Biopharma Outlook

November 24, 2025

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Feb 5, 2024 (Severe Disease in Women)
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October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)

Links to Stifel Biopharma Special Topic Publications

Aging Biology, Part II

[Nov 21, 2025]

Breast Cancer

[Oct 28, 2025]

Medicine, Progress & AI

[Sep 11, 2025]

Obesity Drug Update

[July 9, 2025]

Oncology Update

[Jun 5, 2025]

Healthcare Future

[May 30, 2025]

Aging Biology, Part I

[Mar 26, 2025]

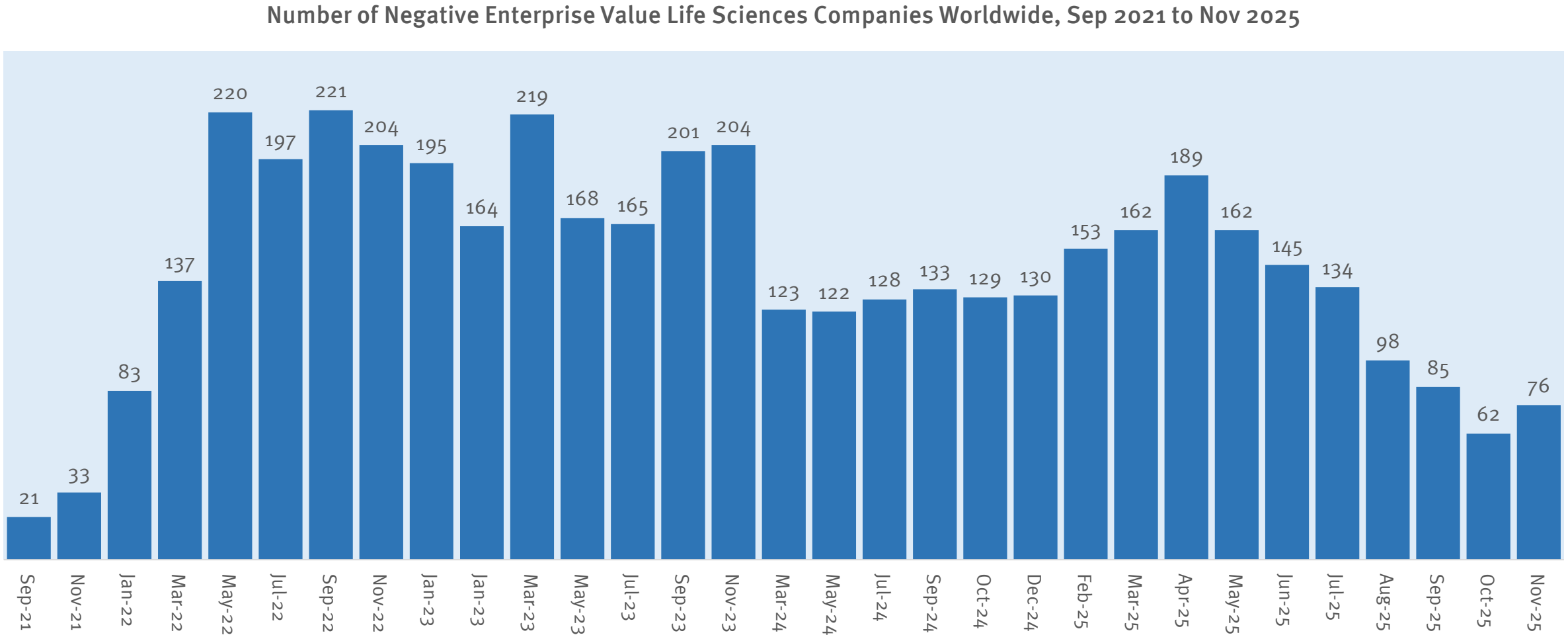
2025 Biotech Outlook

[Jan 8, 2025]

Biopharma Market Update

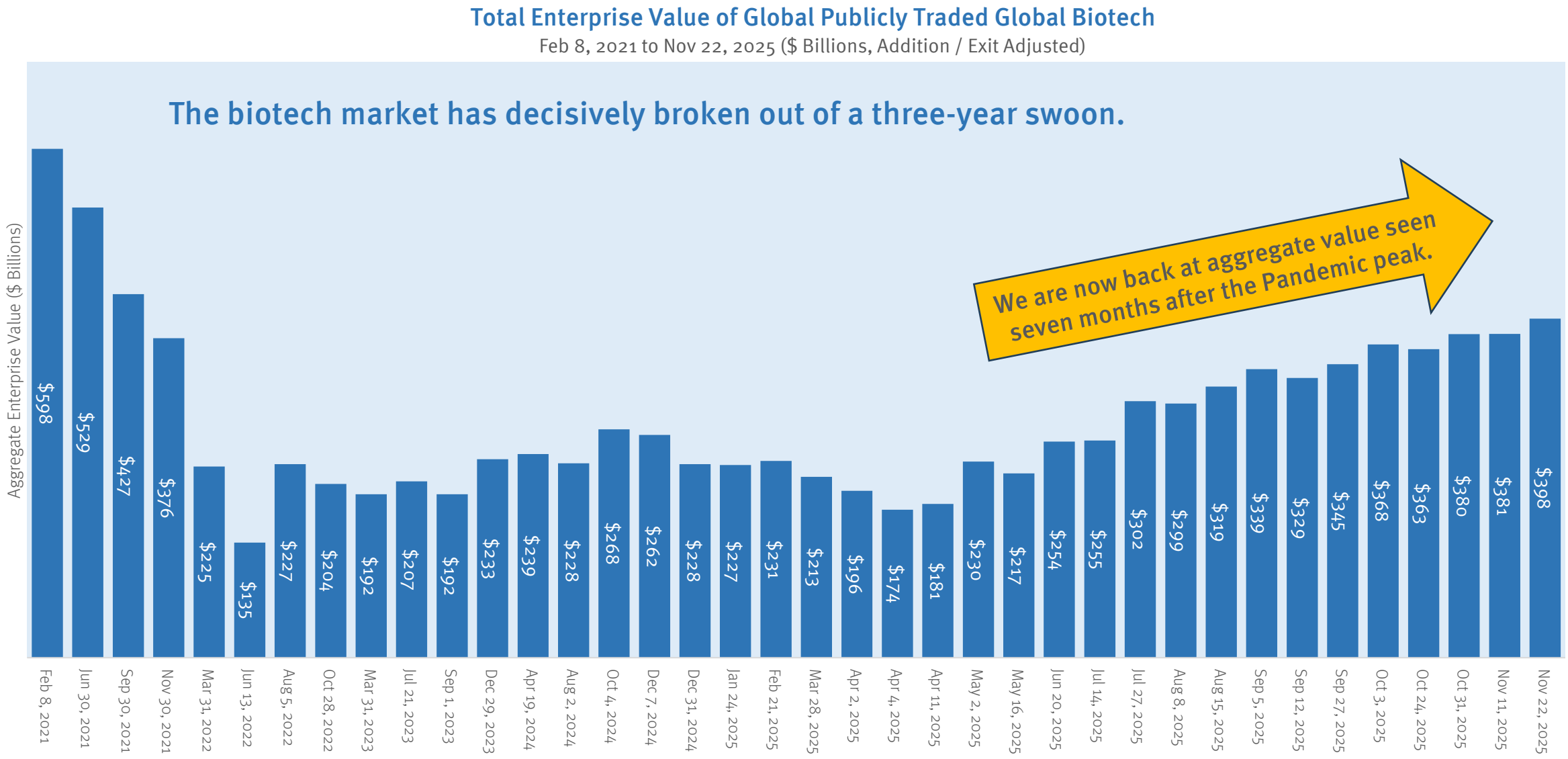
Number of Negative Enterprise Value Life Sciences Companies is Down Substantially From Six Months Ago

Despite a slight bump up in negative EV companies in recent weeks we are seeing strong signs that the life sciences market is normalizing.



