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Implications of the Inflation Reduction Act for the biotechnology industry; sensitivity of investment and valuation to drug price indices and market conditions

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ABSTRACT

The Inflation Reduction Act of 2022 contains landmark provisions authorizing the government to negotiate the price of selected drugs covered by Medicare Part D. The biopharmaceutical industry has criticized these provisions as a threat to innovation arguing that reducing future revenues could disincentivize equity investment in biotechnology. This research examines the sensitivity of private and public equity investment in the biotechnology industry to drug price indices and market conditions from 2000-2022. The analysis shows that equity financing and valuation in the biotechnology industry were strongly associated with equity market conditions but not indices of either producer or consumer drug prices. These

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results do not support claims of an association between changing drug prices and the availability of equity capital to emerging biotechnology companies, which currently sponsor the majority of all clinical trials. These results add to evidence that the IRA may not have a negative impact on pharmaceutical innovation.

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1. INTRODUCTION

This working paper analyzes the sensitivity of equity investment in biotechnology companies to changes in drug prices in the context of industry's argument that government policies intended to make prescription drugs more affordable could negatively impact pharmaceutical innovation. These arguments have been central to industry's criticism of the Inflation Reduction Act of 2022 (IRA) (US Congress 2022), which contains provisions that authorize the federal government to negotiate the price paid by Medicare part D prices for selected drugs (US Congress 2022, CMS 2023a, 2023b, Cubanski et al. 2023, Sullivan 2023) and require manufacturer rebates on prices that increase faster than the rate of inflation (Sarpatwari 2022, Cubanski et al. 2023, Sullivan 2023). Industry critics argue that these provisions of the IRA threaten biopharmaceutical innovation by reducing the availability of the capital resources required for research & development (R&D).[1]

Two distinct theses underlie these arguments. The first is that reducing drug prices will reduce revenues to pharmaceutical producers, directly decreasing the amount of capital available for R&D. The second is that reducing future revenues will depress earnings expectations and indirectly depress corporate valuations and disincentivize equity investment. Both theses are predicated on theories that posit that a firm's revenue contributes to its strategic capital allocations, valuation, and ability to attract capital through equity offerings.

In a previous report, we examined the first thesis by characterizing the finances of public biopharmaceutical companies from 2000-2018. Consistent with aforementioned theories, there was a strong association between revenue and R&D expense for 78 of the largest pharmaceutical companies, which collectively account for the large majority of product sales as well as >85% of all revenue and R&D spending. There was, however, no association between revenue and R&D for 1,299 smaller, emerging biotechnology companies, which typically had no marketed products, little revenue, and negative earnings, and derived much of their capital for R&D through equity offerings (Vaughan and Ledley 2021, Vaughan et al. 2024). Significantly, these smaller companies conduct the majority of all clinical trials and originate the majority of drug

[1] There is an extensive body of writing in opposition to the drug pricing provisions of the IRA from industry-funded academic researchers, commissioned reports, and blogs. Examples include: Philipson and Durie (2021, 2021a), Fleming (2022), Longo (2022, 2023), Gassull et al. (2023), PHAR (2023), Philipson et al. (2023), PhRMA (2023).

approvals (Aitken et al. 2019, Dowden and Munro 2019, Aitken and Kleinrock 2021, Aitken et al. 2022, 2023, Thomas and Wessel 2023).

These findings were incorporated into a model of the drug development pipeline that apportioned drugs at each phase of clinical development to large or small companies, adjusted the number of clinical trials based on the observed elasticity of R&D spending in companies of different sizes, and allowed products in early-stage development by small companies to be acquired by large firms for late-stage development. The results suggested that revenue reductions of up to 10% might be mitigated through existing best practices of product licensing or acquisition with strategic allocation of R&D cost reductions (Vaughan et al. 2024). These results also suggested, however, that the pipeline of new products could become more dependent on early-stage innovation in smaller biotechnology companies and, as such, more vulnerable to indirect effects of price reductions on financing through equity offerings.

The present work examines the second thesis, namely that reducing drug prices could indirectly depress equity investment in biotechnology. Specifically, we ask whether drug price indicators and market conditions are associated with changes in investment in equity offerings or valuations in the biotechnology industry. We do this through a retrospective analysis of the association of private or public equity offerings in biotechnology companies or the NASDAQ Biotechnology Index (NBI) with indices of producer or consumer drug, equity market conditions, and debt market conditions from 2000-2020. The study period spans the launch of Medicare Part D in 2006 and the Affordable Care Act in 2014 as well as successive periods of economic recession and growth.

The results do not support an association between drug prices and either equity investment or valuation in the biotechnology industry. This suggests that the drug price reductions anticipated under the IRA may not have a negative impact on the availability of equity capital required for innovation in the biotechnology industry.

This work also extends previous studies characterizing the distinctive business model of the biotechnology industry (Pisano 2006, 2006a, Pisano 2010, Cleary et al. 2021, Aitken et al. 2022) by suggesting that the drivers of equity investment and valuation in biotechnology may be different from those influencing the valuations of large pharmaceutical producers. As such, evidence-based policy regarding R&D or drug pricing must consider not only impacts on large,

profitable pharmaceutical companies that are dependent on product revenues for operating and innovation capital, but also emerging, equity-reliant biotechnology companies as well as the dynamic interactions of these industries.

Outline of this research

Section 2, Background and Objectives, provides background on Medicare Part D, the provisions of the IRA related to drug pricing, and previous studies by the Congressional Budget Office (CBO) and academic authors aimed at assessing the potential impact of the IRA on pharmaceutical innovation. These studies provide the foundation for the two hypotheses tested in this paper concerning the association of indices for drug prices and market conditions with equity investment or valuations in the biotechnology industry.

Section 3, Results, provides descriptive statistics of investment and valuations in the biotechnology industry as well as indices for drug prices, equity market conditions, and debt market conditions from 2000-2020. We then describe the results of multivariate analyses of the association between equity financing availability and drug prices, controlling for market conditions and assessing the robustness of these results with different indices of market conditions as well as lags that account for timing effects.

Section 4, Discussion, presents our empirical findings in the context of arguments that the IRA represents a threat to pharmaceutical innovation. The present results provide no evidence to support the argument that the price reductions anticipated by the IRA represent a direct or indirect threat to innovation and also highlight the potential sensitivity of innovation to broader market conditions. and their limitations

Section 5, Conclusion.

Appendix, includes the Methods, describing datasets and models used in this analysis, as well as supplemental tables.

2. BACKGROUND AND OBJECTIVES

Medicare spending on prescription drugs and design of the IRA

The Medicare Part D program was created by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 and first implemented in 2006 to provide older Americans with coverage for self-administered (outpatient) prescription drugs (Congress 2003, CRS 2004). The

complex law provides for government contributions to privately-operated, Medicare Part D prescription drug plans that distribute the costs of prescription drugs between government, plan sponsors (insurers), and out-of-pocket payment for premiums or deductibles (CRS 2004, KFF 2020). In 2022, 50 million Americans were enrolled in Medicare Part D plans. Gross spending through Medicare Part D,[2] including payments by government, private plans, and out-of-pocket spending by beneficiaries, was in excess of $240 billion or about 40% of total US spending on prescription drugs (Swagel and Phillip 2022). Government spending on drugs through Medicare Part D totaled >$125.7 billion, an average of $509.50 spending per beneficiary (CRS 2023a, Cubanski and Damico 2023). These metrics do not reflect manufacturers' rebates, which have been estimated to rise from 25.4% to 373.3% of brand name drug spending from 2014-2018 (Feldman et al. 2021).

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 included provisions that explicitly prohibited the new program from engaging in drug price negotiations or establishing either a formulary of preferred products or pricing structure (CRS 2004, CRS 2023a). Instead, drugs prices were established through negotiation between plan sponsors, Pharmacy Benefit Managers (PBMs), dispensing pharmacies, or manufacturers without "interference"[3] from the government (CRS 2023a).

The Inflation Reduction Act of 2022 (IRA) aims to lower the cost of high-priced, brand-name drugs by allowing the Secretary of Health and Human Services (HHS) to negotiate "maximum fair prices" for certain single-source drugs through a new Medicare Drug Price Negotiation Program. The price negotiation program involves identification of a discrete number of drugs meeting pre-articulated criteria followed by a scripted process of information exchange, price boundaries, and negotiation using defined criteria.[4] Ten drugs were selected for price negotiation

[2] "…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 as CMS is prohibited from publicly disclosing such information."

