VitalTransformation
The impact of health technology made simple

Inflation Reduction Act – Two Years On

Investor Behavior, R&D Impacts, & Proposed Solutions

Version – April 14, 2025

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Executive Summary

IRA has led to:

- A 35% reduction in early-stage phase I and II therapies under development from 2021-2023 among small and midsize biotech companies as measured from IRA's introduction; the average time of phase II and III development is roughly 40 months each, we would expect to see a considerable reduction in the number of FDA approvals in roughly 5 to 6 years.
- A statistically significant reduction in the size of VC investments for small molecules with a high exposure to the Medicare-aged population, defined as exposure greater than 59% of the median population with measured prevalence by indication above the age of 65, after the introduction of the IRA. We see no corresponding reduction in the size of investments for small molecules with a Medicare exposure below the median.
- A statistically significant decline of 74% in the median size of VC investments treating indications with a high exposure to the Medicare-aged population in our cohort – these include Dementia, Non-Small Cell Lung Cancer, Prostate Cancer, Multiple Myeloma, Leukemia (AML), Head and Neck Cancer, Alzheimer's Disease, and others. We also see a marked shift in the number of clinical trials from small to large molecules in areas with a high exposure to the Medicare-aged population, such as neurology and autoimmune disease classes.

When indications have exposure to the IRA's impacts, we observe divergent results between large and small molecules; this presents statistically significant evidence of disincentives caused by IRA for the Medicare-aged population.

Removing the 'pill penalty' by beginning IRA price setting for both small and large molecules after 13 years increases approvals targeting the Medicare-aged population by roughly 20%.

Beginning IRA price setting after 15 years is estimated to reduce the number of medicines lost to the Medicare-aged population by roughly 50%.

Background

- The CBO predicted that therapies not developed due to the IRA will only be 1% of the total over 30 years, or 15 new therapies of a predicted 1,300. This total has been widely disseminated by the media.
- Less discussed is CBO's accompanying statement, "CBO did not predict what kind of drugs (therapies) would be affected," that is, the CBO modeled the IRA's impacts in the aggregate.
- IRA's price setting will fall upon the most successful products, which will eventually affect most manufacturers. The profits of the Biopharma sector follow a classic Pareto curve where 20% of successful products fund a substantial portion of the entire R&D ecosystem.
- Importantly, the CBO's analysis did not segment the IRA's impacts by large or small molecules, or by measuring a specific indication's exposure to the Medicare-aged population, nor by differentiating late-stage phase III research or from different clinical phases where the IRA's impact is most likely to first appear by changing VC/Angel investing behavior.
- Research presented on September 17th, 2024, to the Senate Finance Committee replicated the CBO's aggregate approach, stating that the declines in the market are not caused by the IRA, but follow the broad market trend and recession caused by the COVID-19 pandemic.
- Responding to these limitations, Vital Transformation (VT) built a research cohort to identify the IRA's impacts in early-stage phase I and II developments for both large and small molecules in firms with a valuation ≤ $2 billion, IRA's impacts on a given indication's exposure to the Medicare-aged population, and changes to early-stage investment patterns since the law's passage.

Methodology

IRA's Impact on Early-Stage Investments

- VT extracted a cohort of 1137 clinical trials from the period of January 1, 2018, through May 6, 2024, of US companies with a market capitalization or valuation ≤ $2 billion USD as it is a standard forward looking risk-weighted net present value of a successful firm at the time of a therapeutic product's FDA submission for marketing authorization.
- VT then engaged in a company by company search in Biomedtracker and clinicaltrials.gov, to determine which of these development programs had a therapy showing potential for success. This research yielded 228 'lead assets', segmented by indication and clinical trial phase.
- These developments were further filtered to focus on only those lead assets in Phase I and II clinical trials, yielding 161 e arly-stage therapies.
- VT executed a forensic audit of all investment activity that could be identified for each lead asset from the period of Janua ry 1st, 2018, through August 16th, 2024, using the combined resources of Pitchbook, Biomedtracker, Securities and Exchange Commission audited Federal filings, and published annual corporate reports.
- IRA's investments and R&D impacts have been calculated in July 2024 constant dollars with a cost of capital of 10%.
- Our investment criteria is focused on revenue generated from VC, angel, equity, partnering and licensing activity – debt assumed by the developing company has been excluded. Where a clear audit trail of investment or ownership was not possible, those companies and developments have been excluded from our analysis.
- The focus of this analysis is Type-1 novel FDA approved therapies; follow-on indications or post-approved combination therapies have been excluded from this analysis.

Sources Used in our Research

- Medicare B & D Dashboards
- SEC 10-K, 10-Q Corporate Filings
- Annual audited shareholder reports and Press Releases
- Clinicaltrials.gov
- Pitchbook
- Biomedtracker
- IQVIA - MIDAS

$2 billion as a valuation - VC expectations of their return on investment

	rNPV			VC Values	Comparison of rNPV and VC valuation	VC's Equity interest			
Development phase	Exp. PV of costs at phase launch	Expected PV of after-tax cash flows at phase launch	rnPV at Phase launch	VC Values	VC value/rNPV value	VC contribution	VC equity interest (based on VC valuation)	VC equity interest (based on rNPV valuation)	Difference
Phase I	$ 77.91	123.73	$ 45.82	$ 34.11	74%	$ 50.00	59.4%	52.2%	7.3%
Phase II	$ 117.23	253.82	$ 136.59	$ 87.31	64%	$ 50.00	36.4%	26.8%	10%
Phase III	$ 241.10	964.16	$ 723.05	$ 357.63	49%	$ 50.00	12.3%	6.5%	6%
NDA submission	$ 2.4	2099.87	$ 2,097.47	$ 1,464.84	70%	$ 50.00	3.3%	2.3%	1%

VC Equity %

- $2 billion is a standard forward-looking risk-weighted net present value (rNPV) of a successful firm at the time of a therapeutic product's FDA submission for marketing authorization – this is why it is used as the valuation baseline for our analysis.
- VC equity as a percent of a firm's total funding peaks between Phase I and II, which is the focus of this research.
- Our valuation of $2 billon per firm was filtered in our clinical trial query in Biomedtracker, and verified when developing our cohort of lead assets by Pitchbook from 5/9/24 – 9/15/24.

Source: Journal Of Investment Management, Vol. 22, No. 1, (2024), pp. 36–57 © JOIM 2024

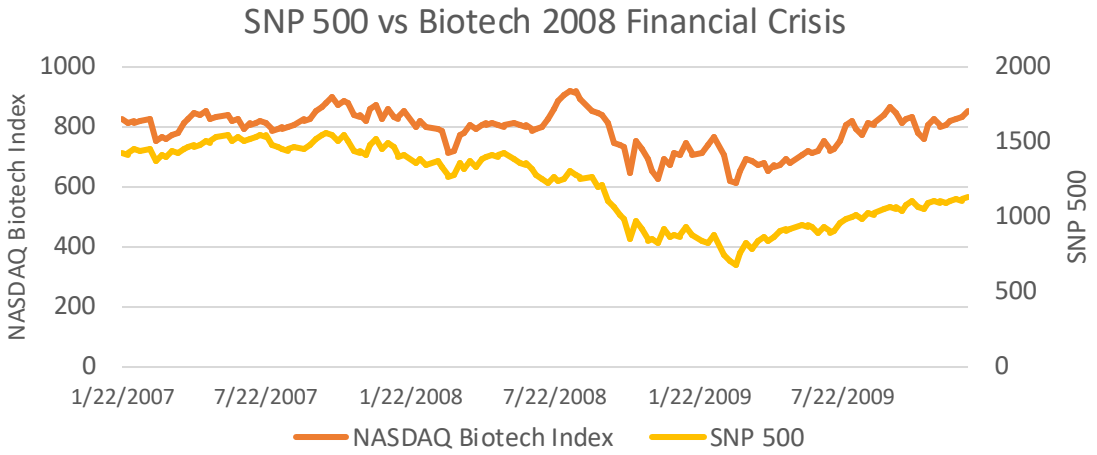
IRA's Impacts Upon VC, Angel and Early-Stage Investments
Phase I and II Developments

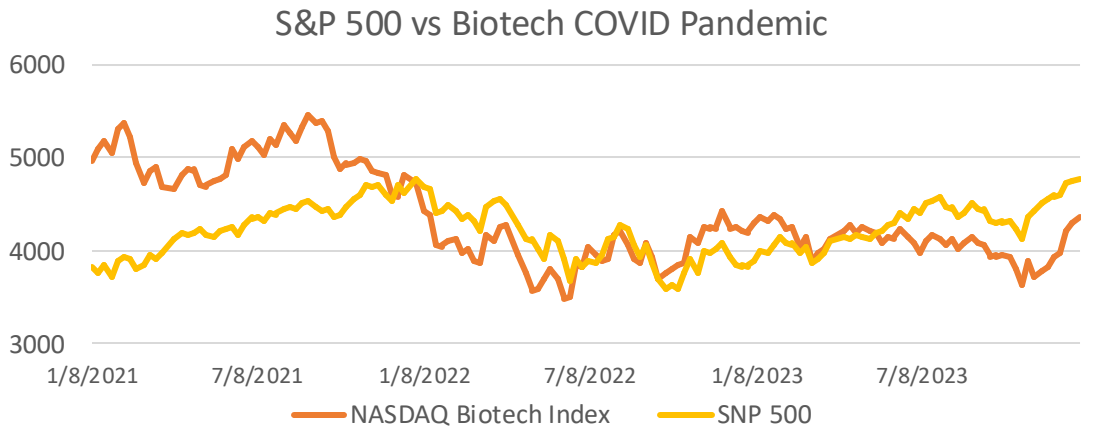
"When you only have nine years to pay back that return for a small molecule, versus thirteen, which IRA has done . . . you don't hear me funding a small molecule program."