Source: CapitalIQ

Biotech Stocks Are Up 129% Since Liberation Day and Up 75% for the Year

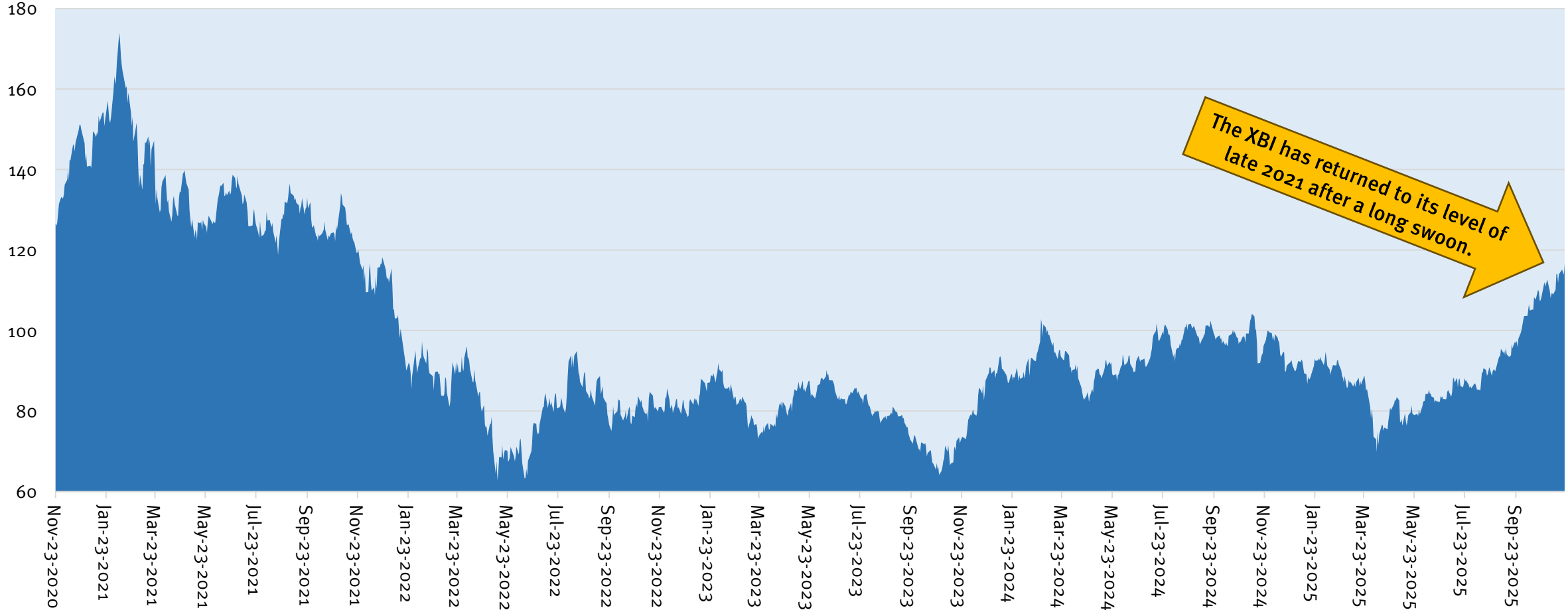


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

The XBI, a Proxy for the Broad U.S. Biopharma Market, is Recovering From a Four-Year Down Period

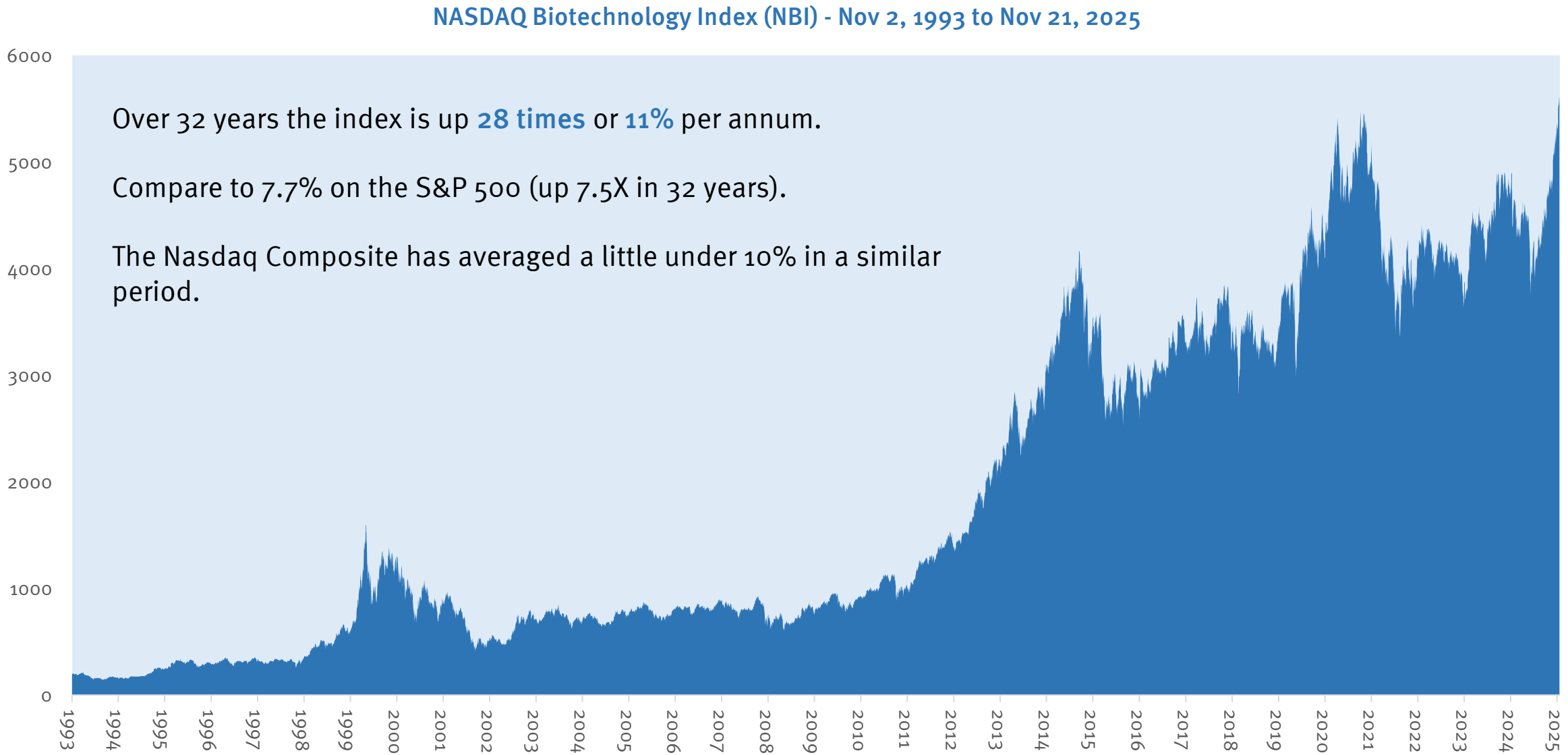
The XBI closed at 116.65 last Friday, getting ever closer to our forecast of hitting 120 for this year. The XBI is up 30% for the year.