[3] ''(i) NONINTERFERENCE.—In order to promote competition under this part and in carrying out this part, the Secretary— ''(1) may not interfere with the negotiations between drug manufacturers and pharmacies and PDP sponsors; and ''(2) may not require a particular formulary or institute a price structure for the reimbursement of covered part D drugs. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, (Public Law No: 108-173) Text - H.R.1 - 108th Congress (2003-2004): Medicare Prescription Drug, Improvement, and Modernization Act of 2003 | Congress.gov | Library of Congress

[4] The criteria defined in: 42 USC 1320F-3 negotiation and renegotiation process. https://www.congress.gov/bill/117th-congress/house-bill/5376/text

in 2023 (CMS 2023, 2023a, 2023b, CRS 2023) with the first price reductions scheduled for 2026. A total of 100 drugs will be selected for negotiation in the first five years of the Act.

Relationship between pharmaceutical markets and innovation

Pharmaceutical R&D investments are widely considered to be driven by market-pull mechanisms that prioritize development opportunities based on the size of the available market, anticipated revenue, and estimates of the return on investment (Grabowski and Vernon 2000). This is consistent with theories that view profit and returns on investment as drivers of innovation.

The widely quoted study of the relationship between market research and pharmaceutical innovation by Acemoglu and Linn (2004) suggested that a 1% increase in the market for a therapeutic class of drugs can be associated with as much as a 6% increase in the number of branded drugs for those conditions. Similar conclusions were reported by Dubois et al. (2015), who observed considerable elasticities between market size and new drug innovation such that a $2.5 billion increase in market size was associated with one additional drug launch. Consistent with these observations, Vernon (2005) has postulated that lowing drug prices would reduce the

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"(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."

expected return on investment in R&D making these investments less attractive, raising the cost of capital, and increasing the firm's reliance on external debt.

Empirical evidence for a relationship between market size and pharmaceutical innovation also arises from studies of the industry's response to the passage of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, which substantially increased the market for many drugs (Lichtenberg and Sun 2007, Zhang et al. 2009). Some studies suggest that this exogenous shock was associated with an increase in R&D spending, clinical trials, and drug launches specifically for conditions that were most impacted by Medicare Part D payment (Blume-Kohout and Sood 2008) but not for other conditions (Dranove et al. 2014). Other studies, however, showed that passage of Medicare Part D had limited effects on pharmaceutical patenting, which is often considered a metric for innovation (Lemley et al. 2020, Shen 2022). It has also been suggested that the effects of market pull on research (R) may be less pronounced than the effect on development (D) (Byrski et al. 2021). A study of vaccine development by Finklestein (2004) suggested that market-driven innovation may primarily involve products that are "…*on the shelf for whom the decision to begin clinical trials is responsive, on the margin, to increases in the expected economic return*…"

There is also evidence for technology push mechanisms driving pharmaceutical innovation. For example, Toole (2012) examined the relationship between government funding for basic research and new drug approvals, demonstrating that a 1% increase in research stock (accumulated R&D spending) was associated with a 1.8% increase in approval of new molecular entities. These effects, however, may also involve market pull mechanisms since the availability of new technologies may create products that represent new markets involving previously untreatable conditions or products that are superadded to existing regimens.

The argument that reducing drug prices could lead to decreases in innovation is based primarily on the inference that, given the limited price elasticities of prescription drug markets,[5] reducing drug prices will reduce the size of the available market. The most direct evidence for this association comes from studies characterizing the pharmaceutical industry's response to the

[5] Pharmaceutical prices are generally assumed to be inelastic based on the RAND Health Insurance Experiment (https://www.rand.org/health-care/projects/hie.html) (Newhouse 1993) and is generally consistent with more recent literature (Yeung et al. 2018). Elasticities may vary by medication class, disability associated with the condition, and do not consider the effects of generic substitution.

Clinton health care proposals included in the Health Security Act (HSA), which was proposed to Congress in 1992 and rejected in 1994 (Skocpol 1995). A study by Golec et al. (2010) examined 111 pharmaceutical firms with at least 8 years of public financial data (including biotechnology, brand name, and generic firms) during the period 1991-1995 when the HSA was actively debated. The study found that drug prices increased only slightly if at all. Companies also experienced abnormal, negative returns, and R&D intensity dropped significantly over this period. Similarly, Lichtenberg (2003) observed that the valuations of pharmaceutical companies dropped substantially in response to the Clinton health care proposals and argued that decreases in R&D spending and innovation were related to these decreases in valuation. His analysis suggested that the Clinton proposals resulted in a temporary reduction in the number of new product approvals with a 10-15-year lag by 2.9 drugs/year or 9.9%. Significantly, all of these studies were performed on datasets comprising limited numbers of large pharmaceutical companies with products, product sales, and profits.[6]

Projecting the impact of the Inflation Reduction Act on innovation

Several studies have modeled how the reduction in drug prices anticipated under the IRA or the earlier, unsuccessful Elijah E. Cummings Lower Drug Costs Now Act in 2021 (US Congress 2021) could impact pharmaceutical innovation (Philipson and Durie 2021, 2021a, Gassull et al. 2023, Philipson et al. 2023, PhRMA 2023, Rome et al. 2023). Rome et al. (2023) simulated the impact the IRA would have had on pharmaceutical sales from 2018-2020, suggesting that Medicare spending would have been reduced by $26.5 billion, representing a 5% reduction in Medicare spending. An initial report from the Congressional Budget Office (CBO) estimated that the Elijah E. Cummings Lower Drug Costs Now Act could have led to a loss in pharmaceutical revenue of about 2.7% by 2029 and 10% over the following decade (Swagel 2019). Subsequent CBO reports related explicitly to the IRA refined these projections, suggesting that by 2031 price

[6] Specifically, Giaccotto et al. (2003) based their analysis explicitly on "major pharmaceutical companies in the US" from 1952-2001 while Giacotto et al. (2005) focused on PhRMA member companies. Grabowski and Vernon (2000) focused on ten companies 1962-1975, five companies 1962-1993, and eleven "major drug firms." Other studies by Vernon were variously based on the world's "20 largest companies" (Vernon, 2003) or the "30 largest pharmaceutical firms from 1994-1997" or 14 of the 30 largest companies (Vernon, 2005). Lichtenberg (2003) based his analysis of the relationship between pharmaceutical R&D and market value, tangible assets, R&D stock, and cash flows on an analysis of 64 large pharmaceutical companies. The study by Golec et al. (2010) included 111 firms with at least 8 years of data in Compustat spanning 1992-1995, which excludes firms with public offerings during this time and, consequently, all but the earliest public biotechnology companies. A recent study by Ho and Pakes (2024) was based on "16 of the largest pharmaceutical firms (by capitalization)."

negotiation could lower average drug prices by 9% for Medicare Part B and by 8% for Medicare Part D, and that mandatory inflation rebates could lower net spending by 2% (CBO 2022, 2023). Philipson and Durie (2021a) projected a 12% loss of revenue through 2039, which they argue is conservative while also acknowledging that the analysis does not account for revenue gains through new drug approvals.

Philipson and Durie (2021) estimated the elasticity of R&D spending relative to revenue through a meta-analysis of ten studies examining the impacts of changes in price or market size on pharmaceutical markets or R&D spending. These papers described R&D elasticities ranging from 0.22 (Vernon 2005) to 5 (Acemoglu and Linn 2004) with an average of 1.54 and a median of 1 (Philipson and Durie 2021). The subsequent analyses (Philipson and Durie 2021a, Philipson et al. 2023) were based on the average elasticity of R&D spending of 1.54 (154%) such that their estimated 12% reduction in revenue would produce an 18.5% reduction in R&D spending (Philipson and Durie 2021a). This elasticity is substantially higher than the values of 50% projected by the CBO (2023), 23% by Dubois et al. (2015), and 8.4% by Vaughan et al. (2024).

Philipson and Durie (2021, 2021a) further assume a proportional relationship between decreases in R&D spending and the number of new drug approvals and suggest that the IRA would reduce drug approvals by 18.5%, representing 135 fewer drug approvals through 2039. They suggest that this represents a loss of 331.5 million life years (Philipson and Durie 2021, 2021a, Philipson et al. 2023).

The CBO projects expected revenue and costs associated with a drug by clinical phase in both an IRA and pre-IRA regulatory setting (Adams and Hernstadt 2021). To estimate revenues in an IRA environment, the CBO modeled the negotiated maximum fair price for drugs using a Nash bargaining framework in which both parties want negotiation to succeed because (i) the manufacturers would receive the negotiated price times volume sold (which is greater than no revenue under no agreement) and (ii) the government receives the incremental benefit of the number of beneficiaries times the per-year value above the next best alternative. This is compared against distributions of non-IRA revenues determined by proprietary information provided by CMS or manufacturers concerning Medicare Part D drug prices net of rebates, applied proportionally by share of global revenue. Cost distributions are determined according to phase-specific costs described by DiMasi et al. (2016).

