilization of products subject to price negotiation in the first year of the IRA

Brand Name (Generic name)	QALYs/year per Beneficiary	Total Health Value		Residual Health Value[b]
		QALYs	$[a]	
Enbrel (etanercept)	0.08	19,161	$1,993	-$7,993
NovoLog (insulin aspart)[c]	N/A	N/A	N/A	N/A
Januvia (sitagliptin)[c]	N/A	N/A	N/A	N/A
Stelara (ustekinumab)	0.14	8,200	$853	-$3,453
Xarelto (rivaroxaban)	0.03	167,382	$17,408	-$2,034
Eliquis (apixaban)	0.02	214,490	$22,307	-$14,307
Imbruvica (ibrutinib)	0.13	15,472	$1,609	-$9,850
Jardiance (empagliflozin)	0.06	135,132	$14,054	$5,867
Farxiga (dapagliflozin)	0.05	45,440	$4,726	$1,640
Entresto (sacubitril[d]/valsartan)	0.04	45,663	$4,749	$478
TOTAL	0.55	650,940	$67,698	-$29,652

Dollar values are in millions and inflation-adjusted to 2018. [a] Calculated with WTP/QALY of $104K. [b] Total health value minus Medicare part D spending including amounts paid by the Medicare Part D plan sponsors and beneficiaries but not manufacturers' discounts or rebates. [c] NovoLog and Januvia are not included in this analysis as the reports studying these drugs did not meet our inclusion criteria for estimating the value generated by these products individually. [d] Sacubitril is the New Molecular Entity in this combination product. Neprilysin is the drug target.

Considering these drugs individually,

- Jardiance and Farxiga are both inhibitors of SGLT2 channels with indications for diabetes and heart failure. These drugs exhibit similar effectiveness. In direct comparison, the differential effectiveness was 0.014 QALYs/year (Reifsnider, Kansal et al. 2021). In our review, these drugs generated 0.06 and 0.05 QALYs/year, respectively. Overall Medicare Part D spending on Jardiance was greater than spending on Farxiga, generating a total health value of 135,132 QALYs versus 45,440 QALYs or $14.1 billion versus $4.7 billion, and a positive residual health value of $5.9 billion versus $1.6 billion.

- Eliquis and Xarelto are both factor Xa inhibitors indicated for prevention and treatment of blood clots in atrial fibrillation and for treatment of deep vein thrombosis. These drugs generated 0.02 and 0.03 QALYs/year, respectively. In direct comparison of these two drugs, the differential effectiveness was 0.010 QALYs/year (Harrington, Armstrong et al. 2013). In the 2023 ICER (Institute for Clinical and Economic Review) Special Assessment to inform CMS Drug price negotiation, each drug was compared to warfarin. Both Eliquis and Xarelto were "rated as demonstrating high certainty of a small net benefit when compared to warfarin" (Tice, Richardson et al. 2023). Medicare Part D spending on Eliquis was 1.9 times higher than spending on Xarelto, generating a greater health value of 214,490 QALYs versus 167,382 QALYs or $22.3 billion versus $17.4 billion. Medicare Part D spending was also higher for Eliquis than Xarelto ($36.6 billion versus $19.4 billion). As a result, both drugs generated a negative residual health value (-$14.3 billion for Eliquis and -$2.0 billion for Xarelto). It should be noted that the QALYs/year for both drugs were based on use of these products for both prevention of stroke and treatment of atrial fibrillation, and that the low QALYs/year are due to the fact that the health benefit accrues only to the small fraction of treated patients who may have had a stroke without treatment in a given year.
- Entresto is indicated for treatment of symptomatic heart failure and provided 0.04 QALYs/year over standard/usual care for heart failure. Medicare Part D spending on Entresto generated a total health value of 45,663 QALYs or $4.7 billion and a positive residual health value of $478 million.
- Imbruvica is indicated for several forms of lymphocytic leukemia as well as a complication or organ transplant (graft versus host disease) and generates an average of 0.13 QALYs/year. Medicare Part D spending on Imbruvica generated a total health value of 15,472 QALYs or $1.6 billion for a relatively small number of beneficiaries compared to other drugs considered in this analysis and had a negative residual health of -$9.8 billion primarily due to a posted list price of $16,734/month, the highest among products chosen for Medicare negotiation. Cost-effectiveness studies suggest that the producer's price for Imbruvica is 2-3 times higher than the value provided by the drug as a first line therapy (Barnes, Divi et al. 2018).
- Stelara and Enbrel are anti-inflammatory drugs indicated for Psoriasis, inflammatory bowel disease and other inflammatory disorders. Stelara generated the greatest QALYs/year (0.14) for those taking the drug among the products chosen for price negotiation but the fewest