XBI, Nov 23, 2020 to Nov 22, 2025



Source: CapitalIQ.
Note: The XBI is the value of SPDR Series Trust - State Street SPDR S&P Biotech ETF (ARCA:XBI).

The Nasdaq Biotech Index Hit its All-Time High Last Week

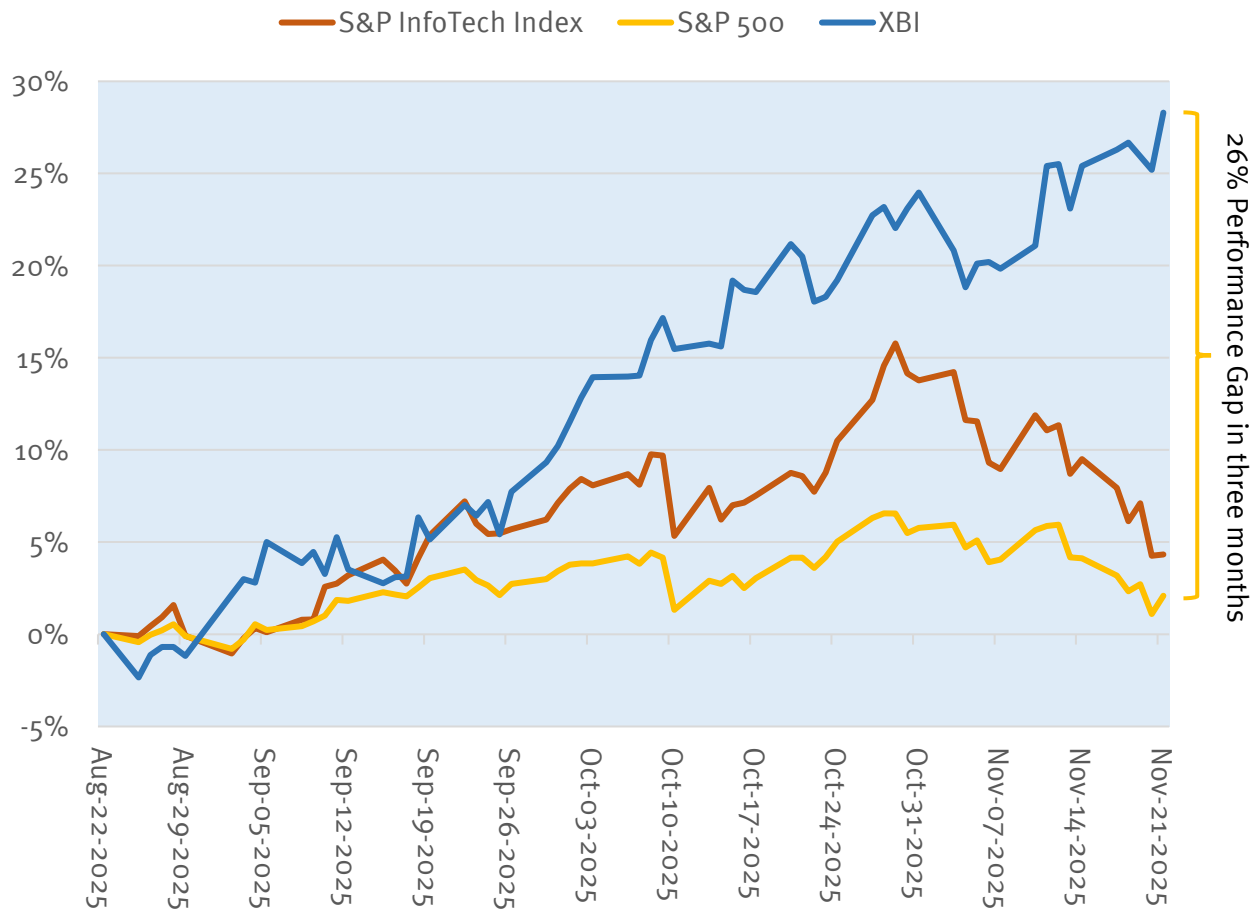


Source: CapitalIQ.

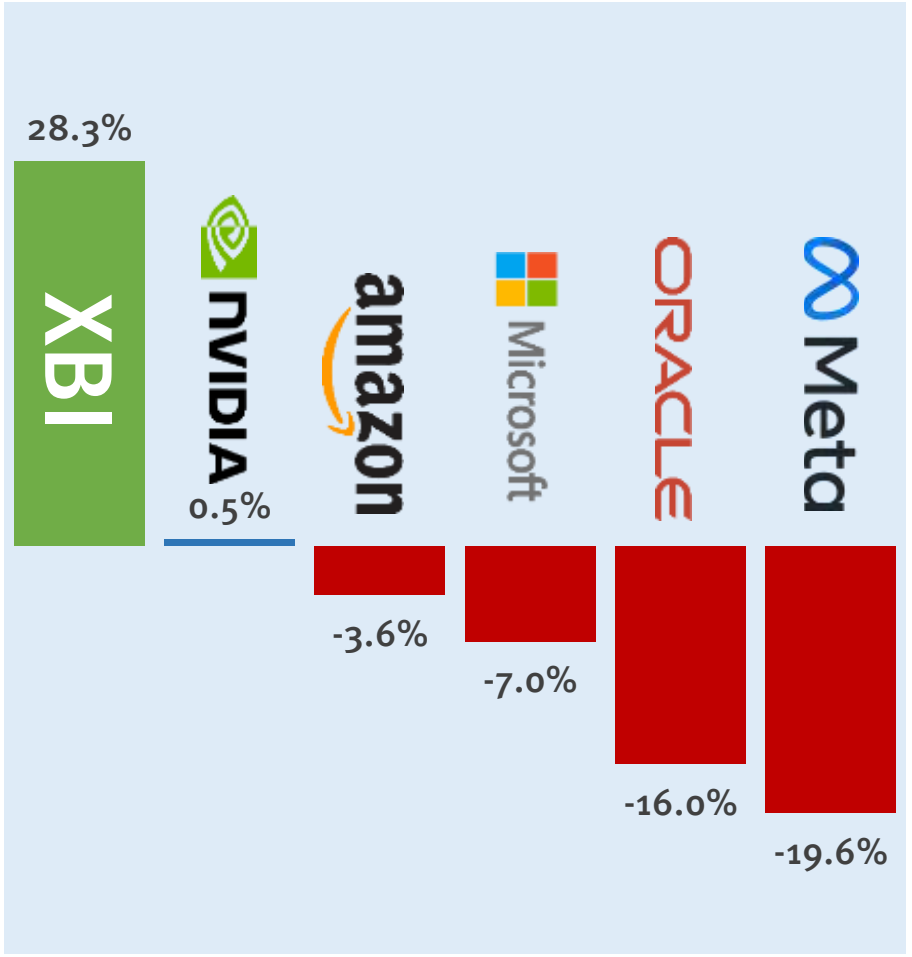
U.S. Biotech is Thriving While InfoTech is Diving

We are seeing heavy sector rotation into the midcap and small cap biopharma space as investors are increasingly avoiding tech. This has intensified in the last month.