Steven Potts, CEO of SLAM BioTherapeutics, Chair, Drug Development Council of the International Cancer Advocacy Network

Vital Health Podcast, 10/8/24

In 2008, the NASDAQ biotech index increased in value against S&P 500

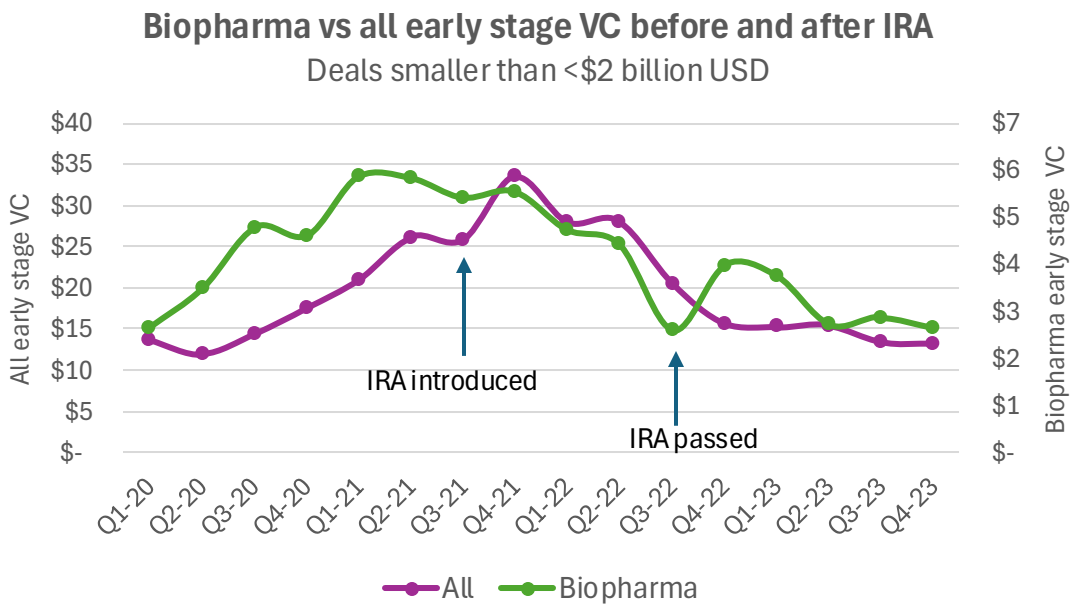




- During the 2007/2009 global financial crisis, the NASDAQ Biotech Index performed better than the broad market S&P 500.
- However, when one looks at the performance of the NASDAQ Biotech Index compared to the S&P 500 during the COVID-19 pandemic, the biotech index performed less well than the broad market average, with a marked divergence after the introduction of IRA.
- These charts show a marked change in the perception of the value of biotech against broad market declines – this implies an impact of the IRA upon biotechnology valuations.

Source: NASDAQ and New York Stock Exchanges

Biopharma VC and angel deals decline below total VC market after IRA's introduction



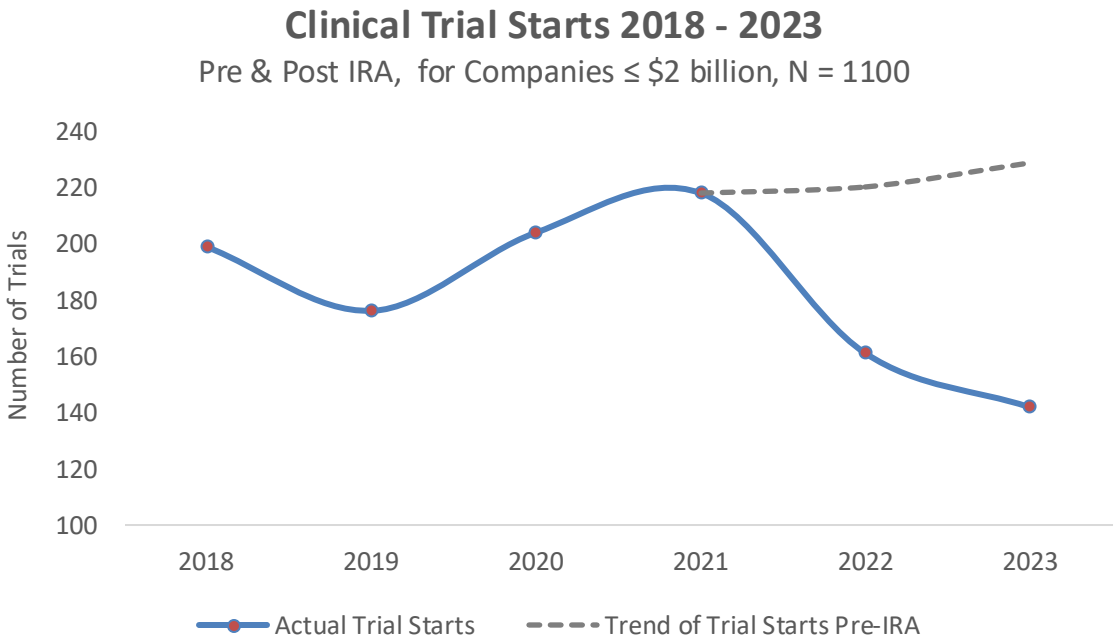
Source: Pitchbook, early-stage VC and angel biopharmaceutical investments

On December 21, 2023, the CBO released a letter stating, "There is currently no evidence of a systematic decrease in the percentage of venture capital flowing to pharmaceutical companies after August 2022."

Vogel et al., Nature, and others have stated that early-stage and late-stage biopharma funding decreases since 2021 were due to the pandemic.

However, when one tracks the movement of early-stage VC funding relative to the legislative history of the IRA, we find that biopharma VC, which grew faster compared to all VC before IRA, drops below general VC growth after IRA's introduction.

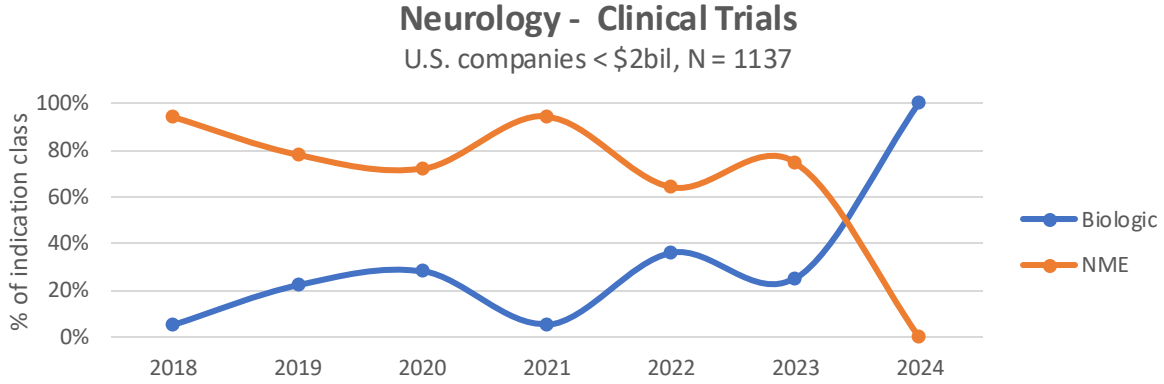
There has been a 35% reduction in clinical trial starts since the introduction of IRA

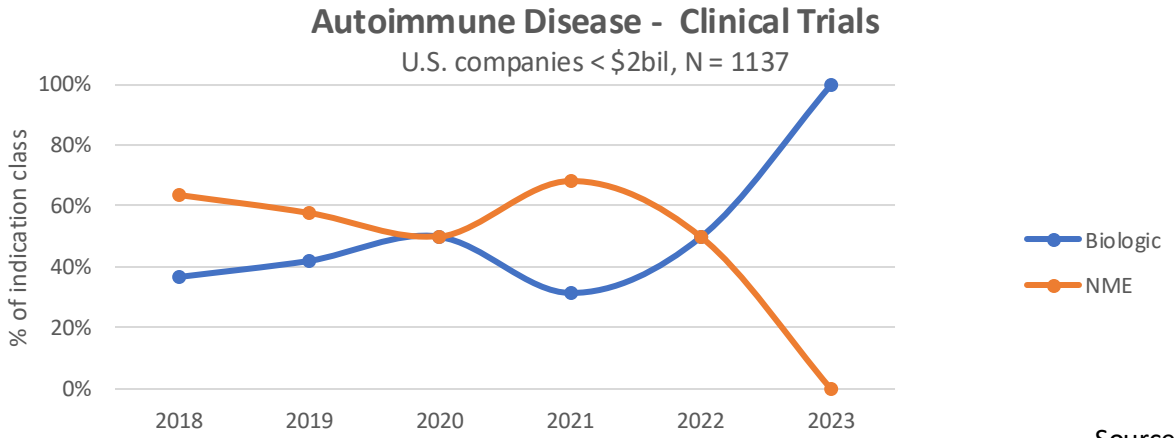


Source: Biomedtracker, Clinicaltrials.gov

- From our cohort of early-stage clinical trials for companies with a valuation of less than $2 billion, we find a total decline of 35% in clinical trial starts after the introduction of the IRA on September 27th, 2021.
- This decline, as measured in monthly clinical trial starts before and after the introduction of the IRA, is statistically significant ($p \leq 0.0179$).
- As the average length of clinical development for phase II and III combined is 80 months, we would expect a considerable reduction in the number of FDA approvals in roughly 5 to 6 years.

There is a shift in the number of clinical trials moving from small (NME) to large (Biologic) molecules in areas with a high exposure to the Medicare-aged population





- Database of 1137 clinical trials being launched by US companies with a market capitalization or valuation of less than $2 billion USD.
- We restricted this search to Phase I and II trials only, to capture early-stage developments that could react to the passage of IRA.
- In the clinical areas of Autoimmune disorders and Neurology, where we would expect to see a high-exposure to the Medicare-aged population, we observe a large shift in the number of clinical trials being launched from small (NME) to large (Biologic) molecules.