beneficiaries, 58,569. Medicare Part D spending on the drug generated a total health value of 8,200 QALYs or $853 million but a negative residual health value of -$3.5 billion. Enbrel had four times more beneficiaries (239,511), generated fewer QALYs/year (0.08), and created a total health value of 19,161 QALYs or $2.0 billion with a negative residual health value of -$8.0 billion.

- Januvia and Novolog are not included in this analysis. These drugs are typically used in combination, and the health benefit they provide has been studied in different combinations and in comparison to various other products. However, none of these reports met our inclusion criteria for estimating the value generated by these products alone.

Excluding Januvia and NovoLog, total Medicare Part D spending was $97.3 billion and the total health value created by these sales is estimated to have been $67.7 billion from 2017-2021. This results in a negative residual health value (i.e., net Medicare Part D spending) of -$29.7 billion. This estimate of the residual health value includes the amounts paid by the Medicare Part D plan sponsors and beneficiaries but does not take into account manufacturer's discounts or rebates. As such, these values likely overestimate Medicare Part D spending on these products and underestimate the residual health value accruing to beneficiaries.

There is no publicly available data concerning rebates for the products in this analysis and it is notoriously difficult to ascertain the rebates on Medicare Part D spending (Anderson-Cook, Maeda and Nelson 2019, Feldman, Rome et al. 2021, Dicken 2023). Attachment B details different estimates of Medicare Part D rebates from 2017-2021 based on published analyses and the residual health value created in each scenario. Considering an annual rebate of 17.5% (CMS 2014), there would be a negative residual health value of -$12.6 billion. Considering the average rebate increasing from 17.5% in 2014 to 25% in 2021, there would be a negative residual health value of -$6.9 billion. Considering the average rebate increasing from 25.6% in 2017 to 34.1% in 2021 (Feldman, Rome et al. 2021), there would be a positive residual health value of $400 million. Considering average rebates increasing from 34.6% in 2017 to 45% in 2021 (Feldman, Rome et al. 2021), there would be a positive health value of $10.4 billion. More data is required on the rebates associated with these products to resolve these different estimates of the residual health value.

These data also represent a snapshot of the value created over a particular five-year period (2017-2021) that may not be representative of the full product life cycle. In 2017, the first year of the study period, the ten drugs in this study had been on the market for a median of 6 years (average 7.8) years, were entering the peak sale years of the product life cycle (Grabowski and Vernon 2000), and did not yet have generic or biosimilar competition. Moreover, from the year of approval through 2021, these products increased in price by an average of 263% (median 176%/drug; range 78% to 701%) with an average annual price increase of 18%/year (median 15%/year; range 13%/year to 30%/year) or an average 15%/year higher than the rate of inflation (median 12%/year; range 9/year % to 29%/year).[13] Assessment of the residual health value in the first five years after approval or after emergence of generic or biosimilar products would result in a lower price relative to the total health value and greater residual health value. A complete assessment of the health value generated by a product relative to its costs requires an assessment of drug sales and prices across the product life cycle (Garrison Jr 2010, Garrison Jr, Mansley et al. 2010, Hoyle 2011, Schöttler, Coerts et al. 2023).