The CBO model pairs revenue and cost estimates per drug in each clinical trial phase for a regulatory regimen before and after IRA price negotiations. The model estimates which drugs would not provide a positive return (i.e., expected revenue greater than cost) after price negotiation and that these drugs would be discontinued.

Both the CBO (2021) and Philipson and Durie (2021a) predict that pharmaceutical companies will reduce R&D expenditures, and possible future revenue streams. The CBO model further anticipates that decreases in revenue could significantly affect earnings, the equity value of firms, and the debt-to-equity ratio, increasing the cost of capital. With these additional factors, the CBO estimates that this could lead to a cumulative 19% reduction in pharmaceutical revenue. Both the Philipson and the CBO models further assume that the number of candidate products abandoned in response to new reductions in revenues will be superadded to the 10-30% of products in development that are currently abandoned due to commercial or strategic considerations (i.e., commercial or strategic failures) rather than considerations of safety or efficacy (DiMasi 2013, Hay et al. 2014, DiMasi et al. 2016, Khmelnitskaya 2021). While the CBO model acknowledges the presence of strategic failures, quoting the 8.4% figure from Khmelnitskaya (2021), this is only factored into their model as an explanation for the observed attrition rate. Neither model considers any actions that may be taken by pharmaceutical companies to maintain a robust pipeline of new products, restore efficiencies, or preserve earnings nor does the model consider other changes in government policy.

Most importantly, both the Philipson and CBO models consider drug development to be a continuous path from the initiation of clinical trials through approval in large pharmaceutical companies with marketed products, revenues from product sales, and positive earnings. Neither model accounts for evidence that up to 47% of drugs launched by large companies were licensed from smaller companies following initiation of phase 2 trials (GlobalData 2020), only 20% of drugs in development originated in large companies, or as many as 70% of drugs in phase 3 clinical trials are sponsored by emerging biotech companies (Aitken et al. 2019, CBO 2021, Aitken et al. 2022, Vaughan et al. 2024). Though they acknowledged that many smaller companies are acquired by larger firms, these studies did not consider the impact of drug price reductions on smaller, emerging biotechnology companies, how changes in global revenue could impact drug discovery or development in smaller companies, or how these companies could play a role in mitigating the negative effects of price reduction.

As the pharmaceutical industry increasingly adopts outsourcing as a strategy for controlling costs and achieving greater efficiency (Khanna 2017) pharmaceutical innovation becomes increasingly dependent on a pipeline of projects that originate or are taken through early-stage development by emerging biotechnology companies. As such, the impact of the IRA on innovation may be critically dependent on the ability of smaller, emerging companies to access capital for R&D rather than on the level of R&D spending in large pharmaceutical companies themselves.

Differences in the financial structure of large and small biopharmaceutical companies and implications for innovation

The global biopharmaceutical industry comprises more than 8,000 companies pursuing dramatically different business models ranging from large, fully integrated pharmaceutical companies that account for a large majority of pharmaceutical sales and R&D spending (GAO 2017), to small, emerging biotechnology companies with science-based business models (Pisano 2006, 2006a). A 2020 study of the 35 largest pharmaceutical companies listed on US exchanges from 2000-2018 showed that these companies reported $1.7 trillion in R&D expense representing 14.5% of their $11.5 trillion total revenue (median 13.7%) or 19% of their $8.58 trillion total gross profit (net revenue) (Ledley et al. 2020). Others have reported that R&D spending by companies in the Pharmaceutical Research and Manufacturers Association has increased from 13% of gross profit (net revenue) in the early 2000 to greater than 25% in 2018 and 2019 (CBO 2021). Vaughan et al. (2024) showed that, for 79 companies with market capitalizations ≥$7 billion between 2000 and 2018, there was a strong association between revenue and R&D expense as well as a strong association between changes in revenue and changes in R&D. These companies were uniformly profitable and derive operating capital almost entirely from revenue or debt. These companies offer stock almost exclusively as part of executive compensation or employee stock option plans and engage in substantial stock buybacks, making equity transactions a net negative source of capital.

On the other end of the spectrum are many small, emerging biotechnology companies. These companies have been described as having a science-based business model that creates value through biomedical science or pharmaceutical R&D (Pisano 2006a, 2010, Cleary et al. 2021). They typically have no products, generate little or no product revenue, and have persistently negative earnings (Pisano 2006a, Cleary et al. 2021, Vaughan et al. 2024) but are currently

responsible for the majority of all clinical trials and an increasing fraction of product approvals (Aitken et al. 2019, Dowden and Munro 2019, Aitken and Kleinrock 2021, McNamee et al. 2021, Aitken et al. 2022, 2023).

Vaughan et al. (2024) also showed that 1,299 public biotechnology companies with market capitalization <$7 billion from 2000-2018 had greater median R&D expense than median revenues and that there was no evidence for an association between revenue (including both product revenue and revenue from research partnerships) and R&D expense. Vaughan et al. (2024) also demonstrated that there was a positive association between R&D and new investment (proceeds from sale of common and preferred stock) suggesting that these companies derive much of the capital for innovation from new investment rather than revenue.

This work also modeled the impact of drug price reductions on the pharmaceutical pipeline accounting for the proportion of clinical trials performed by large and small companies and differences in the elasticity of R&D spending to revenue in companies of different size. This model suggested that revenue reductions of up to 10% in all companies could have little or no effect on new drug approvals. The model suggests that any negative effects of reduced R&D spending in larger companies could be mitigated by (i) continued R&D spending by smaller companies in the face of revenue reductions; (ii) continued licensing or acquisition of clinical stage products by large companies; and (iii) the best practices of larger companies in allocating R&D resources to different stages of clinical development. These results also suggest, however, that sustained innovation could be sensitive to changes in the level of new investment in the biotechnology industry, which represents an important source of capital for R&D in these companies.

Research hypothesis

The present study asks whether there is evidence that changes in drug prices could impact the availability of equity capital. In theory, this would occur if the negotiated "maximum fair price" reduces the size of the available market, thus reducing the net present value (NPV) of the product pipeline in the absence of price elasticity. This could, in turn, reduce estimates of the fair market value of biotechnology firms/stocks made using NPV-based methods (Nelson and Mukherji 1998, Bogdan and Villiger 2010), making investment in these companies less attractive and reducing the availability of equity capital for R&D (Fleming 2022, Herring et al. 2022, Yip et al.

2022). Moreover, it should be noted that the discount rate for investment in biotechnology firms may already be high given the high failure rate of emerging firms (Cleary et al. 2021) and that high failure rate of products in clinical trials may create a particularly high discount rate for investment biotechnology companies (Villiger and Bogdan 2005, Bogdan and Villiger 2010). As such, biotechnology companies could be particularly sensitive to changes in drug prices compared to larger pharmaceutical companies (Stewart et al. 2001).

This retrospective study tests the hypothesis of an association between changes in drug price and the availability of equity capital that enables innovation in the biotechnology industry. In the present study, two hypotheses were tested:[7]

H1: There is a positive association between changes in drug prices and the dollar value of equity financing raised by the biotechnology industry. Data was aggregated quarterly.

H2: There is a positive association between changes in drug prices and valuation of the biotechnology industry. Data was aggregated monthly.

These hypotheses were tested by examining public and private equity offerings by biotechnology firms as well as an index of valuations in the biotechnology industry as indicators for the availability of equity capital. Drug prices were represented by the Producer Price Index: Pharmaceutical and Medicine Manufacturing ("PPI") or Consumer Price Index: Prescription Drugs ("CPI"). Our model recognizes that changing drug prices is not the only factor in availability of equity capital to the biotechnology industry. Liquidity in both equity and debt markets should also impact the ability to finance innovation by altering access to and the cost of equity capital. A bullish equity market provides investors with more capital for investment, making riskier investments more attractive (Crawford 1987, Purcell 1999, Booth 2016), whereas higher interest rates may raise research costs and lower the expected return on investment (de Visser et al. 2020). We capture these conditions using the S&P 500 or Dow Jones Industrial Average (DJIA) indexes as indicators of equity market conditions, the Federal Funds Effective Rate or Federal Discount Rate as indicators of debt market conditions, and year fixed effects.