Cumulative Returns of XBI (Biopharma) vs. Tech and S&P 500, Aug 22 to Nov 21, 2025



Total Return, Aug 22, 2025 to Nov 21, 2025

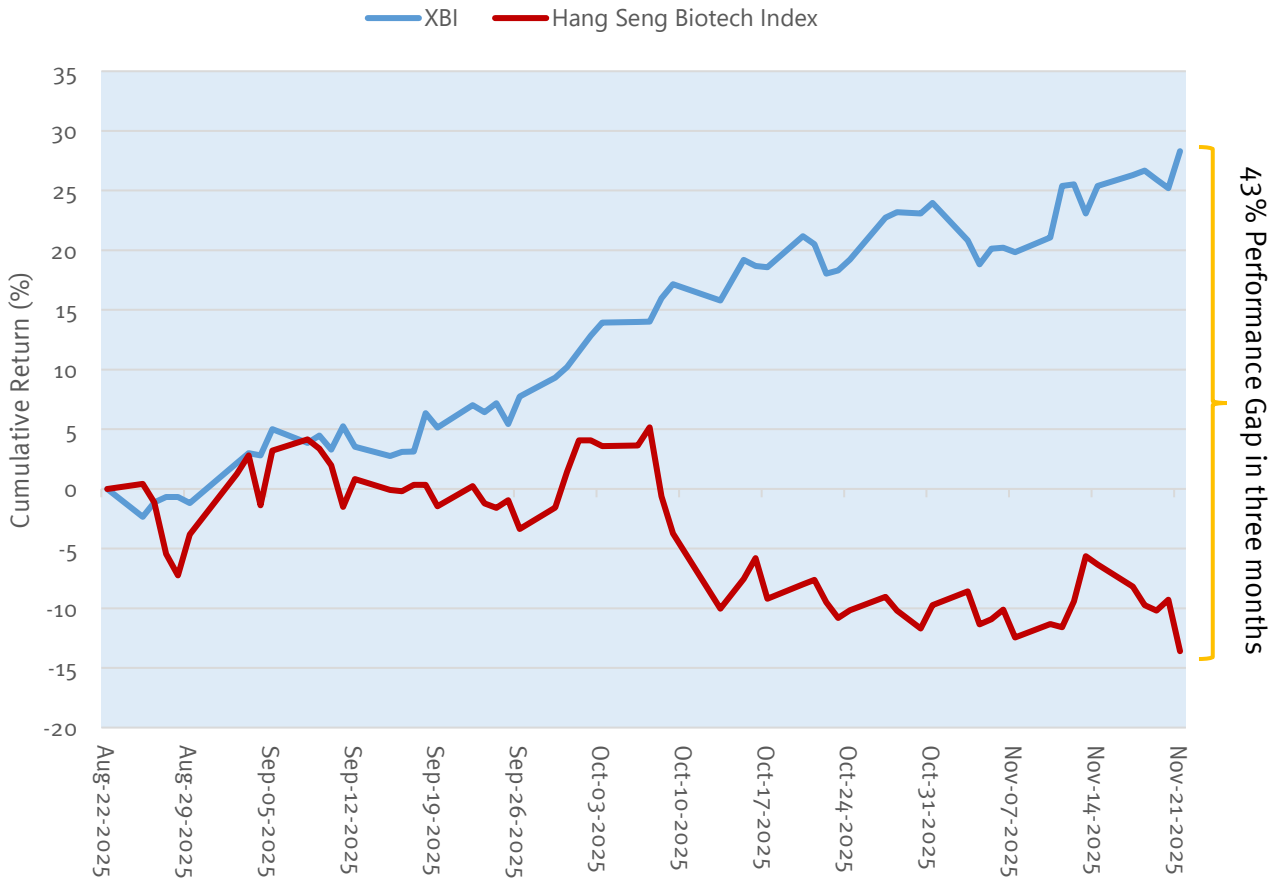


Source: CapitalIQ.

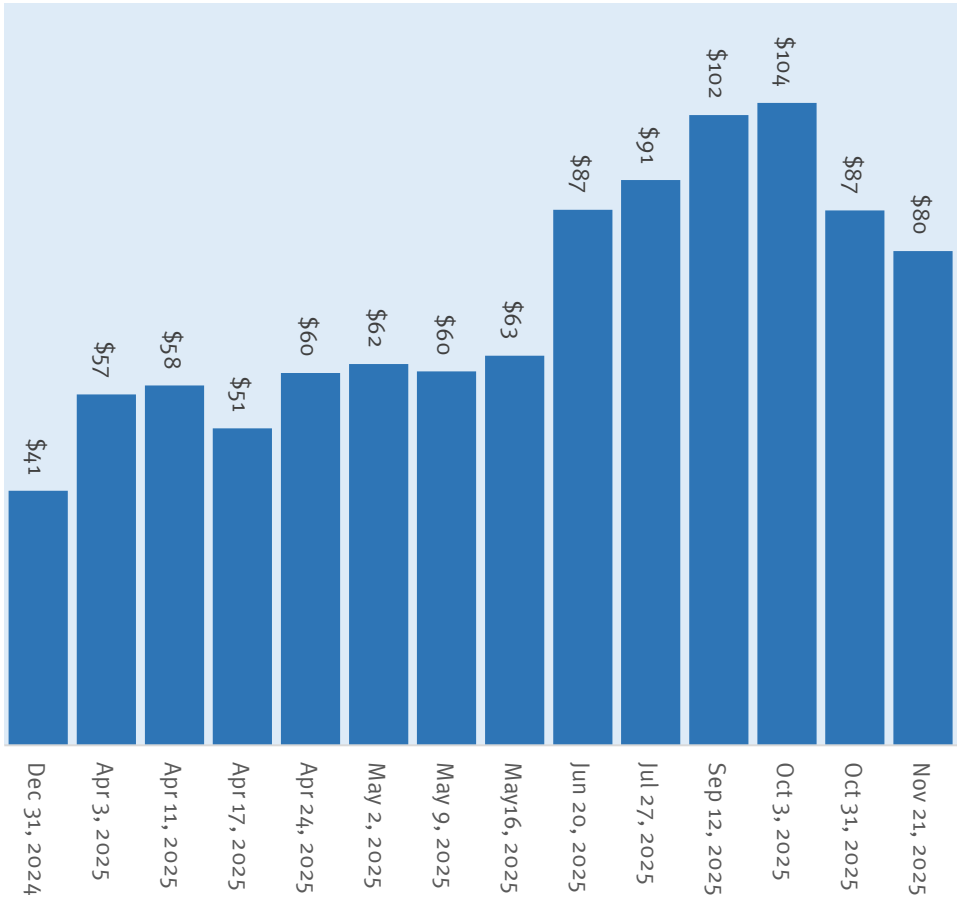
U.S. Biotech is Thriving While China Biotech is Diving

Chinese biotech stocks had an outstanding year up through September and then took abrupt drop seven weeks ago – which has continued ever since. At the moment, over 200 companies are trying to go public in Hong Kong, and most are unlikely to get out. Chinese investors have become increasingly nervous about biotech valuations on the Hong Kong exchange.

Cumulative Return of U.S. Biopharma (XBI) vs. Chinese Public Biotech (Hang Seng), Aug 22, 2025 to Nov 21, 2025



Total Enterprise Value of the China Biotech Sector ($ Billions), Dec 31, 2024 to Nov 21, 2025



Source: CapitalIQ and Stifel Investment Banking Department Analysis

What's Ignited the Biopharma Rally? Multiple Causes for Optimism

GOVERNMENT PRICING ACTIONS ARE MANAGEABLE

- Unpredictable but less severe MFN, pricing & tariffs.
- Pragmatic Administration: Focus on bringing manufacturing to U.S.
- Pharma manufacturing ask is manageable; commitments ≠ actions.
- MFN boosting revenue via government programs (e.g., obesity drugs).