4. CONCLUSIONS

This empirical study describes the cost basis for assessing federal support for the discovery and development of the ten drugs selected for price negotiation in the first year of the IRA and a foundation for assessing the public's return on investment in this support. We argue that the "maximum fair price" for a drug must not only be equitable to those with unmet medical needs who may benefit from use of the drug, but also provide equitable returns on both public and private sector investments. This perspective builds on studies that contextualize federal support for the basic and applied research underlying technological innovation as an early investment in that innovation (Mazzucato 2013). As such, federal support for biomedical research should provide a return on investment to the public sector commensurate with the scale and risk of these investments (Lazonick and Mazzucato 2013, Mazzucato 2013, Mazzucato 2015, Cleary, Jackson and Ledley 2020, Laplane and Mazzucato 2020).

[13] Data from: "Here are 25 Medicare Part D drugs that have skyrocketed in price," By Noah Tong. Aug 10, 2023 https://www.fiercehealthcare.com/payers/here-are-25-medicare-part-d-drugs-have-skyrocketed-price. Original data source: AARP Public Policy Institute analysis of data from the Centers for Medicare & Medicaid Services' Medicare Part D Spending by Drug Dashboard and Medi-Span Price Rx Pro. No data available for Farxiga.

It is significant that the IRA explicitly lists "Prior Federal financial support for novel therapeutic discovery and development with respect to the drug" among the factors that CMS can consider in price negotiations alongside "Research and development costs of the manufacturer for the drug and the extent to which the manufacturer has recouped research and development costs."[4] This implicitly recognizes the role of both public and private investments in enabling commercialization of these products alongside factors related to the costs of commercializing the product, market competition, and the value the product provides to those with unmet medical needs.

In considering the cost of discovering and developing a product alongside market dynamics, the IRA resembles other federal policies regarding "fair" or "reasonable" pricing in different contexts, which typically consider price in the context of both consumer interests and investment. For example, legal precedent for the concept of determining a "reasonable price" holds that this "…involves balancing of the investor and consumer interests…" and should allow companies to achieve returns "…commensurate with returns on investments in other enterprises having corresponding risks…"[14] Additionally, government procurement requires that contracting officers determine a "fair and reasonable" price, recognizing that this may involve consideration of competition, market factors, manufacture or acquisition costs, profit, and cost of money among other factors.[15]

The IRA explicitly authorizes CMS to consider manufacturer data on their costs for research and development of these drugs as was well as federal spending on discovery and development.

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[14] "…involves a balancing of the investor and consumer interests," which does not, however, 'ensure that the business shall produce net revenues.' ... From the investor or company point of view it is important that there be enough revenue not only for operating expenses but also for the capital costs of the business. These include service on the debt and dividends on the stock... By that standard the return to the equity owner should be commensurate with returns on investments in other enterprises having corresponding risks." Quoted in Congressional research Service op cit and referencing: FPC v. Hope Natural Gas Co., 320 U.S. 591, 603 (1944) (citing Chicago & Grand Trunk Ry. v. Wellman, 143 U.S. 339, 345–46 (1892); and Missouri ex rel. Southwestern Bell Tel. Co. v. Public Serv. Comm'n, 262 U.S. 276, 291 (1923).

[15] For example, Title 48—Federal Acquisition Regulations System CHAPTER 1—FEDERAL ACQUISITION REGULATION SUBCHAPTER C—CONTRACTING METHODS AND CONTRACT TYPES PART 15—CONTRACTING BY NEGOTIATION Subpart 15.4—Contract Pricing 15.404-1 Proposal analysis techniques. "(a) General. The objective of proposal analysis is to ensure that the final agreed-to price is fair and reasonable."; "4) "Cost analysis may also be used to evaluate data other than certified cost or pricing data to determine cost reasonableness or cost realism when a fair and reasonable price cannot be determined through price analysis alone."; " (c) Cost analysis is the review and evaluation of any separate cost elements and profit or fee in an offeror's or contractor's proposal, as needed to determine a fair and reasonable price or to determine cost realism, and the application of judgment to determine how well the proposed costs represent what the cost of the contract should be, assuming reasonable economy and efficiency." https://www.law.cornell.edu/cfr/text/48/15.404-1

While the Act does not explicitly describe how this information will factor into determining a "maximum fair price," considerations of investment, risk, and return are central to the concept of identifying a "fair" price that can be agreed by both buyers and sellers. In this context, the "maximum fair price" of a drug cannot be solely determined relative to the value provided by a pharmaceutical product (i.e., cost-effective), but should also consider the investments made by both pharmaceutical manufacturers and government and the expected returns based on the scale of these investments and the risk.