Sources: Biomedtracker, Pitchbook, SEC filings, Clinicaltrials.gov

Charles River cuts 3% of workforce

Sep 12, 2024

FIERCE Biotech

"Charles River CEO James Foster said he did not expect demand for the CRO's services would improve throughout the rest of 2024 . . .Foster warned that demand for Charles River's services could decline further in the remainder of the year."

PharmExec.com News Multimedia Conferences Publications

What's Causing the Slowdowns in Trial Starts?

March 5, 2024
By Miranda Schmalfuhs

BioWorld™

Biopharma clinical updates February 2024

Clinical trial updates in 2024 fall below last year's averages

By Amanda Lanier March 28, 2024

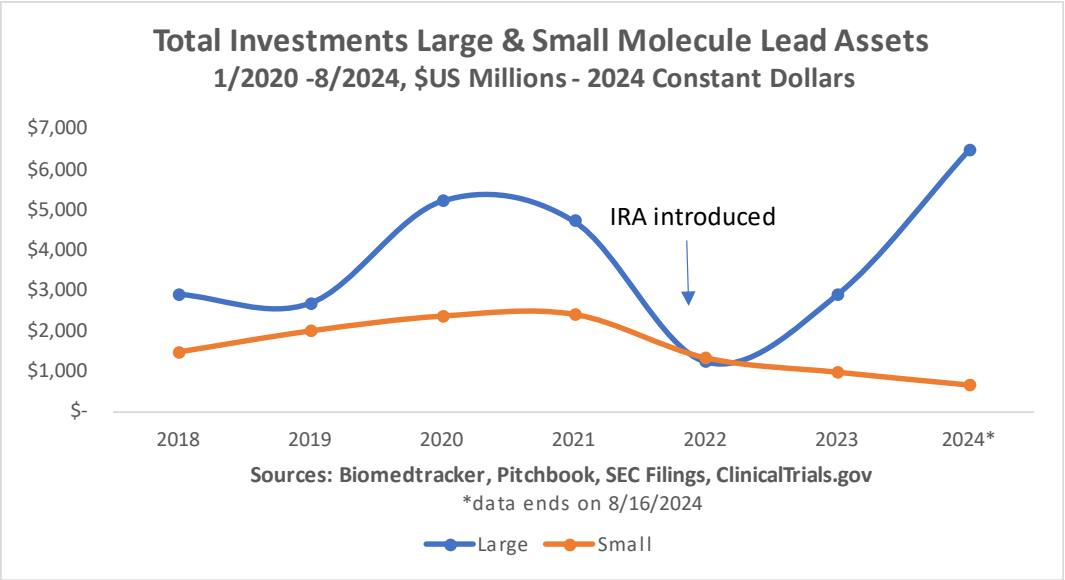
Charles River to close '15 smaller sites' as demand for early research declines

ENDPOINTS NEWS

November 8, 2024 11:28 AM EST

There is a shift from small (NME) to large (Biologic) molecules in the total aggregated amount invested into early-stage clinical trials

U.S. companies ≤ $2 billion, Phase I and II, 2024 constant dollars, 1/1/2018 – 8/16/2024



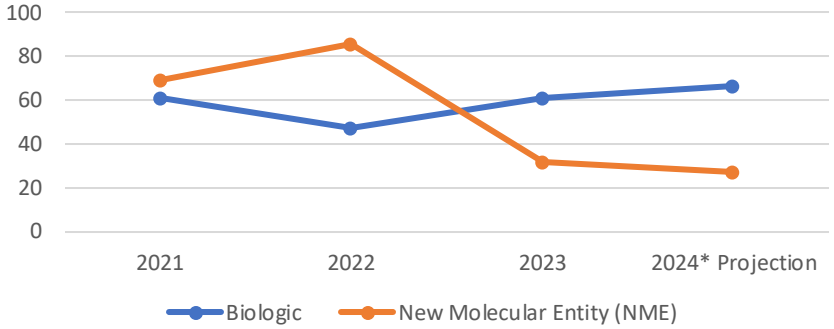
Sources: Biomedtracker, Pitchbook, SEC filings, Clinicaltrials.gov

- Vital Transformation constructed a dataset of 161 lead assets under Phase I and II clinical development by US companies with a valuation ≤ $2 billion from our cohort of clinical trials.
- At the time of the introduction of IRA in 2021, we see a reduction of 68% in the overall funding of small molecules and a marked shift in the trend of total annual investments.
- We observe a substantial drop in large molecule funding in 2022, followed by a bounce in increased funding from 2023 forward, thus resuming a consistent trend before and after IRA.
- The total aggregate funding for biologics in our cohort is now 10x larger than that of small molecules, based upon 7 months of data in 2024.

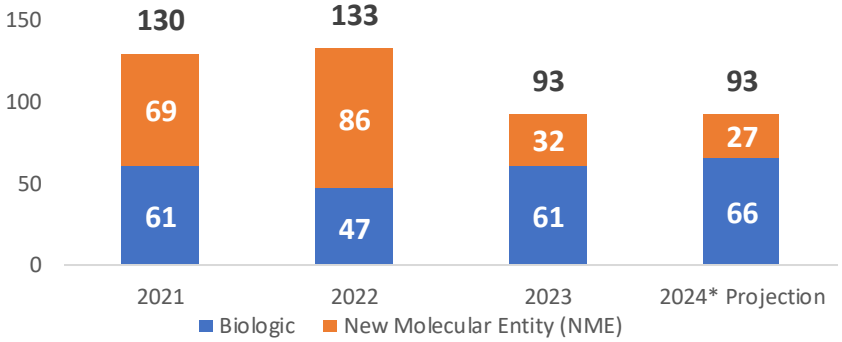
Since the IRA's introduction, the mix of small and large molecule programs has skewed heavily toward large molecules

U.S. company lead assets, ≤ $2 billion, Phase I and II, 1/1/2021 – 8/16/2024

Small molecule programs have declined compared to large molecules



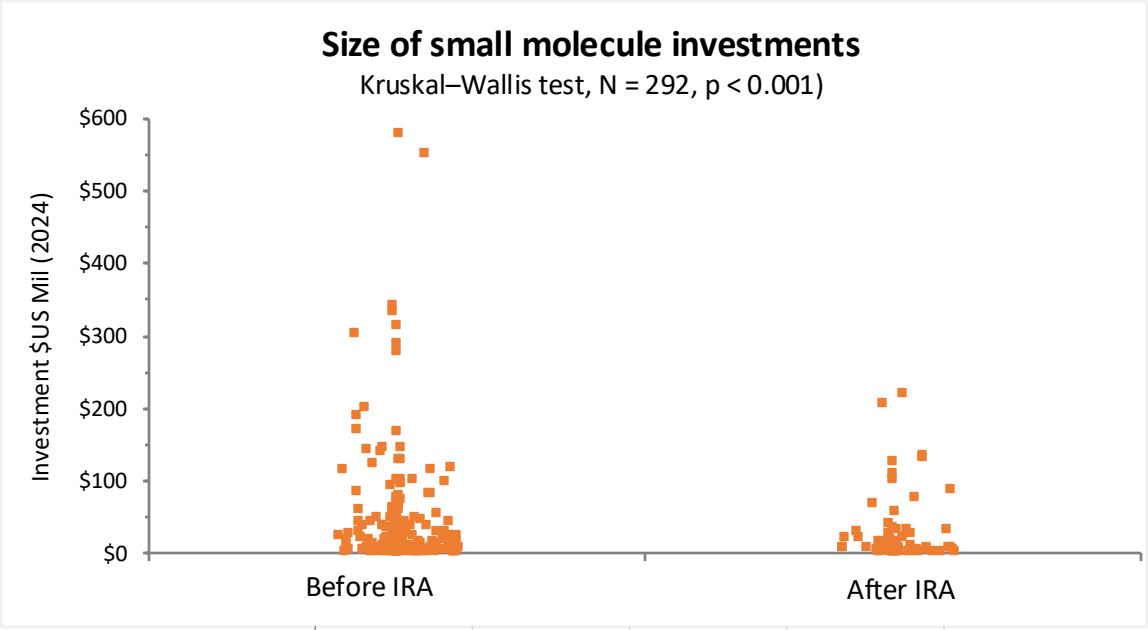
Large molecules are 68% of the 2024 cohort under development



- In our cohort of 161 lead assets, small molecule therapies under development made up roughly half of our cohort before the passage of the IRA.
- Since the IRA's introduction there has been a marked decline in small molecule lead assets.
- 2021 –2023 are actuals. For 2024, we project that 70% of developments will be for large molecules.