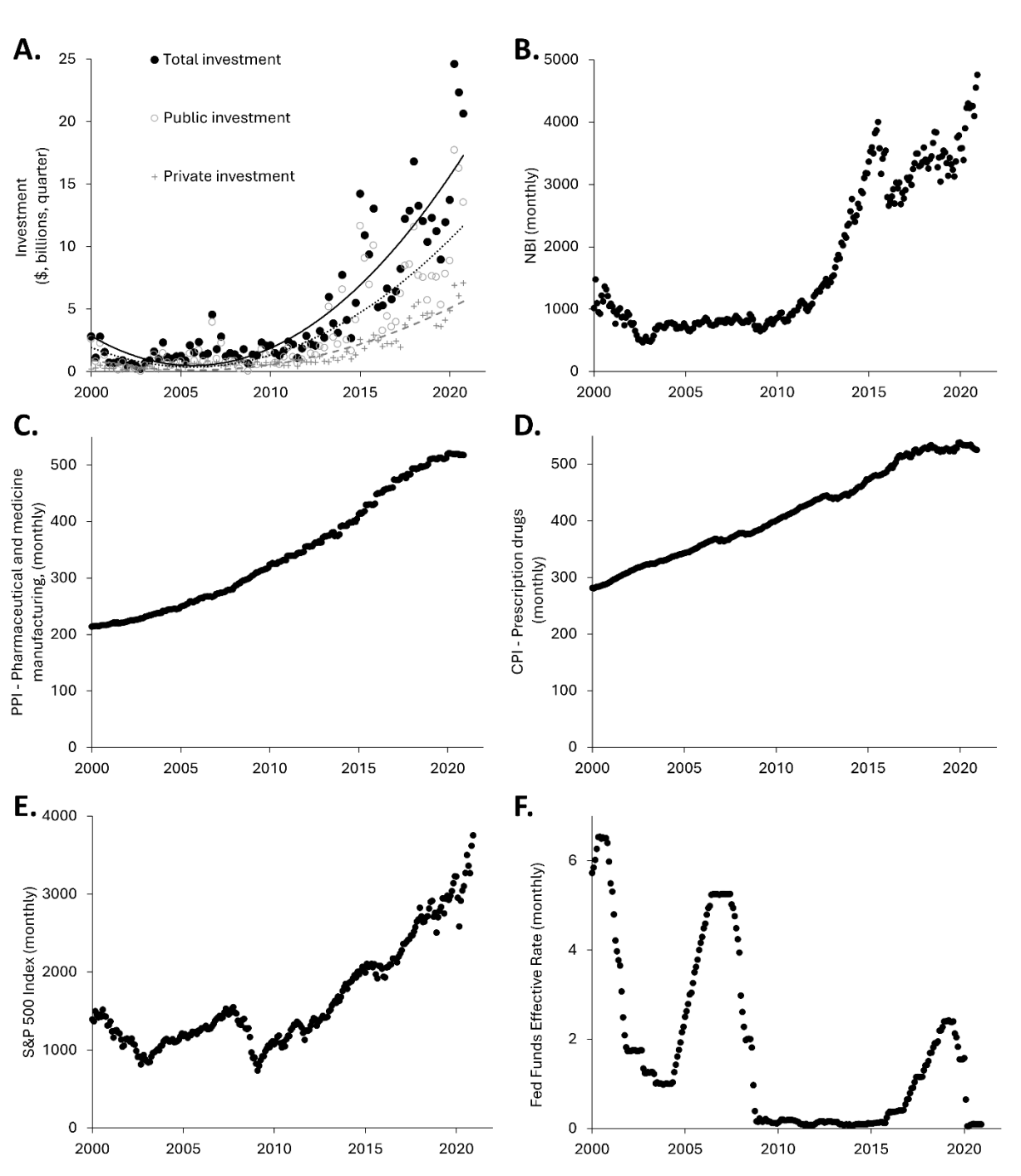
[7] Data sources, variable definitions, regression models and methods are described in the Methods (See Appendix).

3. RESULTS

Descriptive statistics

Figure 1 A-F illustrates the data used in this analysis from 2000-2020. Descriptive statistics are provided in Table 1. The BioCentury BCIQ database included data on 8,229 equity offerings representing a total investment of $406.78 billion from 2000-2020, aggregated quarterly. The dataset comprised: (i) 4,057 private offerings ($129.04 billion) including 3,086 categorized as venture offerings ($104.21 billion) and 971 uncategorized offerings ($24.82 billion) and (ii) 4,172 public offerings ($277.74 billion) including 459 initial public offerings (IPOs) ($50.47 billion), 1,649 follow-on offerings ($183.91 billion), and 2,064 uncategorized offering ($43.36 billion). There was considerable variation in both total, public, and private quarterly financings (Figure 1A), with lows following the crash of the dot-com bubble after 2000 to highs in 2015 and again in 2020.

Figure 1. Trends in dependent and independent variables 2000-2020



A. Total investment and private investment in biotechnology (quarterly); B. NASDAQ Biotechnology Index (NBI) (monthly). C. Producer Price Index: Pharmaceutical and Medicine Manufacturing (PPI) (monthly); D. Consumer Price Index: Prescription Drugs (CPI) (monthly). E. S&P 500 Index (monthly); F. Federal Funds Effective Rate (monthly).

Table 1. Descriptive statistics

A: Data for investment analysis aggregated quarterly						
	Number	**Minimum**	**Mean**	**Median**	**Max**	**Std. Dev.**
Total investment	84	0.21	4.84	2.26	24.63	5.43
Public investment	84	0.02	3.31	1.52	17.73	3.85
Private investment	84	0.14	1.54	0.76	7.09	1.70
PPI	84	214.70	344.96	328.20	520.40	101.17
CPI	84	282.40	414.24	409.37	537.95	79.00
S&P 500	84	797.87	1658.79	1413.38	3756.07	687.86
Fed Funds	84	0.05	1.68	1.01	6.54	1.88
B: Data for valuation analysis aggregated monthly						
	Number	**Minimum**	**Mean**	**Median**	**Max**	**Std. Dev.**
NBI	252	464.93	1739.59	1018.21	4759.14	1203.39
PPI	252	213.90	344.30	327.30	521.40	100.83
CPI	252	281.20	413.33	407.62	538.15	78.82
S&P 500	252	735.09	1655.94	1396.18	3756.07	677.94
Fed Funds	252	0.05	1.70	1.03	6.54	1.89

Total investment, Public investment, Private investment = (billions). PPI = Producer Price Index: Pharmaceutical and Medicine Manufacturing. CPI = Consumer Price Index: Prescription Drugs.

The NBI is a capitalization-weighted index of NASDAQ-listed companies classified according to the Industry Classification benchmark as "biotechnology" or "pharmaceuticals."[8] Since most public biotechnology companies are listed on the NASDAQ exchange and many large pharmaceutical manufacturers are listed on the New York Stock Exchange, NBI is considered an indicator of industry's entire valuation. While there was considerable variation in the NBI over time (Figure 1B), the index exhibited lows from 2003-2010 followed by >10-fold growth to highs in 2015 and again in 2020.

[8] **NASDAQ Biotechnology Index (NBI):** "*The Nasdaq Biotechnology Index is designed to measure the performance of a set of Nasdaq-listed biotechnology and pharmaceutical companies.*" https://indexes.nasdaqomx.com/docs/methodology_NBI.pdf

From 2000-2020, the PPI[9] estimates changes in the price received by pharmaceutical manufacturers relative to prices received in 1981. This index exhibited largely monotonic growth, rising 3.4-fold over the 1981 benchmark (Figure 1C).

The CPI[10] estimates changes in the price paid for prescription drugs at retail pharmacies including both out-of-pocket costs and third-party reimbursements relative to 1984. This index rose. CPI experienced a 2-fold growth over this timeframe with small decreases in 2007, coincident with the start of the great recession in 2007, and in 2012-13, coincident with the rollout of the Affordable Care Act of 2013, and little or no growth from 2016 through 2020 (Figure 1D).

The S&P 500 index was included as an indicator for general equity market conditions.[11] This index had lows following the collapse of the dot-com bubble and after the financial crisis of 2008-2009, followed by consistent growth from 2010-2020 (Figure 1E).

The Fed Funds Rate was used as an indicator for debt market conditions.[12] Decrease in the Fed Funds Rate reflects efforts to provide economic stimuli following the crash of the dot-com bubble in 2000, the recession of 2007-2009, and again in response to the pandemic in 2020 (Figure 1F).

Association between biotechnology investment and valuations, market conditions, and drug prices

Table 2 shows that the amount raised through equity offerings and the NBI valuations were positively associated with general market conditions (S&P 500) and negatively correlated with

[9] **Producer Price Index by Industry: Pharmaceutical and Medicine Manufacturing (PPI):** "*The Producer Price Index measures average change over time in the selling prices received by domestic producers for their output. The prices included in the PPI are from the first commercial transaction for many products and some services."* U.S. Bureau of Labor Statistics, Producer Price Index by Industry: Pharmaceutical and Medicine Manufacturing [PCU32543254], Federal Reserve Bank of St. Louis; https://fred.stlouisfed.org/series/PCU32543254, October 8, 2021.