For private investments, the expected returns involve traditional financial or accounting metrics of economic value. For government investments, the expected returns involve social value. Social value has been defined as the "…benefits or reductions of costs for society … that go beyond the private gains and general benefits of market activity" (Phills, Deiglmeier and Miller 2008) or the value accruing to "…non-investor stakeholders affected by business: individuals, employees, communities, and society" (Lingane and Olsen 2004). In a preliminary case study of the social value created through pharmaceutical innovation, we found that the health benefit (i.e., the estimated residual health value net of price paid) that new products provide for those with unmet medical needs represents the largest proportion of social value (Chaves da Silva, submitted).[16]

The present data describing NIH funding leading to approval of the drugs selected for Medicare price negotiation and the residual health value created by Medicare Part D spending on these drugs may inform the forthcoming price negotiations. These data suggest that the magnitude of the federal investment in these drugs is comparable to publicly available data on industry investments in recent drug approvals and suggest that there may be a narrow margin between the total health value created by these drugs and the price paid through Medicare Part D. The data provided to CMS as part of the negotiating process should allow CMS to make direct comparisons between the NIH funding data described here and the costs incurred by companies in developing these drugs and should also allow a more rigorous assessment of the residual

[16] The concept that pharmaceutical innovation generates multiple forms of value is embodied in the ISPOR "value flower" (Lakdawalla et al. 2018, Neumann et al. 2022). In our model, social value included in our model were job creation, scientific advances, and payments to public sector institutions. (Chaves da Silva et al. submitted)

health value created taking into account more precise data on the price paid along with rebates, discounts, or other post sale adjustments.

The narrow margin between the health benefit provided by these drugs and the price paid is predictable given increasing focus on value-based pricing. The principle that a drug's price should be comparable to the total health value received (Shafrin, Lakdawalla et al. 2023, Tremblay, Poirier and Monfort 2024) does not provide a margin for social return on federal investments in these products. This approach could allow manufacturers to realize most of the return from product sales (Basu, Veenstra et al. 2023). Instead, we argue for the principle that there should be a balance between the risk and return of public and private investments (Lazonick and Mazzucato 2013, Laplane and Mazzucato 2020) and consideration of a maximum fair price in which the residual (net) health value to the public is comparable to the private returns to industry.

APPENDIX

Attachment A.

Search parameters for identifying NIH funding for research related to drugs selected for Medicare price negotiation				
Brand Name (Generic Name)	**PubMed Search Input**	**Approval Year**	**Search End Year[a]**	**First-in-class Drug[b]**
Januvia (sitagliptin)	("dipeptidyl peptidase 4"[MeSH Terms] OR "dipeptidyl peptidase 4"[All Fields])	2006	2007	FIC
Stelara (ustekinumab)	(("interleukin 12"[MeSH Terms] OR "interleukin 12"[All Fields] OR "il 12"[All Fields] OR ("interleukin 23"[MeSH Terms] OR "interleukin 23"[All Fields] OR "il 23"[All Fields])))	2009	2010	FIC
Eliquis (apixaban)	factor Xa	2011	2012	Xarelto (factor Xa inhibitor, 2011)
Xarelto (rivaroxaban)	factor Xa	2011	2012	FIC
Entresto (sacubitril/ valsartan)	Neutral Endopeptidase	2015	2016	FIC
Imbruvica (ibrutinib)	bruton's tyrosine kinase	2013	2014	FIC
Enbrel (etanercept)	(("tumour necrosis factor alpha"[All Fields] OR "tumor necrosis factor alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields])) AND "immunology"[MeSH Subheading]	1998	1999	FIC
NovoLog (insulin aspart[c)]	N/A	N/A	N/A	N/A
Farxiga (dapagliflozin)	sodium glucose transporter	2013	2014	Invokana (SGLT2 inhibitor, 2013)
Jardiance (empagliflozin)	sodium glucose transporter	2013	2014	Invokana (SGLT2 inhibitor, 2013)