Early-stage investments into small molecules have declined after IRA

U.S. companies ≤ $2 billion



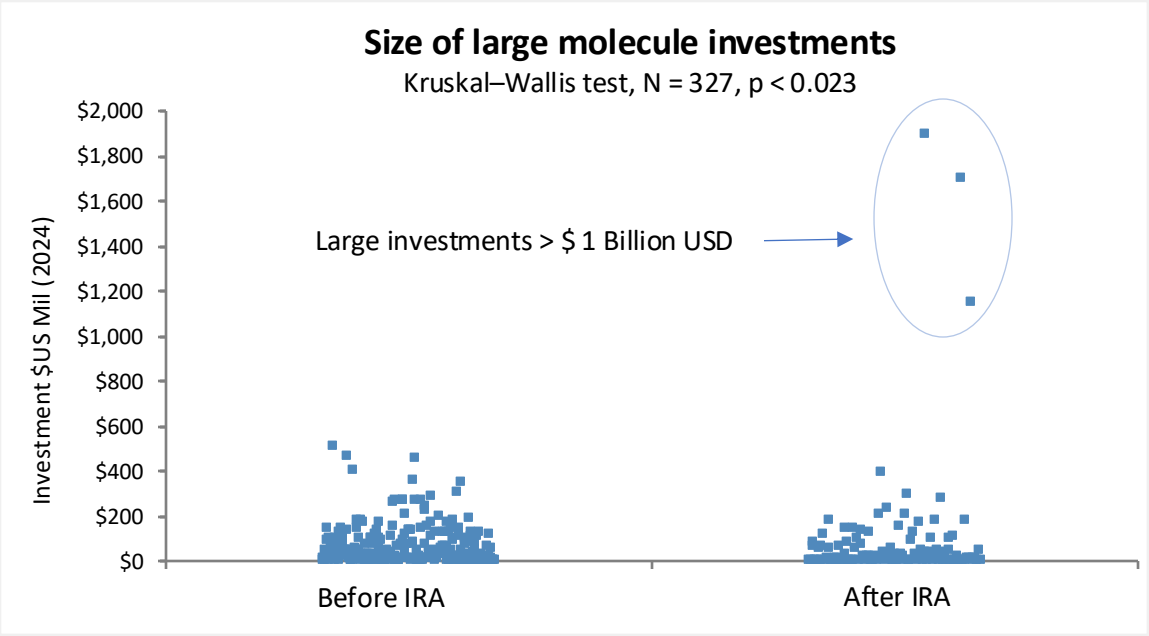
Investment $US Mil (2024) by IRA	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Before IRA	$0.07	$4.11	$14.72	$46.00	$577.30
After IRA	$0.25	$2.09	$6.18	$26.61	$218.36

- To determine if the size of early-stage small molecule investments was impacted by the introduction of the IRA, a Kruskal–Wallis test for a difference in the median size of investments pre and post IRA was utilized comparing the size of investments into 161 lead assets under Phase I and II clinical development in small and midsize biotech companies.

- The results of this test showed a statistically significant decline in the size of investments into small molecules after the introduction of the IRA ($p < 0.001$, X^2 approximation = 6.65).

Investments into large molecules have also declined after IRA, but are impacted in the aggregate by several large outliers

U.S. companies ≤ $2 billion



Investment $US Mil (2024) by IRA	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Before IRA	$ 0.20	$ 11.75	$ 45.60	$ 117.44	$ 514.30
Ater IRA	$ 0.27	$ 4.12	$ 20.60	$ 76.00	$ 1,900.00

- A Kruskal–Wallis test indicates a statistically significantly decline in the median size of investments into large molecules post IRA ($p < 0.0013$)
- The total of investments into large molecules increased in 2023 and 2024 due primarily to three large post-IRA investments of over $1 billion each; the shift in median or mean size of investments is not statistically significant.
- The Medicare exposure for these large investments was near or below the median in our cohort (HER2+ Breast Cancer with 50%, alpha-1 antitrypsin deficiency (dAATD) with 27%, and kidney transplant rejection with 60%) (slide 20).

IRA's Impacts on New Therapies for the Medicare-Aged Population

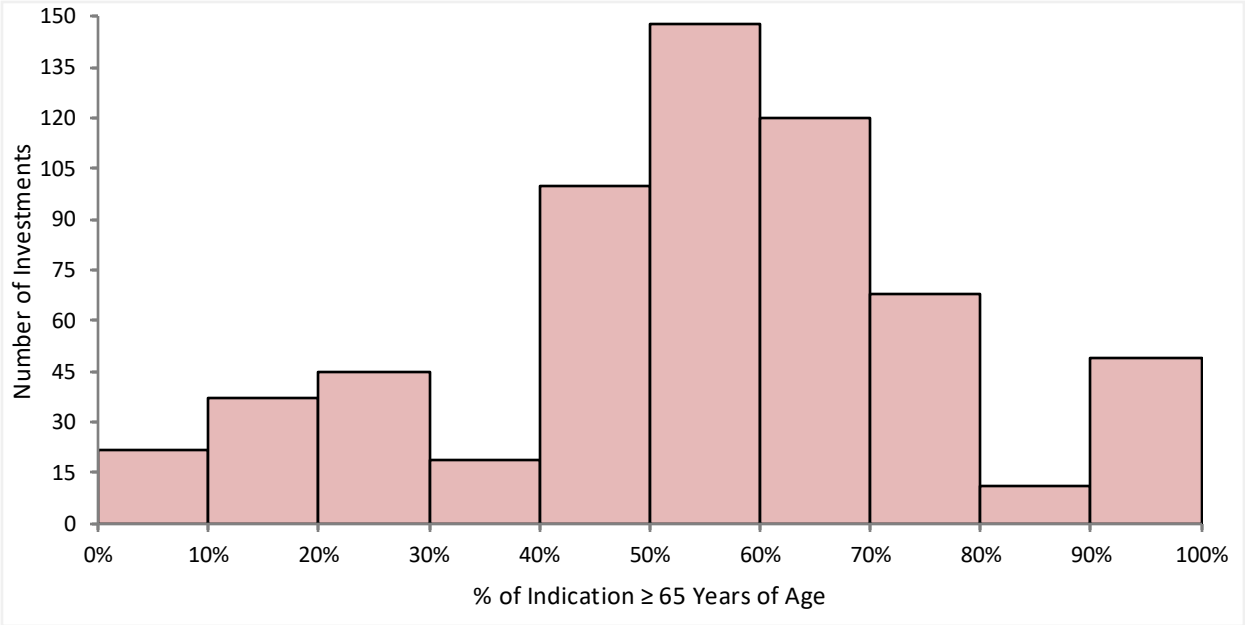
"I've defunded some programs and we've told our companies. . . stay away from any disease of aging where you're going to be heavily dependent on Medicare."

Peter Kolchinsky, Founder of No Patient Left Behind, Founder and Managing Director, RA Capital Management

Vital Health Podcast, 1/17/24

Cohort distribution of exposure to the Medicare-aged population by individual investment

N = 619, 1/1/2018 – 8/16/2024



	Minimum	1st quartile	Median	3rd quartile	Maximum
% ≥ 65	0%	43%	59%	65%	95%

This chart shows the frequency distribution of 619 individual investments by their exposure to the Medicare-aged population by indication, i.e., the percent of each individual therapy's population measured by indication that is over 65 years of age, and thus those investments are exposed to IRA price setting.

Our thesis is that the higher an indication's exposure is to the Medicare-aged population, the more likely it is that investors will change their behavior after the introduction of IRA.

In our entire cohort, the median exposure to the Medicare-aged population is 59%.

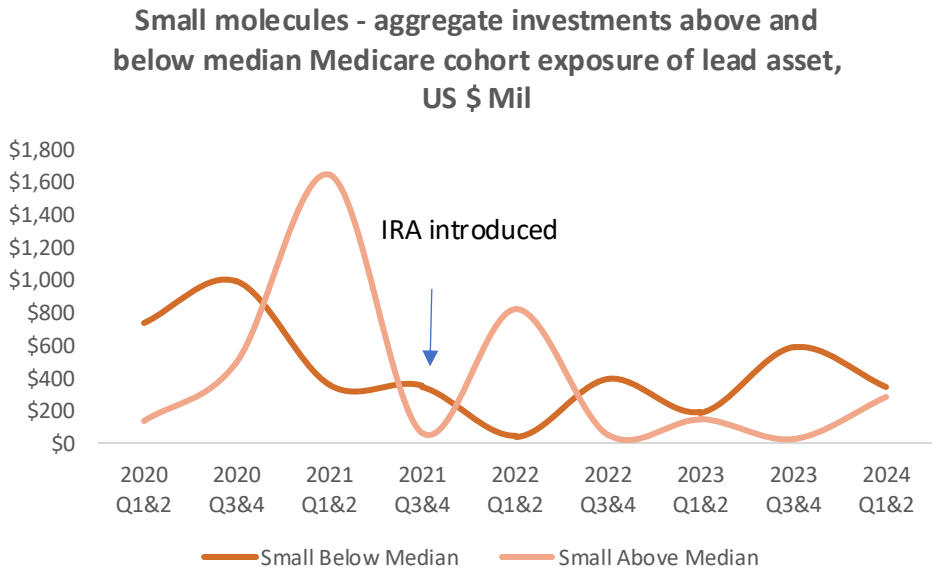
Investments aggregated by indication with a high exposure to the Medicare-aged population have seen a 74% decline in their median size after the introduction of the IRA. U.S. companies ≤ $2 billion, N=244

Indication	# of Investments	% Population ≥ 65	$ Before IRA	$ After IRA
Non-Small Cell Lung Cancer (NSCLC)	36	72%	$2,045	$1,040
Alzheimer's Disease (AD)	30	95%	$178	$108
Multiple Myeloma (MM)	26	65%	$1,936	$843
Acute Myelogenous Leukemia (AML)	25	61%	$1,036	$535
Pancreatic Cancer	13	69%	$267	$302
Head and Neck Cancer	11	70%	$123	$59
Prostate Cancer	11	63%	$1,721	$43
Gastric Cancer	10	60%	$337	$72
Non-Tuberculous Mycobacteria (NTM)	8	60%	$178	$85
Wet Age-Related Macular Degeneration (Wet AMD) (Ophthalmology)	8	90%	$200	$626
Acute Renal Failure (ARF)	7	67%	$176	$0
Cartilage and Joint Repair	7	75%	$49	$14
Amyotrophic Lateral Sclerosis (ALS)	6	64%	$68	$204
Idiopathic Pulmonary Fibrosis (IPF)	6	90%	$110	$37
Kidney Transplant Rejection	6	60%	$324	$1,347
Rheumatoid Arthritis (RA)	6	61%	$44	$0
Acute Decompensated Heart Failure (Acute HFrEF)	5	80%	$175	$16
Dementia	4	95%	$716	$0
Autoimmune Disorders	3	61%	$50	$0
Mesothelioma	3	80%	$380	$0
Renal Cell Cancer (RCC)	3	71%	$35	$47
Stroke Prevention in Atrial Fibrillation (SPAF)	3	76%	$0	$15
Bladder Cancer	2	75%	$51	$45
COVID-19 Treatment	2	65%	$24	$0
Cerebral Edema	1	80%	$2	$0
Chronic Cough	1	90%	$44	$0
Influenza	1	65%	$0	$132
		Total	**$10,268**	**$5,569**
		Median	**$175**	**$45**

- To determine if investors are avoiding the Medicare-aged population after IRA's introduction, we tested those indications where the disease prevalence over 65 years of age was greater than the cohort median of 59%, i.e., a 'high' exposure.
- We find that, since the introduction of the IRA, the median size of 244 individual investments show a statistically significant decline of 51% ($p \leq 0.008$).
- Measured at the cohort level, the median indication has seen a reduction in its aggregate investment of over 74%.