OTHER GOVERNMENT POLICIES ARE POSITIVE

- M&A brakes off: Less focus on antitrust enforcement.
- FDA approval pace in 2025 on track: 43 approvals, 20 CRLs (vs. 59/19 in 2024).
- DOGE damage at FDA being addressed by Makary.
- New PRV voucher program (June) bodes well for approvals.

MACRO AND RATES

- Inflation down massively from pandemic highs.
- Unemployment low but not too low.
- Long bond yield down this year to 4%.
- COVID not returned; employees returning to work.
- AI is a huge positive productivity enhancer.
- VIX creeping up (negative).

SCIENCE, DATA AND SECTOR

- Numerous positive data catalysts (e.g., AbiVax).
- Higher quality science in biotech (e.g., RNA therapies).
- Breakthroughs delivered: GLP-1, VEGF x PD1.
- More 'good companies' in public markets following cleansing.

Why Biotech and Drug Stocks are Rallying Even Though the Rest of the Market is Hurting

Jaimy Lee, *MarketWatch*, Nov 19, 2025 (excerpt)

Biopharma is back, and it's smarter, slimmer and more strategic than before. The industry is outperforming the broader market, with the long-suffering State Street SPDR S&P Biotech exchange-traded fund XBI up 26% for the year and the State Street SPDR S&P Pharmaceuticals ETF XPH gaining 22%.

In comparison, the S&P 500 has dropped more than 3% over a four-day losing streak amid growing concerns that a deeper pullback may be developing. The index is up less than 13% so far this year, after being up as much as 17.2% year to date just three weeks ago.

Like many of the drugmakers making strides right now, Lilly inked a deal with the Trump administration that offers concessions on price in exchange for the ability to sell its weight-loss drug Zepbound to Medicare beneficiaries for the first time and for three years of tariff relief. Novo Nordisk, Pfizer, AstraZeneca and others have also made drug-pricing deals with the U.S. government.

In fact, Pfizer was the first to do so, catching many in the industry by surprise. The embattled drugmaker had a rough start to the year, with an activist investor pushing for change, a falling stock price and a postpandemic restructuring on its hands. Yet given the strategic prowess that Pfizer has been known for under CEO Albert Bourla, the company secured the TrumpRx deal and an up to $10 billion acquisition of obesity-drug developer Metsera against Novo's unsolicited bid.

That's one of several deals of note this month. Others include Merck's $9.2 billion acquisition of a flu biotech called Cidara Therapeutics on Friday and Johnson & Johnson's bid for cancer-drug developer Halda Therapeutics for $3 billion on Monday. J&J's shares are up 40% in 2025, while Merck's stock is down about 3%.

The average biopharma deal in 2025 has been 90% larger than last year, though there have been fewer deals than in years past, according to Ernst & Young. "The headwinds are there, right?" said Subin Baral, EY-Parthenon's global life sciences deals leader.

Source: https://www.marketwatch.com/story/why-biotech-and-drug-stocks-are-on-the-mend-even-though-the-rest-of-the-market-is-hurting-739d7317

Playing the Long Game in Biotech's Recovery

Andy Acker and Dan Lyons, *Janus Henderson*, Nov 18, 2025

At the time of this writing, biotech appears to be on track to deliver one of its best years of annual returns since the sector's heady days of the Covid pandemic. The S&P Biotechnology Select Industry Index, a benchmark of small-, mid- and large-cap biotech stocks, is up 25% for the year through October. Should the gains hold, it would be the first year of double-digit returns for the index since 2020 – a feat made all the more remarkable given that by early April, the benchmark was down by more than -20%.

Several events help explain the turnaround, from improved clarity about tariffs and drug pricing policy in the U.S. to a rise in merger and acquisition (M&A) activity. But we continue to see an undercurrent of developments that could deliver more positive returns. To make the most of the potential opportunity, here's what we think investors should consider.

The growing need for M&A

Historically, biotech stocks have benefited in periods when M&A activity accelerates, as deals – particularly large, multibillion-dollar acquisitions – unlock value, free up capital, and draw investor interest to the sector. Since 2021, rising interest rates and regulatory uncertainty have led to a downswing in total deal value. But there are signs these headwinds may be abating.

After rising to near 5% in 2023, 10-year Treasury yields now sit closer to 4% and could decline further if the Federal Reserve, which began easing monetary policy this year, continues to cut its benchmark rate. At the same time, the Food and Drug Administration (FDA) has overcome worries about recent funding and staff changes to meet review deadlines and even advance drug innovation through the rollout of an expedited approval pathway for important new medicines.

And in August, Pfizer reached a landmark deal with the White House, agreeing to an additional $70 billion in U.S. capital spending and selling select drugs to consumers at a discount. With the agreement seemingly satisfying administration priorities but avoiding the most draconian policy proposals (e.g., broad, most favored nation drug pricing), the biopharma industry has seen a pathway for preserving drug revenues. As such, M&A deal volume nearly doubled to $31 billion in the third quarter of 2025, up from just over $17 billion the prior quarter. More M&A could follow. Roughly $300 billion in drug revenue is at risk of losing market exclusivity between now and 2030, one of the industry's biggest "patent cliffs" in nearly two decades. With deadlines looming, drug companies are under increasing pressure to replenish pipelines quickly and have, by one estimate, as much as $1.2 trillion in balance sheet capacity to make acquisitions. An uptick in M&A can boost the biotech sector's performance broadly, but investing in the individual companies being acquired often yields the biggest payoff. In 2025, M&A deals have typically been done at double-digit premiums to the preannouncement stock price, with a handful of purchases exceeding 100%.

Source: https://www.janushenderson.com/en-us/institutional/article/playing-the-long-game-in-biotechs-recovery/

Playing the Long Game (cont.)

Janus Henderson INVESTORS

Capital markets that favor proven drug innovation

Even so, the outlook for biotech does not depend on M&A alone. Drug development is another key component, and here again we think trends are positive. Amid elevated interest rates, biotech initial public offerings slowed to a trickle. But funding from other public and private sources (such as follow-on equity offerings and venture capital) has lately started to climb, reaching $102 billion in 2024, up from $71 billion the year before.

Capital investments are the lifeblood of drug development, and a groundswell of breakthrough therapies is helping attract investor interest. This includes the first new mechanism of action to be approved in decades for schizophrenia, the first-ever treatments for MASH (fatty liver disease) and Prader-Willi syndrome (a rare genetic disease that impairs children's development), novel drugs for cardiomyopathy caused by TTR amyloidosis, and the first approved treatment for the lung disease bronchiectasis.

By transforming the standard of care, such therapies are seeing strong uptake at commercial launch and offering the potential for attractive earnings growth. According to one industry analysis, only about 20% of companies in the S&P Biotech Index were profitable between the years 2017 and 2024. By 2027, that figure could nearly double to 38% on the strength of ongoing drug research and development. In a sector known for volatility – in part because of the scarcity of earnings – this trend could be a catalyst for attracting a wider investor audience.

Market discipline could also play in biotech's favor. Investors may be starting to warm to the sector, but they continue to favor "de-risked assets" – biotechs whose pipelines offer a strong pathway to development and/or near-term catalysts (such as regulatory approval). In a risk-off market, rewards are more likely to be dominated by companies with innovative pipelines that have shown clear evidence of clinical success.