[10] **CPI for All Urban Consumers (CPI-U); Prescription drugs in U.S. city average:** all urban consumers, seasonally-adjusted Series Id: CUSR0000SEMF01; The CPI collects transaction prices received by the retail pharmacy. If a particular prescription observation is paid for by a third-party payer, then the total price used in index calculation will include both the patient's copayment as well as the insurance reimbursed portion. The three eligible types of payers are: 1) cash, 2) insurance, and 3) Medicare part D. Does not include Medicaid or prescription drugs that are administered in a hospital setting. https://www.bls.gov/ppi/methodology-reports/the-pharmaceutical-industry-an-overview-of-cpi-ppi-and-ipp-methodology.pdf

[11] **The S&P 500® SPX (Index):** "*includes 500 leading companies and covers approximately 80% of available market capitalization*." https://www.spglobal.com/spdji/en/indices/equity/sp-500/#overview

[12] **Federal Funds Effective Rate, Percent, Monthly, Not Seasonally Adjusted:** "*The federal funds rate is the interest rate at which depository institutions trade federal funds (balances held at Federal Reserve Banks) with each other overnight."* Board of Governors of the Federal Reserve System (US), Federal Funds Effective Rate [FEDFUNDS], Federal Reserve Bank of St. Louis; https://fred.stlouisfed.org/series/FEDFUNDS, October 8, 2021

the Fed Funds rate from 2000-2020. This is consistent with the expectation that investment in the biotechnology industry is impacted by the availability of financial capital from equity or debt markets. These data also demonstrate a positive association with both the PPI and CPI.

Table 2. Correlations of total, public or private investments in biotechnology or valuation (NBI) with drug price indices (PPI or CPI) and indicators of market conditions (S&P 500, Fed Funds rate), 2000-2020

A. Investment (quarterly)

	Total investment	**Public investment**	**Private investment**	**PPI**	**CPI**	**S&P 500**	**Fed Funds**
Total investment	1						
Public investment	0.99***	1					
Private investment	0.95***	0.90***	1				
PPI	0.83***	0.79***	0.86***	1			
CPI	0.78***	0.74***	0.81***	0.99***	1		
S&P 500	0.90***	0.87***	0.92***	0.89***	0.84***	1	
Fed Funds	-0.25*	-0.25*	-0.24*	-0.48***	-0.52***	-0.16	1

B. Valuation (monthly)

	NBI	**PPI**	**CPI**	**S&P 500**	**Fed Funds**
NBI	1				
PPI	0.92***	1			
CPI	0.88***	0.99***	1		
S&P 500	0.94***	0.90***	0.85***	1	
Fed Funds	-0.34***	-0.49***	-0.53***	-0.16*	1

PPI = Producer Price Index: Pharmaceutical and Medicine Manufacturing. CPI = Consumer Price Index: Prescription Drugs. Bonferroni-adjusted Pearson correlations. *,**,*** indicate significance at the 0.05, 0.01, and 0.001 levels, respectively.

Table 3 shows the results of regressing the availability of equity capital on drug price indices, the S&P 500, and the Fed Funds rate given year fixed effects in an Ordinary Least Squares (OLS) model (Model I in Methods). Columns (1) and (2) show the results for the total amount of equity capital raised. This multivariable analysis (Model I in Methods) demonstrates a statistically significant positive association between total amount of equity capital raised and the S&P 500 ($\beta = 0.94$, p-value < 0.01 for drug prices represented by PPI; $\beta = 0.99$; p-value < 0.01 for drug prices represented by CPI) but no significant association with the Fed Funds rate. Notably, there is no significant association between the total amount of equity capital raised and either PPI or CPI. Similar associations are observed in Columns (3) and (4) where industry valuation replaces the amount of equity capital raised. There is a significant positive association between the NBI and the S&P 500 ($\beta = 0.35$, p-value < 0.001 for drug price represented by either PPI or CPI) but no significant association with either the Fed Funds rate or with drug prices represented by either PPI or CPI.

Table 3. Association of total investment or valuation (NBI) with drug price indices (PPI or CPI) and indicators of market conditions (S&P 500, Fed Funds Rate), 2000-2020

	Total investment		**NBI**	
	(1)	**(2)**	**(3)**	**(4)**
PPI – Pharmaceutical & Medicine Manufacturing	-0.93		0.40	
	(0.98)		(0.30)	
CPI – Prescription Drugs		-0.55		0.10
		(0.59)		(0.17)
S&P 500	0.50**	0.52***	0.35***	0.35***
	(0.17)	(0.17)	(0.05)	(0.06)
Fed Funds Rate	0.02	-0.00	-0.03	-0.03
	(0.16)	(0.16)	(0.04)	(0.04)
Observations	84	84	252	252
R-squared	0.933	0.933	0.989	0.989

Regression model includes year fixed effects with standard errors calculated with block bootstrapping. *, **, *** indicate significance at the 0.05, 0.01, and 0.001 levels, respectively.

Table 4 disaggregates the amount of equity capital raised into public offerings and private offerings. The results suggest that our findings in Columns (1) and (2) of Table 3 are driven by public equity financing. There is a significantly positive association between the amount of public equity capital raised and the S&P 500 ($\beta = 0.95$, p-value < 0.01 for drug prices represented by PPI; $\beta = 0.99$, p-value < 0.01 for drug prices represented by CPI). There is no significant association between the amount of equity capital raised through private equity financing and the S&P 500. Notably, there is no significant association between either public or private offering equity capital amounts and either PPI or CPI.

Table 4. Association of public or private investment in biotechnology with drug price indices (PPI or CPI) and indicators of market conditions (S&P 500, Fed Funds Rate), 2000-2020

	Public investment		**Private investment**	
	(1)	**(2)**	**(3)**	**(4)**
PPI – Pharmaceutical and Medicine Manufacturing	-2.73		0.12	
	(1.71)		(0.82)	
CPI – Prescription Drugs		-1.37		0.40
		(1.04)		(0.48)
S&P 500	0.95**	0.99**	0.12	0.03
	(0.31)	(0.32)	(0.14)	(0.14)
Fed Funds Rate	0.36	0.32	0.07	0.09
	(0.28)	(0.28)	(0.12)	(0.13)
Observations	84	84	84	84
R-squared	0.865	0.864	0.934	0.934

Regression model includes year fixed effects with standard errors calculated with block bootstrapping. *, **, *** indicate significance at the 0.05, 0.01, and 0.001 levels, respectively.

The results of Model I are robust to aggregating the amount of equity capital raised monthly, rather than quarterly, with a significantly positive association with the S&P 500 ($\beta = 0.52$, p-value < 0.05 for drug prices represented by PPI; $\beta = 0.56$, p-value < 0.05 for drug prices represented by CPI) and no significant association with either PPI or CPI. Public equity capital amounts aggregated on a monthly basis show a significant, positive association with the S&P 500 ($\beta = 1.36$, p-value < 0.05 for drug prices represented by PPI; $\beta = 1.34$, p-value < 0.05 for drug prices represented by CPI) and no significant association with either PPI or CPI. Private offering equity capital amounts raised, when aggregated monthly, have no significant associations with any of the predictive variables (Supplemental Table 1).

Robustness of associations: changes in investment or valuation, lagged effects, alternative metrics

Table 5 shows multivariate analyses of the associations between changes in amount of equity capital raised or changes in NBI with changes in market conditions and changes in drug price indices (Model II in Methods). There continues to be a positive association between NBI and the S&P 500 in a changes, rather than levels, regression ($\beta = 0.99$, p-value < 0.001 when considering change in PPI, $\beta = 0.98$, p-value < 0.001 when considering change in CPI) but no statistically significant association with investment.

Table 5. Association of changes in total investment or valuation (NBI) with changes in drug price indices (PPI or CPI) and indicators of market conditions (S&P 500, Fed Funds Rate), 2000-2020

	Total investment		NBI	
	(1)	(2)	(3)	(4)
PPI – Pharmaceutical and Medicine Manufacturing	6.96		0.67	
	(7.89)		(0.73)	
CPI – Prescription Drugs		-6.62		0.13
		(11.10)		(1.15)
S&P 500	0.41	0.45	0.99***	0.98***
	(1.12)	(1.13)	(0.11)	(0.11)
Fed Funds Rate	0.04	0.04	-0.01	-0.01
	(0.28)	(0.27)	(0.02)	(0.02)
Observations	83	83	251	251
R-squared	0.170	0.163	0.329	0.327

Regression performed on % change in total investment or valuations (NBI) with % change in drug prices (PPI or CPI), S&P 500, and Fed Funds rate. All regressions include year fixed effects and calculate standard errors with block bootstrapping. *, **, *** show significance at the 0.05, 0.01, and 0.001 levels, respectively.