Investments into small molecule indications by exposure to Medicare before and after the introduction of the IRA

1/1/2018 – 8/16/2024

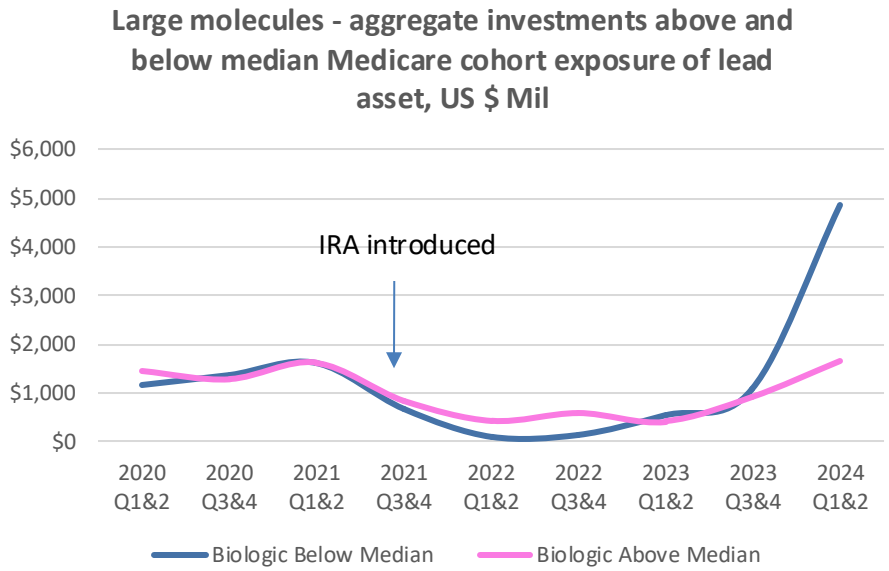


Shifts in early-stage (phase I and II) investments for small (NME) molecule lead assets above and below the median of Medicare exposure (59%) in our cohort before and after introduction of the IRA. Data for U.S. companies with a market value ≤ $2 billion, values in 2024 constant dollars, 1/1/2020 – 6/30/2024.

- Testing the size of investments from 1/1/2018 through 6/30/2024, the size of small molecule investments **above** the median of exposure to the Medicare-aged population show a statistically significant decline post-IRA ($p \leq 0.0488$).
- Small molecules **below** the median of exposure to Medicare we find no statistically significant change in the size of investments post-IRA ($p \leq 0.1748$).
- Small molecules behave differently based upon their exposure to the Medicare aged population after IRA's introduction.

Investments into large molecule indications by exposure to Medicare before and after the introduction of the IRA

1/1/2018 – 8/16/2024

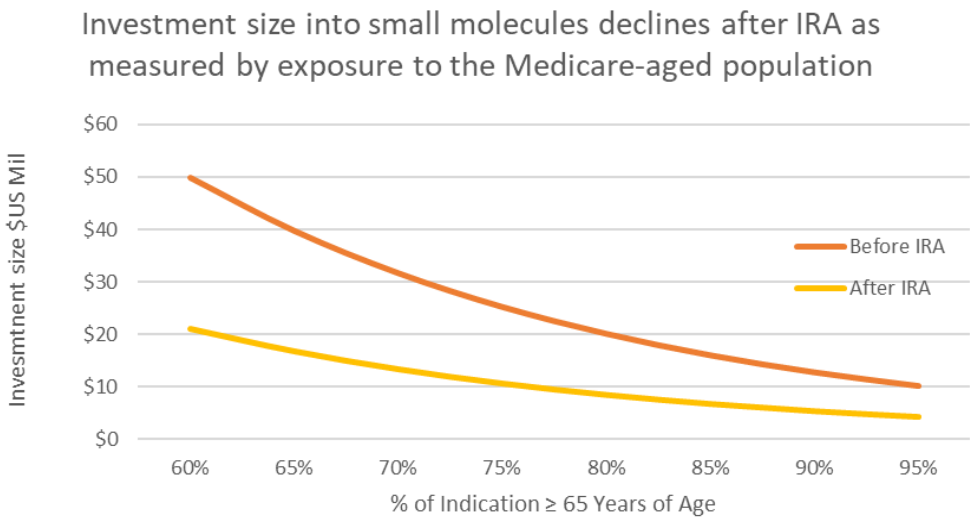


Shifts in early-stage (phase I and II) investments for large molecule lead assets above and below the median of Medicare exposure (59%) in our cohort before and after introduction of the IRA. Data for U.S. companies with a market value ≤ $2 billion, values in 2024 constant dollars, 1/1/2020 – 6/30/2024.

- Testing large molecules showed no statistical difference in the size of investments by median exposure to the Medicare-aged population before and after the IRA – investors into large molecules do not change their behavior based upon Medicare exposure after IRA's introduction.
- Testing the median difference in the decline of investments for both small and large molecules with a high Medicare exposure shows that the decline for small molecules is significantly greater than those for large molecules after IRA's introduction ($p \leq 0.0002$)

Investments into small molecule indications with a high exposure to Medicare before and after the introduction of the IRA

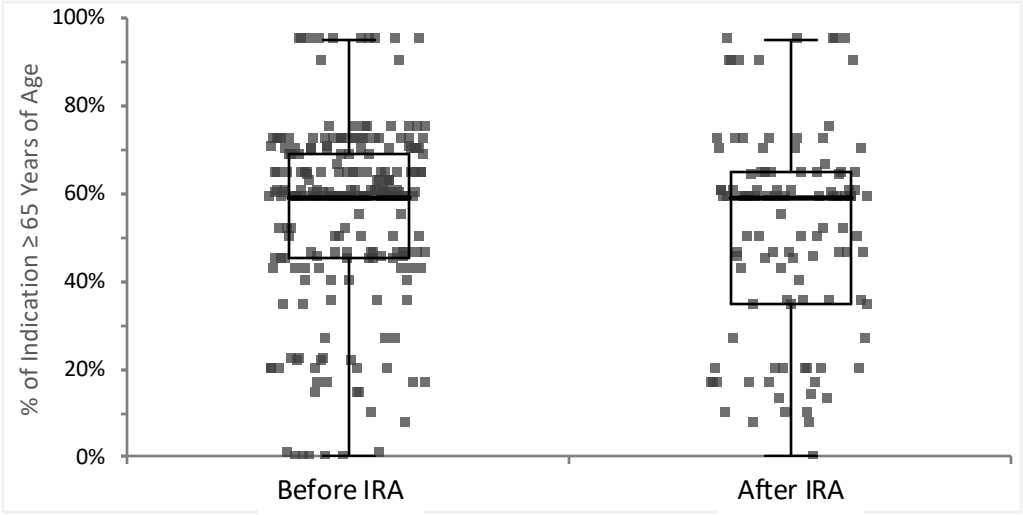
1/1/2018 – 8/16/2024



Multiple regression testing IRA's impact upon the size of early-stage Investments into small molecule indications with a high exposure to the Medicare-aged population, U.S. companies < $2bil, Phase I and II, 2024 constant dollars, 1/1/2018 – 8/16/2024

- This test measures the impact of an indication's exposure to the Medicare-aged population on the size of small molecule investments before and after the introduction of the IRA.
- For indications whose population over 65 years of age is above the median Medicare-aged exposure, the IRA has a statistically significant negative impact (of roughly minus one-half) on the size of investments ($P < 0.0018$).
- If these impacts are due to the pandemic and not the IRA, as stated in several studies, we would expect to observe similar results in large molecules.

Large molecule exposure to the Medicare-aged population before and after IRA is unchanged
1/1/2018 – 8/16/2024



% ≥ 65 by IRA	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Before IRA	0.0%	45.0%	59.6%	68.8%	95.0%
After IRA	0.0%	40.5%	59.0%	64.8%	95.0%

Histogram showing the frequency of investments into large molecules, % of indication population ≥ 65 years of age before and after IRA's introduction. U.S. companies < $2bil, Phase I and II, N = 327

- Testing large molecules by their exposure to the Medicare-aged population shows no statistically significant difference in the median or the mean size of investments before and after IRA's implementation.
- The IRA does impact the size of large molecule investments statistically when testing the entire cohort (slide 17).
- For large molecules, IRA's introduction does not alter their degree of Medicare exposure as the median frequency of investments remains nearly unchanged (59.6% to 59%)
- We interpret this result to mean that, post-IRA, investors perceive large molecules to be a lower investment risk relative to small molecules.

Alternatives to 9 - 13
Legislative Changes to IRA Ensuring R&D in Medicare is Sustainable

"The pharmaceutical industry invests 25% of total sales into R&D. . . what is a company going to do with less revenues? When Lipitor went off patent . . we closed research sites around the globe. Fewer researchers, and fewer research programs. Is this really what we want to do?"