The market's recent volatility underscores the point. At the end of 2024, biopharma companies with a phase 3 drug had an average enterprise value of $701 million. That value was cut almost in half ($379 million) by April 2025, at the height of policy uncertainty, but then rebounded to $730 million by mid-September. For preclinical companies, the story was much different.

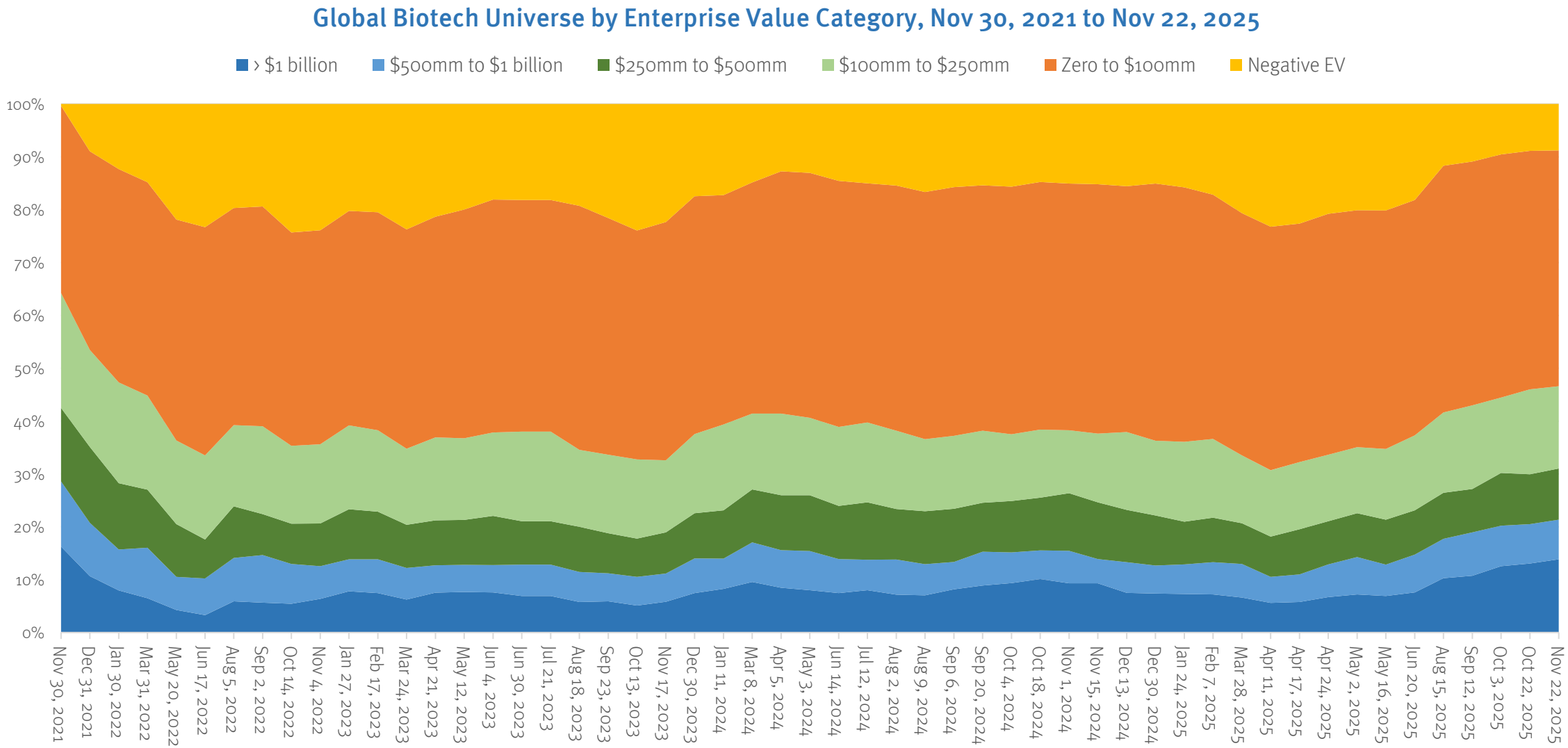
Long term, this discipline could have broader benefits. Biotech is now a leaner and more competitive sector than it was coming out of its 2021 market peak. Today, the number of public biotech firms that can boast "very good" datasets – pipeline drugs with a high probability of meaningfully improving the standard of care for a disease – is estimated to be more than 80%. In 2022, the figure was only 47%. Furthermore, since then, the number of publicly traded biotechs has declined by over 20%.10

In other words, the sector is setting a higher bar for companies to get going, but of those that survive, the opportunity for value creation may be better than ever.

Source: https://www.janushenderson.com/en-us/institutional/article/playing-the-long-game-in-biotechs-recovery/

The “Good Neighborhood” in Global Biotech Is Expanding

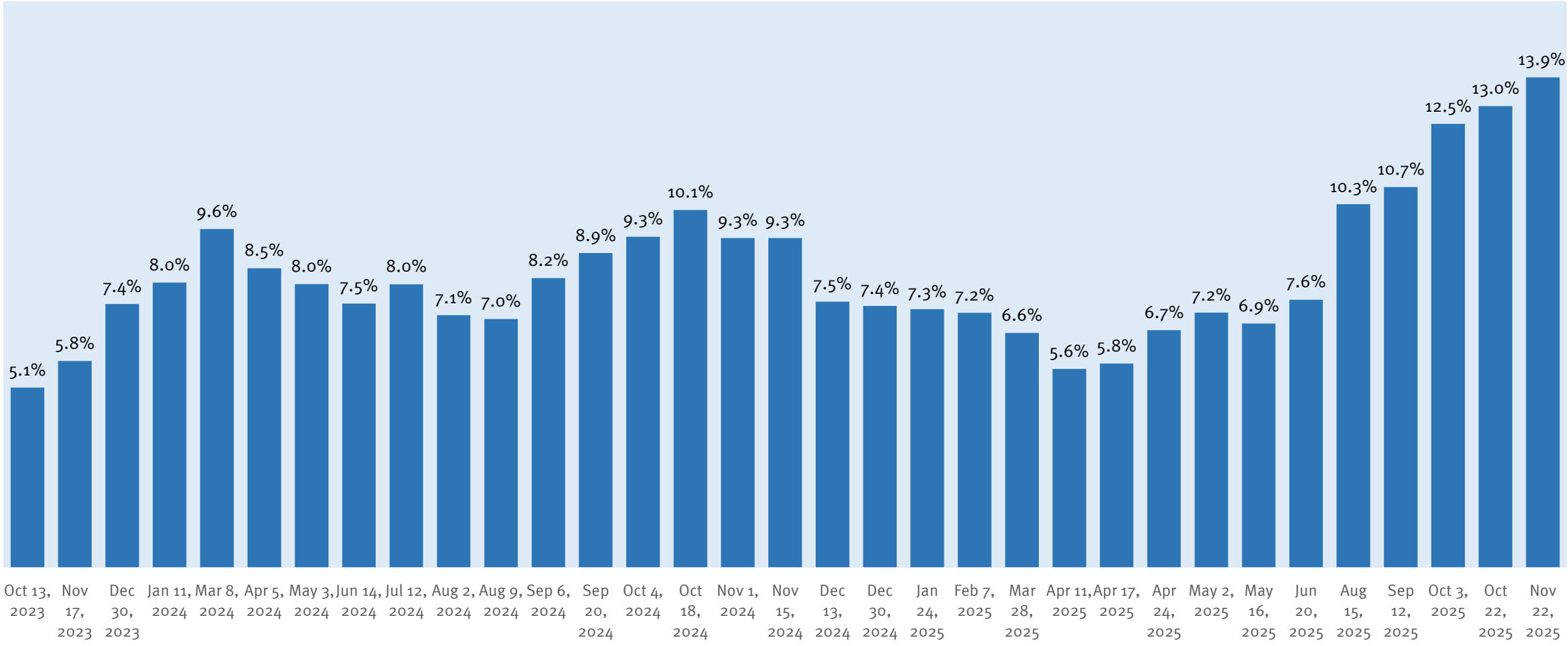
We have seen a very rapid growth in the population of biotechs with EV’s worth more than $500 million.