Table 6 shows multivariable analysis of the S&P 500, Fed Funds rate, PPI, or CPI one period preceding total amount of equity capital raised (quarter) or the NBI valuation (month) (Model III in Methods). In this analysis, there is a statistically significant positive association between NBI and lagged S&P 500 ($\beta = 0.28$, p-value < 0.001 for drug price represented by PPI, $\beta = 0.29$, p-value < 0.001 for drug price represented by CPI) but no evidence for a lagged association with total investment. We anticipate that this results from the longer period of aggregation introducing more confounding factors, but rely on future research for more explanation. There is no evident association between either the total amount of equity capital raised or NBI with either the lagged value of the Fed Funds rate or the PPI or CPI.

Table 6. Lagged regression analysis of factors associated with total investment in biotechnology companies (quarterly lag) or biotechnology valuations (NBI) (monthly lag) and indicators of market conditions (S&P 500, Fed Funds Rate), 2000-2020

	Total investment		NBI	
	(1)	(2)	(3)	(4)
PPI – Pharmaceutical and Medicine Manufacturing	-0.24		0.29	
	(0.68)		(0.23)	
CPI – Prescription Drugs		-0.40		0.10
		(0.65)		(0.18)
S&P 500	0.14	0.14	0.28***	0.29***
	(0.25)	(0.25)	(0.06)	(0.06)
Fed Funds Rate	0.01	0.01	-0.04	-0.04
	(0.17)	(0.16)	(0.05)	(0.05)
Observations	83	83	251	251
R-squared	0.927	0.927	0.986	0.986

Regressions were performed between total investment or valuation (NBI) at $period_t$ and indicators of drug prices (PPI or CPI) and market conditions (S&P 500 and Fed Funds rate) at $period_{t-1}$. Regressions include year fixed effects and calculate standard errors with block bootstrapping. *, **, *** show significance at the 0.05, 0.01, and 0.001 levels, respectively.

The results for all models are comparable when the S&P 500 value is replaced by the DJIA (Supplemental Tables 2-4) or when the Fed Funds is replaced by the Federal Discount Rate (Supplemental Tables 5-7). In supplemental analysis, (Model III in Methods) the lagged predictors regression was rerun with an additional predictive variable, $Investment_{t-1}$. The results of this additional regression present evidence that the lagged investment term significantly predicts NBI valuation, while all other terms do not, suggesting a highly autoregressive trend (Supplemental Table 8). Under no conceived specifications was any association observed between equity capital amount raised or NBI valuations and either the PPI or CPI.

4. DISCUSSION

Passage of the Inflation Reduction Act in 2022 with provisions designed to reduce drug prices led to a barrage of both celebration and criticism in the media, a broad-based academic literature aimed at anticipating the Act's impacts on various sectors of healthcare and the biopharmaceutical industry, and lawsuits from pharmaceutical companies and trade organization aimed at blocking these provisions (Baron and Twinamatsiko 2023). One focus of industry's criticism of the IRA is that it would reduce the capital and incentive for innovation leading to fewer new drugs to treat unmet needs. Industry advocates have argued, for example, that "*The relevant question is the effect of price controls on funding. Investors decide whether to commit their money based on their estimate of future profits. An investor compares the size of the investment to the expected payout, adjusted for time and risk. … Price controls would reduce the expected payout…*"[13]

The industry's claim that reducing drug prices could negatively impact investment is not *a priori* unreasonable based on conventional principles of economics and finance. When confronted with decreases in drug prices, the large pharmaceutical manufacturers, which account for the large majority of product sales, revenues and R&D spending, are likely to adopt strategies designed to preserve earnings, share price, and shareholder value that may include reductions in R&D spending in addition to other cost-savings measures. If it is further assumed that corporate valuations are predicated on the present value of future revenues or earnings, reducing potential revenues from future product sales could negatively impact stock prices and equity investment in emerging biotechnology companies.

This empirical study found no evidence to support these arguments. Specifically, this analysis finds no evidence for an association between indices of drug prices, either producer or consumer prices, and private investments in biotechnology companies, public investments in biotechnology companies, or an index of the valuations in the biotechnology sector while also confirming expected associations of investment and valuations with equity market conditions. Given the prominent role that biotechnology companies play in the drug development process, it is no

[13] Fleming, S. "Drug-Pricing 'Experts' And CBO Underestimate The Threat To Innovation" Forbes, September 30, 2021 https://www.forbes.com/sites/stanfleming/2021/09/30/drug-pricing-experts-and-cbo-underestimate-the-threat-to-innovation/?sh=74a853c1e106

longer appropriate to frame evidence-based policy concerning pharmaceutical innovation or drug prices on economic principles that fail to account for the unique financial structure of the biotechnology industry.

We would emphasize that our results are not at odds with these mainstream economic principles as they apply to large, profitable pharmaceutical companies. Our previous work showed that the R&D elasticity for biopharmaceutical companies with market capitalization ≥$7 billion was 84% (Vaughan et al. 2024), close to the median of values reported by others and consistent with conventional principles. The present study focused explicitly on biotechnology companies where there is no significant association between revenue and R&D but a strong association with proceeds from equity offerings, and equity capital may provide a substantial source of funding for R&D.

The observation that conventional principles of finance may be inapplicable to models of equity investment in biotechnology is consistent with previous observations that the architecture of the biotechnology industry differs significantly from traditional, revenue-driven companies (Pisano 2006, 2006a, Cleary et al. 2021, Vaughan et al. 2024). Pisano has observed that that the biotechnology sector exhibits a "science-based business model in which companies "…*both participate in the creation and advancement of science and attempt to capture financial returns from this participation"* (Pisano 2006, 2006a, 2010). Given the long timelines and risks of drug discovery and development from advances in science (McNamee et al. 2017, Cleary et al. 2020), there is limited rationale for the argument that the net present value or risk-adjusted present value of future product is relevant to temporal valuations of biotechnology or the ROI for most holders of private or public equity.

While the valuations of biotechnology companies may be insensitive to future product revenues, valuations have been shown to be sensitive to factors that signal the value of the company's science and intellectual property. Studies have shown that the valuations of individual firms are impacted by patents, organizational knowledge, association with star scientists or leading academic institutions, corporate partnerships, or certain investors, which may signal the value of the company's science (Zucker and Darby 1996, DeCarolis and Deeds 1999, Nicholson et al. 2002, Guo et al. 2005, Higgins et al. 2011, Rothenstein et al. 2011, Hoenig and Henkel 2015, Colombo et al. 2019). The absence of any evident association between drug prices and the

valuations or equity investment in biotechnology companies in these studies suggests that such firm-specific effects, which would not be evident across the broader biotechnology industry, have a disproportionately important role in determining valuations and investor's expectations.

There is a need for further theoretical and empirical research on the business models of the biotechnology industry and how the advance of science generates equity value and a return for investors who invest in science-based firms. In the 20 years since Pisano's expression of concern about the viability of the biotechnology business model, this model has proven to be a robust platform for innovation in pharmaceutical and other healthcare technology through periods of turbulence in equity and debt markets and profound changes in healthcare practice and market structure. Not only do the present results provide no evidence to support arguments that the drug price reductions anticipated under the IRA would reduce investor interest in the biotechnology industry, but they also suggest mechanisms by which such price reductions could benefit investors. Specifically, Vaughan et al. (2024) suggested that reduced R&D spending in large firms could make these firms more dependent on candidate products licensed or acquired from smaller firms in early phases of development. This increased value of these products to pharmaceutical manufacturers, together with the greater competition for acquisition of these candidate products or firms, could increase the valuations of these smaller companies and provide greater returns for investors.

Finally, more research is required on the potential impact of reducing drug prices on the broader market. Reducing drug prices could reduce the total healthcare costs paid by non-pharmaceutical companies as well as their contributions under the Federal Insurance Contributions Act (FICA), thus, potentially increasing their earnings and returns to their shareholders. In this context, diversified institutional investors, who account for 40-50% [14] ownership of large pharmaceutical companies, might realize greater returns from their broad portfolios because of the drug price reductions under the IRA.

Limitations

There are several limitations to this analysis. First, drug prices increased broadly from 2000-2020 with limited periods of stability or decrease evident in the CPI, but never in the PPI. There

[14] Data from 13F Filings for 2010-2014 (Refinitiv).

is no evidence that the associations observed in these data would apply to decreases in drug prices. Second, the NBI is not independent of the broader NASDAQ exchange, and this relationship with the NASDAQ may be reflected in the significance of the S&P 500 or DJIA index as an independent variable. This limitation is avoided entirely when regressing amount of equity capital raised on drug price indices and market factors. Third, the weighted NBI index and estimates of equity capital raised may disproportionately reflect impacts on companies in the biotechnology industry with product revenues as opposed to early-stage biotechnology companies. This should bias against our results. Fourth, this analysis considered only publicly reported equity offerings and transactions completed in US dollars. Moreover, both the NBI and S&P 500 index are limited to companies listed on US exchanges and may not be representative of investments or valuations of foreign or privately owned firms. In addition, these results are based on a retrospective analysis of corporate finances and there is no evidence that these patterns will persist in the future. Finally, these models consider impacts on the biotechnology industry as opposed to impacts on individual firms.