John LaMattina, former President of Pfizer Global Research and Development, Forbes contributor.

https://omny.fm/shows/vital-health-podcast/john-lamattina-defending-pharma-profits

Methodology

Modeling IRA's price setting at years 9 and 13 and then removing the 'pill penalty'

348 therapies were added by top CMS spending in Part B and D

- Based on the 30 largest selling products over the last 10 years, VT generated two baseline average US revenue curves over the product lifecycle (pre- and post- loss of exclusivity); one for small molecule therapies and one for large molecule therapies. This profile was used to forecast revenues from 2026 to 2035 for the entire current Medicare parts B & D cohort.
- VT built a computer simulation that ranks new therapies by their modeled future sales and then re-sorts the cohort based upon the IRA's assumed negotiated price outcomes.
- Maximum Fair Prices in our modeling incorporate CMS' announcement on August 14, 2024.
- We have adjusted the interpretation of biosimilar entry to account for the exemption of therapies that are likely to be approved within a large molecule's 24-month patent expiration window. In these cases, we assume a biosimilar will enter the market.
- Our IRA impacts are based on net revenues – rebates are calculated by audited revenues declared in SEC 10-K & 10-Q reports, with the indications weighted by disease prevalence for those $\geq$ 65 years of age and exposure to IRA price setting.

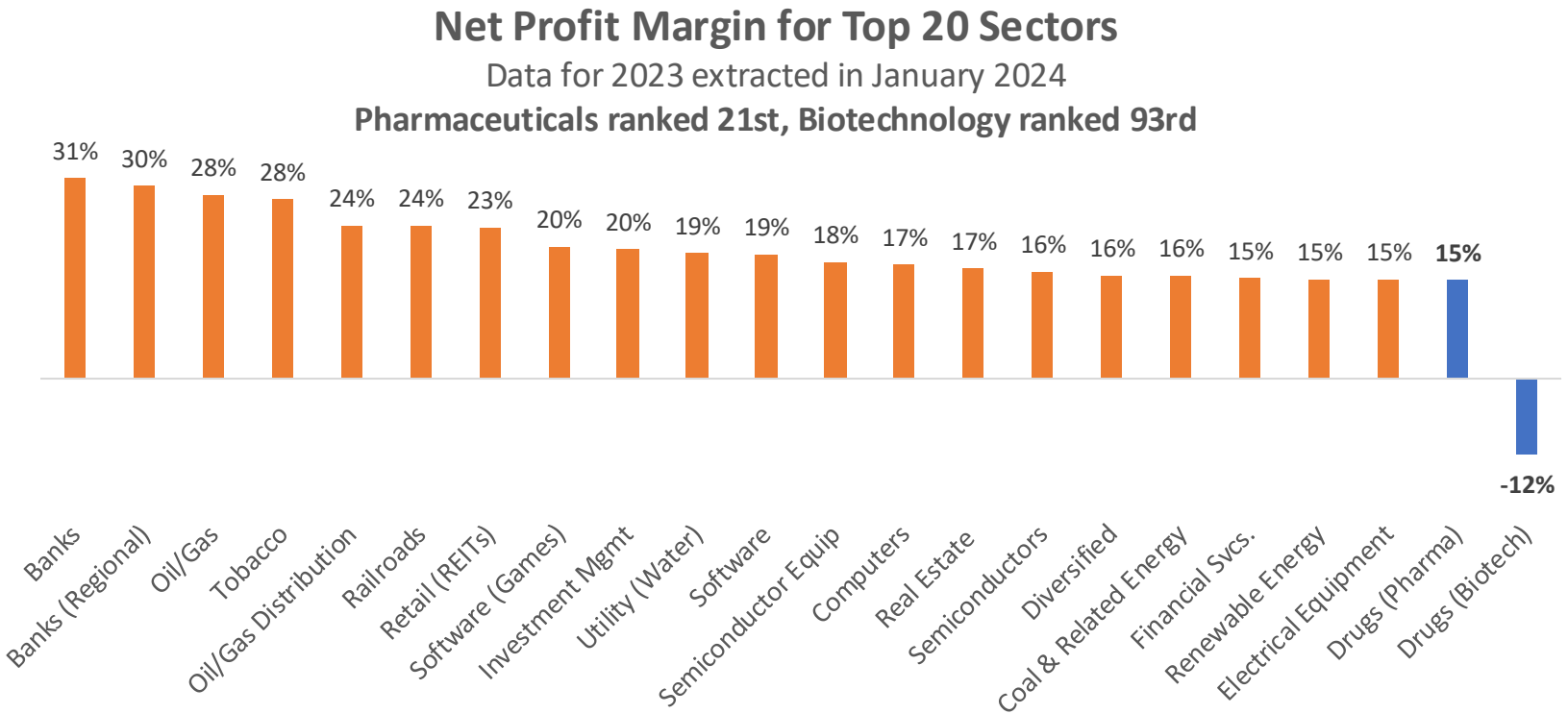
Methodology (continued)

Modeling IRA's price setting at years 9 and 13 and then removing the 'pill penalty'

348 therapies were added by top CMS spending in Part B and D

- Part B therapies are exempted from price setting until 2028, large molecules with Part D revenue are modeled from 2026.
- In terms of price setting, for long-monopoly therapies, where at least 16 years have elapsed since approval or licensure (excluding vaccines), a 40% retention of net revenue is assumed. For short-monopoly therapies, which encompasses all other therapies, a 75% net revenue retention is assumed. For 2030 and after, any extended-monopoly therapies where at least 12 years but less than 16 years have elapsed since approval or licensure (excluding vaccines) 65% net revenue retention is assumed.
- VT alters the modeling assumptions from 9 – 13 years, to just 13 years for all therapies, thereby removing the 'pill penalty'.
- The IRA's impact upon discovery of a new therapy due to reduced net revenue is modeled using a cost of capital of 10% based upon industry revenue allocations as a percentage of free cashflows lost; all monetary values are in constant 2024 USD.

Despite the rhetoric, the U.S. pharmaceutical sector in 2023 was not in the top 20 by net profitability



Source: https://pages.stern.nyu.edu/~adamodar/New_Home_Page/datafile/margin.html

IRA Maximum Fair Prices

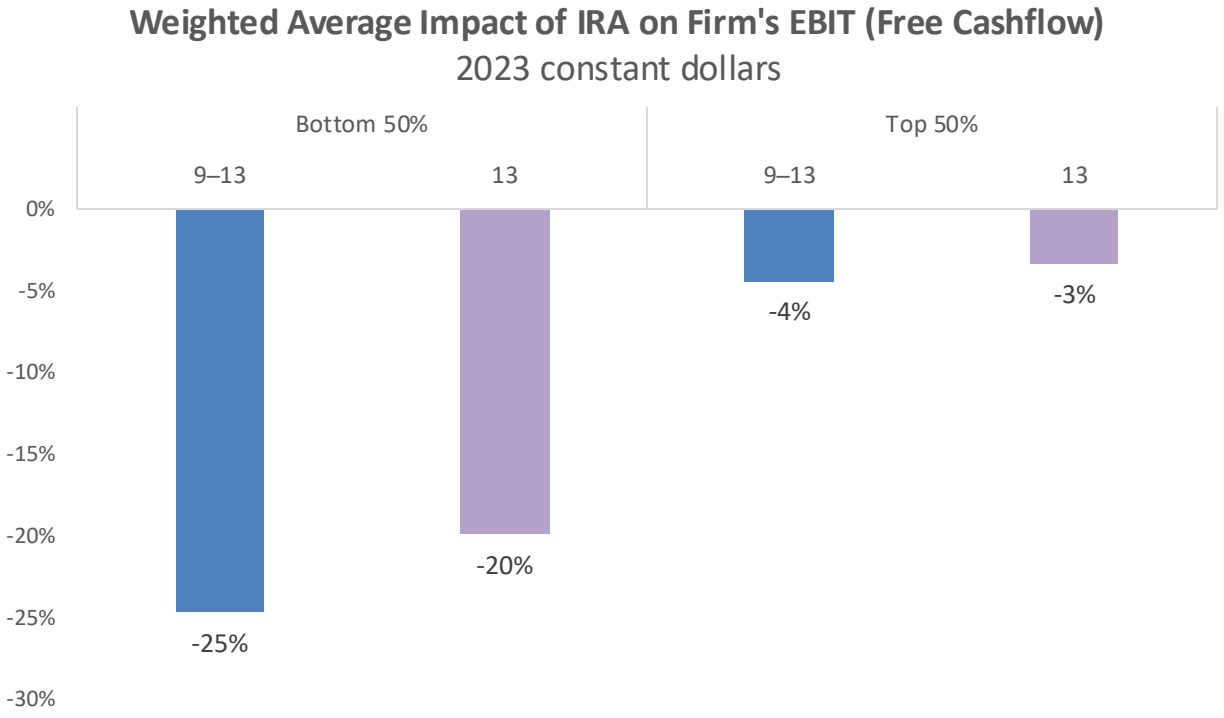
$US Mil

Therapy	List Price Pre-IRA	MFP	Price Change
Eliquis	$ 521	$ 231	-56%
Jardiance	$ 573	$ 197	-66%
Xarelto	$ 517	$ 197	-62%
Farxiga	$ 556	$ 178	-68%
Entresto	$ 628	$ 295	-53%
Enbrel	$ 7,106	$ 2,355	-67%
Imbruvica	$ 14,934	$ 9,319	-38%
Stelara	$ 13,836	$ 4,695	-66%
Januvia	$ 527	$ 113	-79%
Fiasp/NovoLog	$ 495	$ 119	-76%

IRA's announced maximum fair prices (MFPs) are substantially lower than VT's initial 2023 model presented at the BIO conference. Adjustments have been made to our modeling strategy to reflect these changes.

https://www.cms.gov/newsroom/fact-sheets/medicare-drug-price-negotiation-program-negotiated-prices-initial-price-applicability-year-2026