[a] PubMed search was performed from 1980 to search end year. [b] FIC, named drug is first-in-class approved drug based on research describing the biological target (first-to-target) against the same biological target. [c] No target search was performed for insulin aspart, which is considered a follow-on product for recombinant insulin (Humulin) approved in 1982. No data on NIH funding is available prior to 1985.

Attachment B.

Net Medicare Part D spending with rebates estimated from published sources						
	Total Medicare Part D spending (billions)	Applied Rebate				
		None	2014 Part D Rebate Summary	CMS-GAO (extrapolated)	Feldman all drugs (extrapolated)	Feldman Brand drug (extrapolated)
2017	$10.2	-	17.5%	20.7%	25.6%	34%
2018	$14.2	-	17.5%	21.8%	28.9%	37%
2019	$19.1	-	17.5%	22.9%	29.3%	40%
2020	$24.4	-	17.5%	23.9%	31.7%	42%
2021	$29.4	-	17.5%	25.0%	34.1%	45%
Net Medicare Part D spending (billions)	$97.3	$97.3	$80.3	$74.6	$67.3	$57.3
Total Health Value (billions)	$67.7	$67.7	$67.7	$67.7	$67.7	$67.7
Residual Health Value (billions)	-$29.7	-$29.7	-$12.6	-$6.9	$0.4	$10.4

Totals inflation-adjusted to 2018. See text below for explanation.

There is no publicly available data concerning rebates for the products in this analysis and it is notoriously difficult to ascertain the rebates on Medicare Part D spending (Anderson-Cook, Maeda and Nelson 2019, Feldman, Rome et al. 2021, Dicken 2023). According to the 2014 Manufacturer Rebate Summary Report, the most recent data publicly available from CMS[17] is that the average rebate on brand name drugs was 17.5%. Assuming a constant 17.5% rebate from 2017-2021, net Medicare Part D spending on the eight drugs included in Table 8 (excluding NovoLog and Januvia) would be $80.3 billion.

There is, however, evidence that rebates have increased progressively in recent years (Feldman, Rome et al. 2021). A 2023 GAO study, based on CMS data, suggests that the average rebate in 2021 was 25% (Dicken 2023). Assuming linear increase from 2014-2021, net Medicare Part D spending on these drugs would be $74.6 billion (Feldman, Rome et al. 2021). Feldman et al. estimate a higher rebate level, rising linearly from 18.5% in 2014 to 37% in 2017. Extrapolating linear growth through 2021, net Medicare Part D spending on these drugs would be $67.3 billion. Feldman has also identified that rebates on branded drugs are higher, increasing linearly from

[17] https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/information-on-prescription-drugs/partd_rebates, updated September 2023.

25% in 2014 to 37% in 2018. Extrapolating linear growth through 2021, net Medicare Part D spending on these drugs would be $57.3 billion.

The residual health value created by Medicare Part D spending on these drugs is estimated from the total health value created for the beneficiaries minus the amount paid by CMS. Thus, this value is sensitive to different estimates of the rebate on Medicare Part D sales. As shown in Attachment B, estimates of the residual health value created by the eight drugs (excluding Januvia and Novolog) ranged from -$29.7 billion based on total Medicare Part D spending to -$6.9 billion extrapolating rebates from the 17.5% (2014) and 25% (2021) data points available from CMS, to $10.4 billion considering rebates of 34% to 45% from 2017-2021 as reported by Feldman et al. (Feldman, Rome et al. 2021).

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