5. CONCLUSION

This study, together with the companion report by Vaughan et al. (2024), demonstrate that any analysis of pharmaceutical innovation and the potential impacts of reducing drug prices needs to consider differences in the financial structure of large pharmaceutical manufacturers and smaller, science-based biotechnology companies as well as the dynamic nature of the drug development pipeline. Economic models of the IRA's potential impact on pharmaceutical innovation based on conventional assumptions concerning the association between revenue, R&D expense, valuations, or new investment in market-oriented, profitable firms fail to recognize the resiliency that arises from diverse sources of innovation capital as well as the complementary roles of internal and external (acquired) innovation in maintaining the pipeline of new products. Considering these dynamics, we conclude that the reductions in drug price anticipated by the IRA may have little or no effect on pharmaceutical innovation or the number of new drug approvals.

APPENDIX

Methods

Study Design

This retrospective study used multivariable regression to analyze the association between new equity investment in biotechnology companies and corporate valuations with indices of consumer or producer drug prices as well as general equity and debt market conditions from 2000 through 2020.

Data Sources

Variable definitions and data sources are described in Supplemental Table 9. Capital raised through public or private investment in equity offerings by biotechnology companies involved in drug discovery or development were identified in the BioCentury BCIQ database (2023). Equity offerings were identified with (i) Company Type filters: Private Biopharma, Small-Cap Biopharma (<$1 billion), Mid-Cap Biopharma ($1-$50 billion), or Large-Cap Biopharma (>=50 billion); (ii) Lead Product Status filters: Research, Preclinical, IND, Phase 0, Pilot, Phase I, Phase I/II, Phase II, Phase II/III, Pivotal, Phase III, Registration, Approved, Marketed, or Phase IV; and (iii) Financing Type filters: Seed financings, Series A rounds, Series B rounds, Series C rounds, Series D rounds, Series E rounds, rounds beyond series E, IPO, Follow-on, Public equity, and Uncategorized equity rounds. Data included only transactions with currency in US dollars and transaction status indicated as "Completed." Public offerings involving Special Purpose Acquisition Corporations (SPACs) and debt offerings were excluded. IPO proceeds included exercised overallotments and proceeds from the sale of common stock, American Depository Shares, and warrants, but not the exercise of warrants. "Total investment" was calculated as the sum of proceeds from all included offerings. "Private investment" comprises the sum of proceeds from Seed financings, venture rounds from A through E, and rounds beyond series E. "Public investment" comprises the sum of proceeds from IPOs, follow-on offerings, PIPEs, and other public equity deals. New equity offerings are aggregated at the quarterly level for analysis consistent with the timeline associated with underwriting an equity offering and adjusted for inflation using the CPI-U All Urban Consumers (CUUR0000SA0) prior to aggregation.

Industry-level valuations are represented by the NASDAQ Biotechnology Index ("NBI") (NASDAQ 2023). The size-weighted NBI index includes public biopharmaceutical companies having a minimum market capitalization of $200 million, at least 100,000 shares of daily trading volume, no audit concerns, and listing on NASDAQ for at least six months. The set of companies represented by NBI is not congruous with the set of companies in the BioCentury BCIQ database.

Two metrics were used as indicators of pharmaceutical prices (BLS 2021). The Producer Price Index: Pharmaceutical and Medicine Manufacturing (PCU32543254) ("PPI") captures the selling prices received by domestic pharmaceutical manufacturers in their first commercial transaction relative to prices in 1981 (BLS 2023a). Monthly PPI data was obtained from the St. Louis Federal Reserve Economic Data (FRED) (https://fred.stlouisfed.org/series/PCU32543254). The Consumer Price Index: Prescription Drugs (CUSR0000SEMF01) ("CPI") shows the seasonally-adjusted increase in prices received by retail pharmacies from pharmaceutical sales including patient's copayment, insurance, and Medicare Part D, but not Medicaid or prescription drugs that are administered in an inpatient setting, relative to prices in 1984 (BLS 2023). Monthly CPI data was obtained from the Bureau of Labor Statistics (BLS) (https://data.bls.gov/timeseries/CUSR0000SEMF01).

The S&P 500 index (S&P 2023a) was used as an indicator of general stock market conditions. Debt market conditions are represented by the Federal Funds Effective Rate (Fed Funds), the interest rate banks charge to one another for overnight loans (FRED 2023a). Robustness of the analysis was tested using the Dow Jones Industrial Average (DJIA) (S&P 2023) in place of the S&P 500 index and the Federal Discount Rate (FRED 2023) in place of the Fed Funds rate. The analysis used S&P 500, NBI, and DJIA values from the close of the last business day of each period (month or quarter). The Fed Funds rate and Federal Discount Rate are recorded on the first day of each month and are treated as reflecting activity over the previous period. PPI and CPI reflect average values over a month with the last month of each quarter used to represent that quarter.

Statistical methods

Analysis was performed using an ordinary least squares (OLS) regression. Model I was used to assess the association between indicators of investment or valuation and drug price indices, market conditions, and debt conditions, as shown in equation (1):

$$\text{Investment}_t = \beta_0 + \beta_1 \text{Drug prices}_t + \beta_2 \text{S\&P}_t + \beta_3 \text{Fed funds rate}_t + \varepsilon \quad (1)$$

where *Investment*$_t$ is the log of total equity investment amount, public offering equity investment amount, private offering equity investment amount, or NBI, and *Drug prices*$_t$ is either the PPI or CPI. All variables in Model I are aggregated on a quarterly level to test associations with equity investment amounts and on a monthly level to test associations with NBI, as best befits the funding timelines.

Model II considers the association between changes in investment or valuation using equation (1) with each variable represented by the percent change from the previous period (month or quarter).

Model III considers the lagged effect of drug prices or indicators of market conditions at period t-1 on investment or valuation at period t using equation (2):

$$\text{Investment}_t = \beta_0 + \beta_1 \text{Drug prices}_{t-1} + \beta_2 \text{S\&P}_{t-1} + \beta_3 \text{Fed funds rate}_{t-1} + \varepsilon \quad (2)$$

In all three models, *Drug prices*, *S&P*, and *Fed Funds rate* were scaled for comparability between predictive variables and year fixed effects were included to account for time-specific factors and trends. Standard errors were calculated using the block bootstrapping method with 10,000 bootstrap samples drawn from blocks to account for potential time-series correlation (Bertrand et al. 2004). Analyses were performed using R or Excel.

Supplemental Tables

Supplemental Table 1. Monthly association of total, public, or private investment in biotechnology with drug price indices (PPI or CPI) and indicators of market conditions (S&P 500, Fed Funds Rate), 2000-2020

	Total		Public		Private	
	(1)	(2)	(3)	(4)	(5)	(6)
PPI – Pharmaceutical and Medicine Manufacturing	-0.63		-4.21		0.86	
	(1.19)		(2.97)		(2.82)	
CPI – Prescription Drugs		-0.67		-1.12		-0.45
		(0.70)		(1.65)		(1.69)
S&P 500	0.52*	0.56*	1.36*	1.34*	0.80	0.85
	(0.22)	(0.23)	(0.54)	(0.56)	(0.50)	(0.49)
Fed Funds Rate	0.09	0.07	-0.10	-0.08	0.19	0.16
	(0.17)	(0.17)	(0.39)	(0.40)	(0.47)	(0.46)
Observations	252	252	252	252	252	252
R-squared	0.779	0.780	0.486	0.482	0.371	0.371

Regression model includes year fixed effects with standard errors calculated with block bootstrapping. *, **, *** indicate significance at the 0.05, 0.01, and 0.001 levels, respectively.

Supplemental Table 2. Association of total investment or valuation (NBI) with drug price indices (PPI or CPI) and indicators of market conditions (DJIA, Fed Funds Rate), 2000-2020

	Total investment		NBI	
	(1)	(2)	(3)	(4)
PPI – Pharmaceutical & Medicine Manufacturing	-1.14		0.36	
	(0.97)		(0.32)	
CPI – Prescription Drugs		-0.66		0.07
		(0.58)		(0.18)
DJIA	0.57***	0.59***	0.33***	0.34***
	(0.18)	(0.18)	(0.06)	(0.06)
Fed Funds Rate	0.02	-0.01	-0.03	-0.03
	(0.15)	(0.15)	(0.04)	(0.05)
Observations	84	84	252	252
R-squared	0.934	0.934	0.988	0.987

Regression model includes year fixed effects with standard errors calculated with block bootstrapping. *, **, *** indicate significance at the 0.05, 0.01, and 0.001 levels, respectively.