Source: CapitalIQ and Stifel Investment Banking Department Analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Billion Dollar Biotech Population Up 2.5X Since April

Percent of Biotechs with an Enterprise Value of $1bn or More, October 2023 to Nov 2025



Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

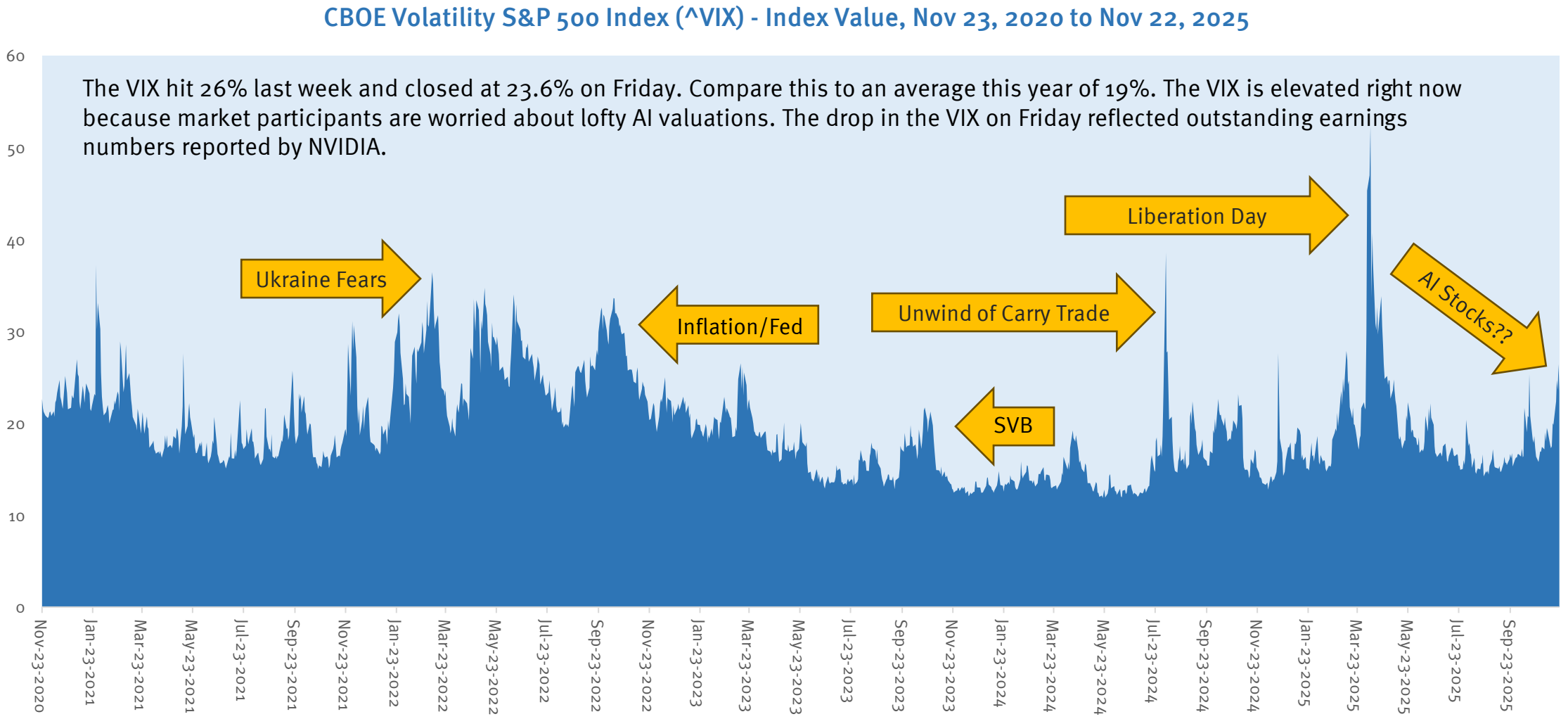
Life Sciences Sector is Now Worth Over $10.5 Trillion

The sector was flat in value last week. We saw strength in the diagnostics field while API and HCIT dropped. Overall, the sector is worth $10.5 trillion – up rather substantially this year.

Sector	Firm Count	Enterprise Value (Nov 21, 2025, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	79	$98,872	-5.7%	-1.2%	6.3%
Biotech	672	$369,265	-0.6%	8.5%	-5.1%
CDMO	36	$162,848	-2.4%	-4.8%	16.4%
Diagnostics	73	$293,884	4.6%	1.9%	18.4%
OTC	28	$21,413	-1.3%	-5.2%	-13.8%
Pharma	679	$6,899,540	0.4%	5.1%	13.1%
Services	38	$190,926	-1.5%	-6.3%	13.0%
Tools	48	$667,639	1.9%	1.0%	2.7%
Devices	169	$1,787,473	-1.1%	-1.5%	-0.4%
HCIT	7	$23,327	-3.0%	-17.4%	12.6%
Total	1829	$10,515,187	0.1%	3.2%	10.7%

Source: CapitalIQ and Stifel Investment Banking Department Analysis

The VIX, a Measure of Market Fear, Has Been Creeping Up



Source: CapitalIQ and Stifel Investment Banking Department Analysis

Global Macro Picture is Relatively Benign

The U.S. is seeing modest economic growth, 3% inflation and unemployment under 5%. This is about as good as it's been in years. Other countries (largely) also have positive economic pictures with a few exceptions. Turkey and Russia have high inflation, and you wouldn't want to be a job-seeker in Spain right now. India, China, Turkey and Australia are experiencing exceptional economic growth rates.