Impact of moving from 9-13 to just 13

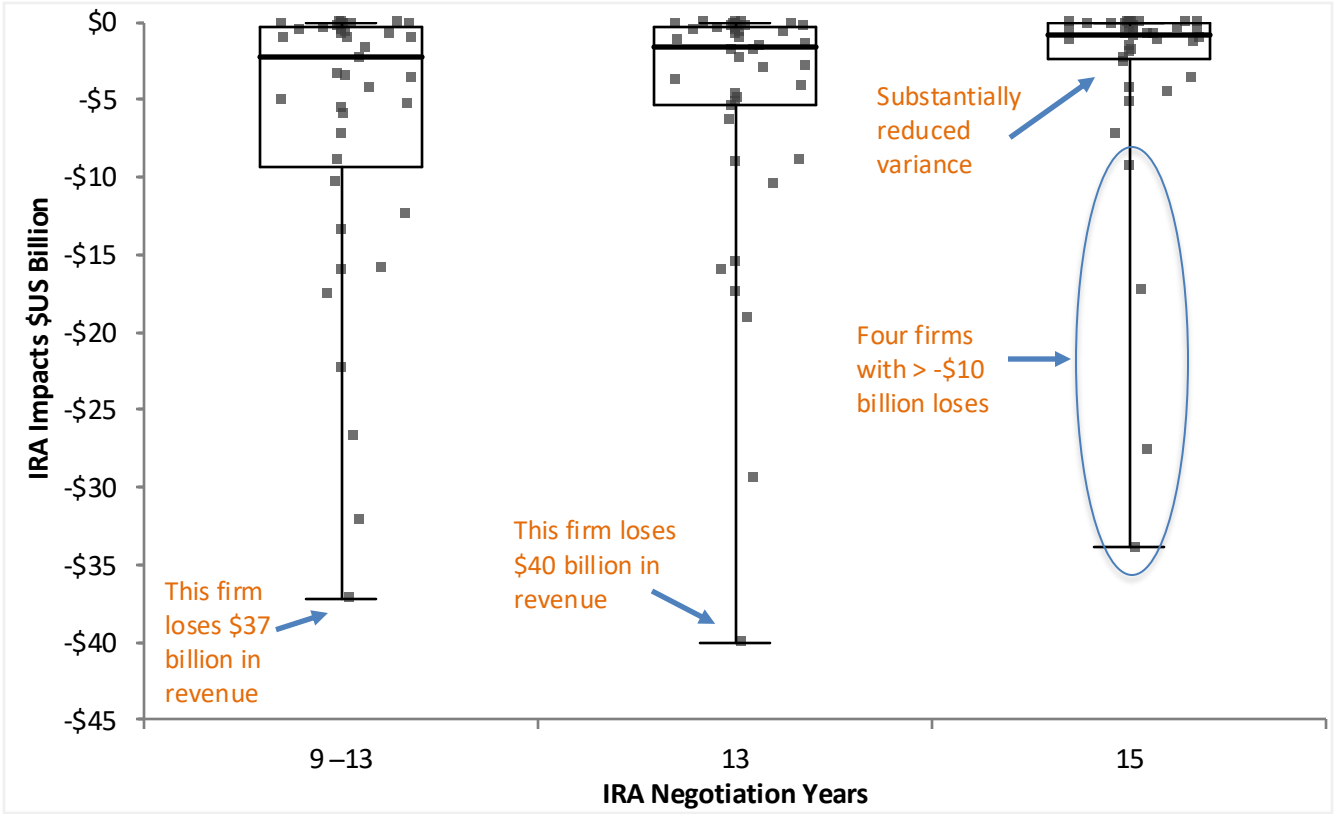


EBIT = earnings before interest expense and taxes, i.e., year-end net cash available to a firm

- IRA's price setting reduces the ability of companies to reinvest their free cashflow into their development pipelines.
- IRA's impacts are not uniform; half the firms in our cohort are far more impacted than the other half. The calculated weighted average impacts are enormous.
- Our IRA model assumes the existing cohort of drugs remains fixed into the future; yet, as previously demonstrated, IRA is causing investors to eschew investment into small molecule therapies having a high exposure to the Medicare-aged population.

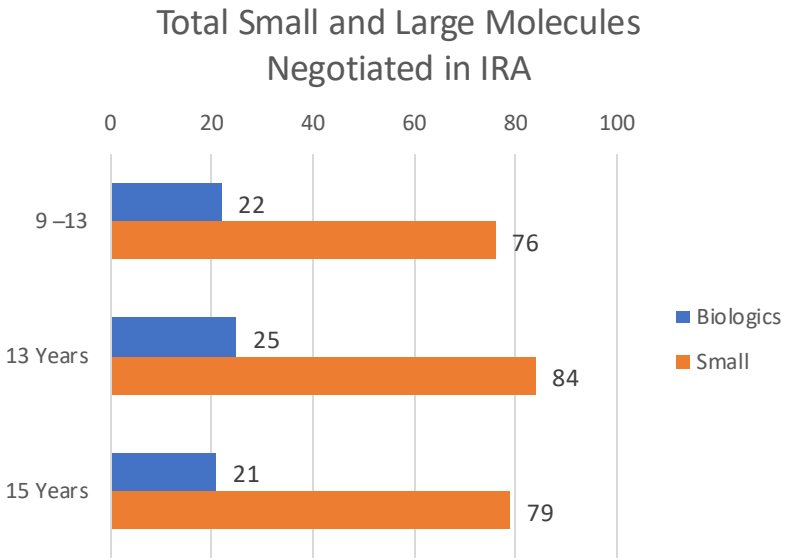
Predicted Statistical Impacts of IRA at the Firm Level, $US Billion

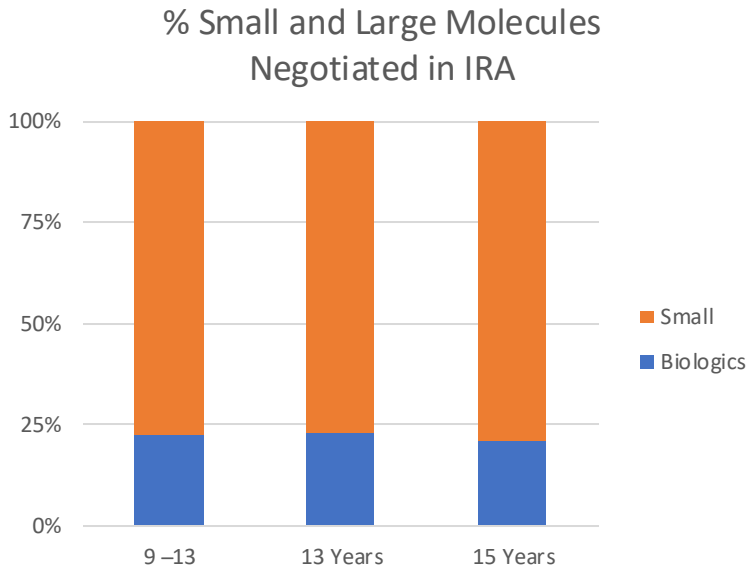
2023 USD basis



- According to our model, the IRA's 9–13 year mandate will have a very negative impact on 40% of the firms in our cohort, with revenue reductions exceeding $10 billion.
- Our model predicts one major U.S. firm to lose nearly $4 billion per year, $37 - $40 billion in total, depending on a 13-year or a 9-13 year scheme.
- Whilst 4 firms still have $10 - $35 billion revenue loses, a 15-year period before IRA's prices are set shows a large reduction in outlier impacts and reduced variance around the median, for a more certain regulatory and investment environment.

Large and small molecule drugs in IRA cohort





- Small molecules represent > 75% of the therapies in our model that will most likely be negotiated under IRA through 2035.
- IRA is causing early-stage investors to avoid investing into small molecules (side 22), which will negatively impact the drugs available to the Medicare-aged population.
- Moving from 9 -13 years to 13 years before MFPs increases the number of therapies in our cohort that are negotiated, but moves these negotiations closer to biosimilar and generic entry, with reduced overall revenue impacts (slide 31) and increases by 20% the therapies being developed for the Medicare-aged population (slide 36).

Sources of the cost basis of our analysis

Research | Open Access | Published: 10 January 2019

Estimating the clinical cost of drug development for orphan versus non-orphan drugs

Kavisha Jayasundara, Aidan Hollis, Murray Krahn, Muhammad Mamdani, Jeffrey S. Hoch & Paul Grootendorst

Orphanet Journal of Rare Diseases **14**, Article number: 12 (2019) | Cite this article

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Journal of Health Economics

Volume 47, May 2016, Pages 20-33

Innovation in the pharmaceutical industry: New estimates of R&D costs ☆

Joseph A. DiMasi [a], Henry G. Grabowski [b], Ronald W. Hansen [c]

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https://doi.org/10.1016/j.jhealeco.2016.01.012