Supplemental Table 3. Association of changes in total investment or valuation (NBI) with changes in drug price indices (PPI or CPI) and indicators of market conditions (DJIA, Fed Funds Rate), 2000-2020

	Total investment		NBI	
	(1)	(2)	(3)	(4)
PPI – Pharmaceutical and Medicine Manufacturing	7.00		0.71	
	(7.77)		(0.76)	
CPI – Prescription Drugs		-6.36		0.27
		(11.00)		(1.24)
DJIA	0.25	0.23	0.86***	0.86***
	(1.13)	(1.13)	(0.12)	(0.12)
Fed Funds Rate	0.06	0.06	0.00	0.00
	(0.28)	(0.27)	(0.03)	(0.03)
Observations	83	83	251	251
R-squared	0.168	0.162	0.266	0.262

Regression performed on % change in total investment or valuations (NBI) with % change in drug prices (PPI or CPI), S&P 500, and Fed Funds rate. All regressions include year fixed effects and calculate standard errors with block bootstrapping. *, **, *** show significance at the 0.05, 0.01, and 0.001 levels, respectively.

Supplemental Table 4. Lagged regression analysis of factors associated with total investment in biotechnology companies (quarterly lag) or biotechnology valuations (NBI) (monthly lag) and indicators of market conditions (DJIA, Fed Funds Rate), 2000-2020

	Total investment		NBI	
	(1)	(2)	(3)	(4)
PPI – Pharmaceutical and Medicine Manufacturing	-0.19		0.33	
	(0.68)		(0.25)	
CPI – Prescription Drugs		-0.39		0.10
		(0.66)		(0.19)
DJIA	0.09	0.09	0.24***	0.25***
	(0.25)	(0.25)	(0.06)	(0.06)
Fed Funds Rate	0.02	0.02	-0.03	-0.04
	(0.17)	(0.17)	(0.05)	(0.05)
Observations	83	83	251	251
R-squared	0.927	0.927	0.985	0.984

Regressions were performed between total investment or valuation (NBI) at $period_t$ and indicators of drug prices (PPI or CPI) and market conditions (S&P 500 and Fed Funds rate) at $period_{t-1}$. Regressions include year fixed effects and calculate standard errors with block bootstrapping. *, **, *** show significance at the 0.05, 0.01, and 0.001 levels, respectively.

Supplemental Table 5. Association of total investment or valuation (NBI) with drug price indices (PPI or CPI) and indicators of market conditions (S&P 500, Fed Discount Rate), 2000-2020

	Total investment		NBI	
	(1)	(2)	(3)	(4)
PPI – Pharmaceutical & Medicine Manufacturing	-0.96		0.40	
	(0.99)		(0.30)	
CPI – Prescription Drugs		-0.59		0.10
		(0.58)		(0.17)
S&P 500	0.50***	0.52***	0.35***	0.35***
	(0.17)	(0.17)	(0.05)	(0.06)
Fed Discount Rate	-0.03	-0.05	-0.03	-0.03
	(0.13)	(0.13)	(0.04)	(0.04)
Observations	84	84	252	252
R-squared	0.933	0.933	0.989	0.989

Regression model includes year fixed effects with standard errors calculated with block bootstrapping. *, **, *** indicate significance at the 0.05, 0.01, and 0.001 levels, respectively.

Supplemental Table 6. Association of changes in total investment or valuation (NBI) with changes in drug price indices (PPI or CPI) and indicators of market conditions (S&P 500, Fed Discount Rate), 2000-2020

	Total investment		NBI	
	(1)	(2)	(3)	(4)
PPI – Pharmaceutical and Medicine Manufacturing	6.77		0.67	
	(7.88)		(0.72)	
CPI – Prescription Drugs		-8.05		0.11
		(11.04)		(1.13)
S&P 500	0.96	1.08	0.98***	0.97***
	(1.20)	(1.19)	(0.11)	(0.11)
Fed Discount Rate	-0.49	-0.55	-0.02	-0.02
	(0.54)	(0.54)	(0.02)	(0.02)
Observations	83	83	251	251
R-squared	0.179	0.176	0.330	0.327

Regression performed on % change in total investment or valuations (NBI) with % change in drug prices (PPI or CPI), S&P 500, and Fed Funds rate. All regressions include year fixed effects and calculate standard errors with block bootstrapping. *, **, *** show significance at the 0.05, 0.01, and 0.001 levels, respectively.

Supplemental Table 7. Lagged regression analysis of factors associated with total investment in biotechnology companies (quarterly lag) or biotechnology valuations (NBI) (monthly lag) and indicators of market conditions (S&P 500, Fed Discount Rate), 2000-2020

	Total investment		NBI	
	(1)	(2)	(3)	(4)
PPI – Pharmaceutical and Medicine Manufacturing	-0.26		0.29	
	(0.67)		(0.23)	
CPI – Prescription Drugs		-0.41		0.10
		(0.65)		(0.18)
S&P 500	0.16	0.15	0.28***	0.29***
	(0.24)	(0.24)	(0.06)	(0.06)
Fed Discount Rate	-0.02	-0.01	-0.04	-0.04
	(0.16)	(0.16)	(0.04)	(0.04)
Observations	83	83	251	251
R-squared	0.927	0.927	0.986	0.986

Regressions were performed between total investment or valuation (NBI) at $period_t$ and indicators of drug prices (PPI or CPI) and market conditions (S&P 500 and Fed Funds rate) at $period_{t-1}$. Regressions include year fixed effects and calculate standard errors with block bootstrapping. *, **, *** show significance at the 0.05, 0.01, and 0.001 levels, respectively.

Supplemental Table 8. Lagged regression analysis of factors including Investment$_{t-1}$ associated with total investment in biotechnology companies (quarterly lag) or biotechnology valuations (NBI) (monthly lag) and indicators of market conditions (S&P 500, Fed Discount Rate), 2000-2020

	Total investment		NBI	
	(1)	(2)	(3)	(4)
Investment$_{t-1}$	-0.07	-0.08	0.60***	0.61***
	(0.11)	(0.11)	(0.06)	(0.06)
PPI – Pharmaceutical and Medicine Manufacturing	-0.22		0.15	
	(0.71)		(0.11)	
CPI – Prescription Drugs		-0.46		0.11
		(0.70)		(0.08)
S&P 500	0.18	0.18	0.05	0.05
	(0.25)	(0.25)	(0.04)	(0.04)
Fed Discount Rate	0.01	0.01	-0.02	-0.02
	(0.18)	(0.17)	(0.02)	(0.02)
Observations	83	83	251	251
R-squared	0.927	0.928	0.991	0.991

Regressions were performed between total investment or valuation (NBI) at period$_t$ and indicators of drug prices (PPI or CPI), market conditions (S&P 500 and Fed Funds rate), and Investment at period$_{t-1}$. Regressions include year fixed effects and calculate standard errors with block bootstrapping. *, **, *** show significance at the 0.05, 0.01, and 0.001 levels, respectively.

Supplemental Table 9. Variable definitions and sources

Variable	Definition	Source
Investment: Funding amount	Includes IPO, follow-on, other public equity deals, uncategorized equity rounds, and venture deals. IPOs include exercised overallotments and proceeds from the sale of common stock, ADS, and warrants, but not the exercise of warrants. Other public equity deals include Private Investment in Public Companies (PIPEs). Financing amounts do not include SPACs or debt deals. Data are aggregated quarterly. Analyses were performed for total investment, public investment (IPOs, follow-ons, and public equity), or private investment (venture and uncategorized equity deals).	BioCentury BCIQ
NASDAQ Biotechnology Index ("NBI")	Size-weighted index of the largest publicly traded biotechnology stocks (month-end).	NASDAQ
Producer Price Index: Pharmaceutical and Medicine Manufacturing ("PPI")	Monthly prices received by pharmaceutical manufacturers relative to prices in December 1981 (not seasonally-adjusted). (PCU32543254)	FRED
Consumer Price Index: Prescription Drugs ("CPI")	Monthly prices paid by urban consumers for prescription drugs relative to prices between 1982 and 1984 (seasonally-adjusted). (CUSR0000SEMF01)	BLS
S&P 500 (S&P)	Size-weighted index of the largest 500 companies traded on U.S. exchanges (month- or quarter-end).	S&P
Fed Funds Rate (Fed Funds)	Monthly Federal Funds Effective Rate at which banks lend to each other (not seasonally adjusted).	FRED

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