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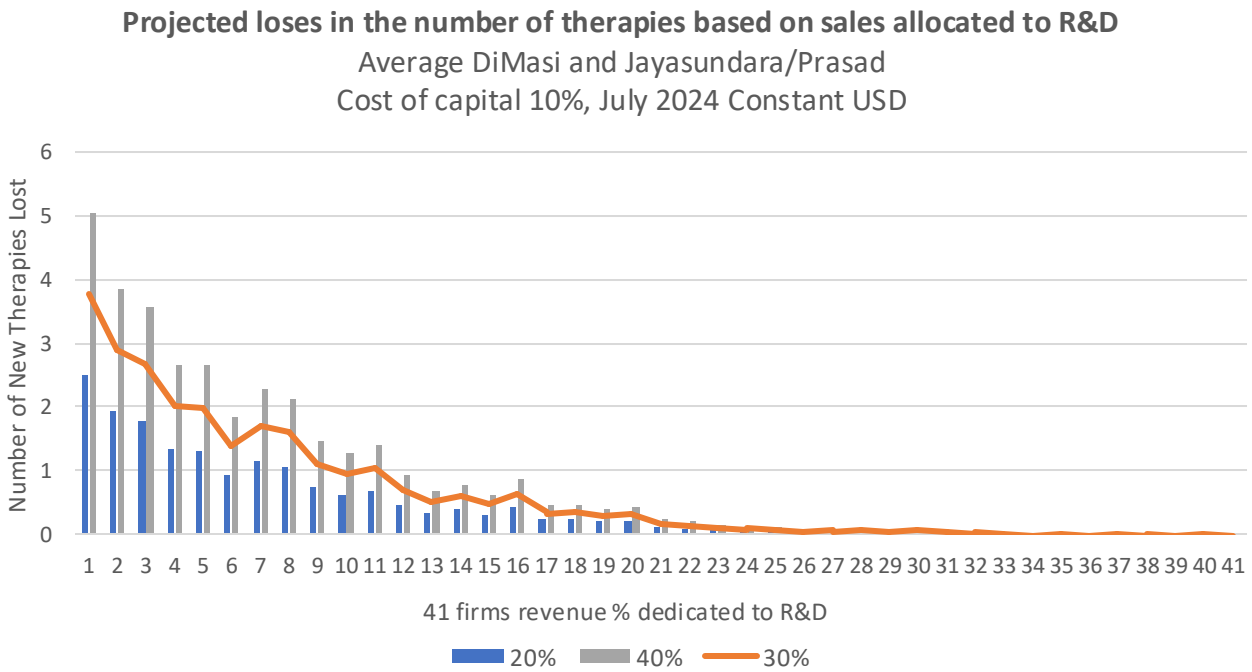
Number of therapies at risk due to IRA revenue losses at the firm level

IRA's MFPs could lead to revenue losses equaling the development costs of 18 - 35 therapies, with an average of 26 new treatments lost over the years of 2026 to 2035



- IRA causes 41 firms in our cohort to forgo the development of 26 therapies, on average.
- Drug losses attributable to IRA are concentrated in a minority of firms.
- The 41 firms in our cohort have 98 FDA approved therapies that are projected to be negotiated under the IRA.
- A projected loss of 26 therapies, estimated from revenue loss, could represent 26.4% of the total number of therapies developed that target the Medicare-aged population.

Removing the 'pill penalty' increases Medicare therapies under development 20%

Cost Impact (USD 2023)	Number of Drugs Lost by R&D Revenue Allocation 20%	30%	40%
9 and 13 years	17.6	26.4	35.1
13 years	14.3	21.5	28.7
15 years	9.0	13.5	18.0

- Using the risk weighted cost estimates of DiMasi and Jayasundara/Prasad for developing a new therapy, we can calculate the impact of modifying IRA's length of price setting.
- Removing the pill penalty and setting MFP prices for both large and small molecules at 13 years points to an improvement of roughly 20% in the number drugs lost to the Medicare-aged population from 2026 - 2035.
- We see the largest impact with MFPs set at 15 years, which improves the R&D incentive structure for the Medicare-aged population with nearly 50% greater approved therapies from 2026 – 2035, this is due to the majority of our IRA impacted therapies being small molecules, with 15 years of historical sales.
- 15 years of market access (or 13) would better allow for functioning market competition to drive down prices, increase certainty for investors and developers, and re-incentivize the development of small moleulc therapies for the Medicare-aged population.

Conclusions and implications

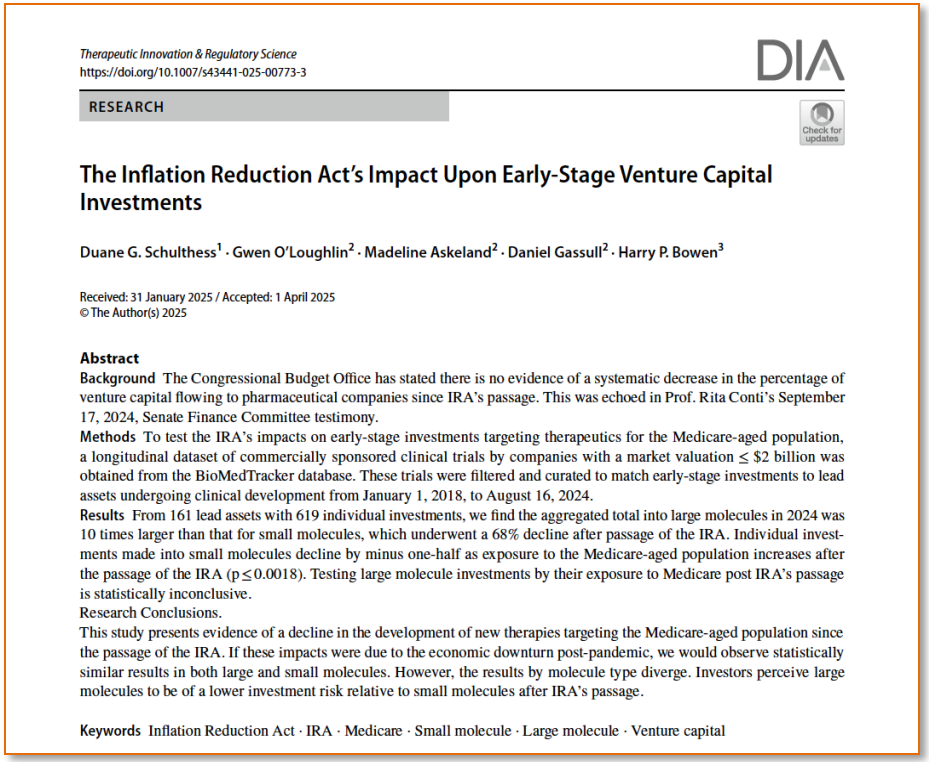
IRA's introduction has led to:

- A 35% reduction in early-stage phase I and II therapies under development by small and midsize biotech companies. As such, we would expect to see a corresponding reduction in the number of FDA approvals in roughly 5 to 6 years.
- A statistically significant shift away from the development of therapies treating indications with a high exposure to Medicare-aged populations including Dementia, Non-Small Cell Lung Cancer, Prostate Cancer, Multiple Myeloma, Leukemia (AML), Alzheimer's Disease and others.
- A shift in the modality of clinical trials from small to large molecules in areas with a high exposure to the Medicare-aged population such as Neurology and autoimmune diseases.
- A statistically significant shift in developments of small molecules away from therapies targeting indications with a high exposure to the Medicare-aged population, with evidence that large molecules are seen as having less risk for early-stage investors.
- A decline in the overall size of early-stage investments; this is indicative of VCs and angels altering their estimates of future rates of return. Our research provides evidence that this is at least partly due to exposure of specific assets to the impacts of the IRA.

Removing the 'pill penalty' and beginning IRA price setting at 13 years for both small and large molecules, our modeling finds a 20% increase in the number of therapies developed that target the Medicare-Aged population.

By increasing the time of IRA MFPs to 15 years, we see an improvement by 50% of the medicines available in Medicare.

The Inflation Reduction Act's Impact Upon Early-Stage Venture Capital Investments



Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-025-00773-3

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The Inflation Reduction Act's Impact Upon Early-Stage Venture Capital Investments

Duane G. Schulthess[1] · Gwen O'Loughlin[2] · Madeline Askeland[2] · Daniel Gassull[2] · Harry P. Bowen[3]

Received: 31 January 2025 / Accepted: 1 April 2025

Abstract

Background The Congressional Budget Office has stated there is no evidence of a systematic decrease in the percentage of venture capital flowing to pharmaceutical companies since IRA's passage. This was echoed in Prof. Rita Conti's September 17, 2024, Senate Finance Committee testimony.

Methods To test the IRA's impacts on early-stage investments targeting therapeutics for the Medicare-aged population, a longitudinal dataset of commercially sponsored clinical trials by companies with a market valuation ≤ $2 billion was obtained from the BioMedTracker database. These trials were filtered and curated to match early-stage investments to lead assets undergoing clinical development from January 1, 2018, to August 16, 2024.

Results From 161 lead assets with 619 individual investments, we find the aggregated total into large molecules in 2024 was 10 times larger than that for small molecules, which underwent a 68% decline after passage of the IRA. Individual investments made into small molecules decline by minus one-half as exposure to the Medicare-aged population increases after the passage of the IRA ($p \leq 0.0018$). Testing large molecule investments by their exposure to Medicare post IRA's passage is statistically inconclusive.

Research Conclusions.

This study presents evidence of a decline in the development of new therapies targeting the Medicare-aged population since the passage of the IRA. If these impacts were due to the economic downturn post-pandemic, we would observe statistically similar results in both large and small molecules. However, the results by molecule type diverge. Investors perceive large molecules to be of a lower investment risk relative to small molecules after IRA's passage.

Keywords Inflation Reduction Act · IRA · Medicare · Small molecule · Large molecule · Venture capital

https://link.springer.com/article/10.1007/s43441-025-00773-3

Disclosure

- Vital Transformation, an international health economics and strategy consultancy, was asked to conduct an analysis of the impact of the Inflation Reduction Act on the biopharmaceutical innovation ecosystem one-year after its signing into law.
- We investigated the IRA's impacts on investments in therapies targeting the Medicare-aged population.
- Our focus was on new drug pipeline developments in small molecule and biological products, as well as the U.S. biopharma ecosystem writ large.
- The analysis was performed by Vital Transformation's Consulting Economist Dr Harry P Bowen, Research Manager Dr Daniel Gassull, Research Partner Gwen O'Loughlin, Research Intern Madeline Askeland, and CEO Duane Schulthess.
- This study was funded by Merck, Amgen, Gilead, Eli Lilly, Genentech, AbbVie, Boehringer Ingelheim, and We Work for Health.
- The opinions included in this work are those of Vital Transformation LLC, and not necessarily those of the project's sponsors.
- The data behind this study can be accessed here, please send inquiries regarding this research here.