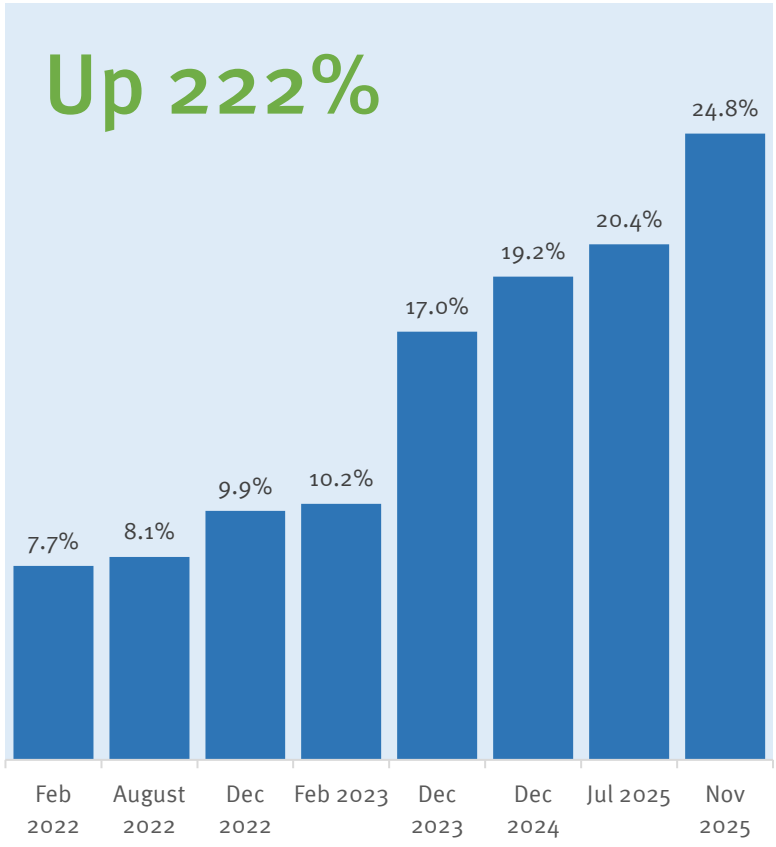
Country/Region	GDP Real ($ooos)	GDP Growth (Y-o-Y%)	CPI (Y-o-Y%)	Unemployment Rate
United States of America	23,685,300	1.99%	3.01%	4.30%
Canada	1,185,194	1.21%	2.36%	6.90%
United Kingdom	2,433,386	1.28%	3.78%	5.00%
Eurozone	8,834,679	1.36%	2.10%	6.30%
Japan	5,780,551	1.07%	2.85%	2.60%
China	18,488,115	4.98%	0.20%	5.10%
Australia	1,846,637	4.06%	3.24%	4.34%
Germany	3,683,867	0.28%	2.33%	3.90%
France	1,844,623	0.88%	0.94%	7.60%
Italy	1,259,003	0.36%	1.24%	6.10%
Spain	894,085	2.78%	3.09%	10.50%
Netherlands	1,362,623	1.58%	3.12%	4.00%
Switzerland	445,780	1.46%	0.10%	2.90%
Brazil	1,145,969	2.55%	4.49%	5.60%
Mexico	1,063,317	0.00%	3.57%	2.98%
Russia	2,532,069	0.60%	7.73%	2.10%
Turkey	864,663	4.80%	32.87%	8.47%
India	2,068,566	6.49%	0.25%	NA
Korea, South	1,393,213	1.66%	2.38%	2.60%

Source: CapitalIQ and Stifel Investment Banking Department Analysis

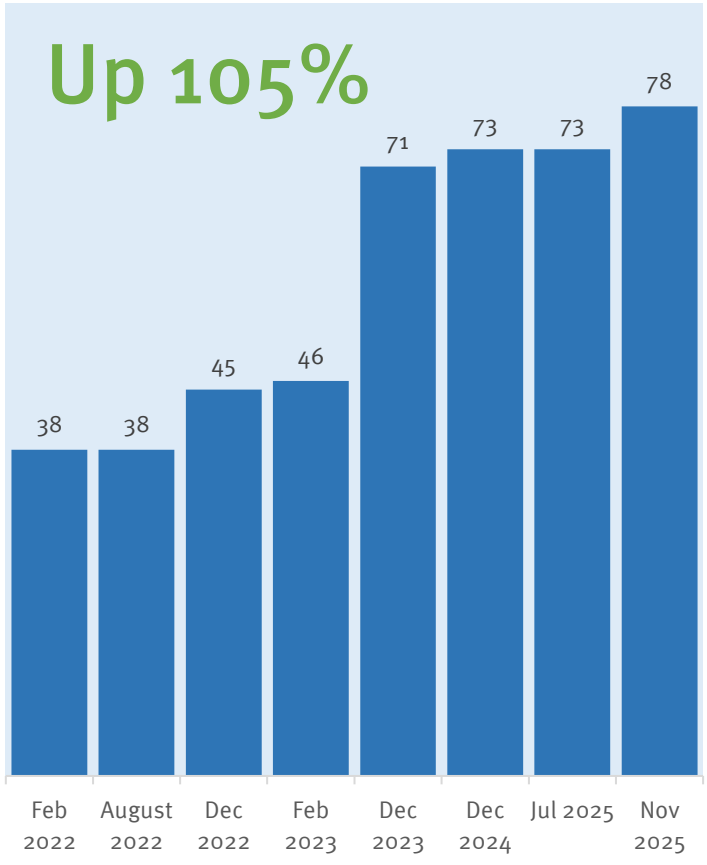
Bio Darwinism: How the Great Cleansing Transformed the Biotech Sector

By our count, nearly a quarter of biotechs on today's U.S. public market have a very good dataset – completely different than before. Today's biotech sector is amazingly good. Compare this metric, for example to just 8% in early 2022. A big change for a little less than four years. This transformation happened through a brutal Darwinian "cleansing" process that preferenced companies with strong datasets for financing. The effect was that many companies dropped off the market. In addition, as boards and CEO's learned that really good data was the ticket to survival, a lot more companies focused on delivering that data. This is evident in the chart below. The cleansing happened both through market dropouts but also as incumbents came around and delivered great data.

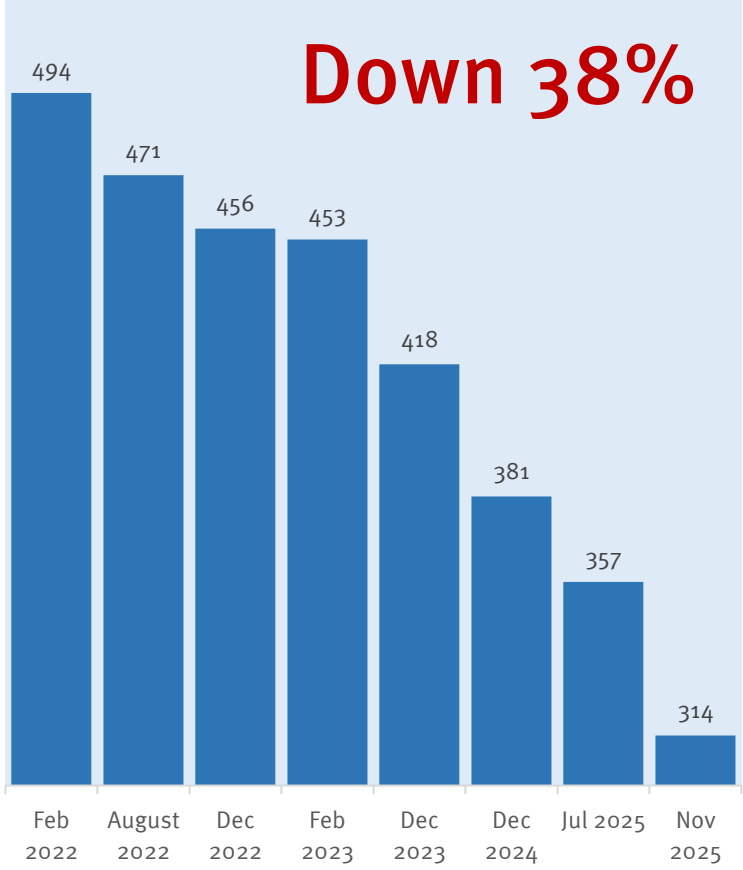
Percent of U.S. Public Biotechs with "Very Good" Data, Feb 2022 to Nov 2025



Count of U.S. Public Biotechs with "Very Good" Data, Feb 2022 to Nov 2025

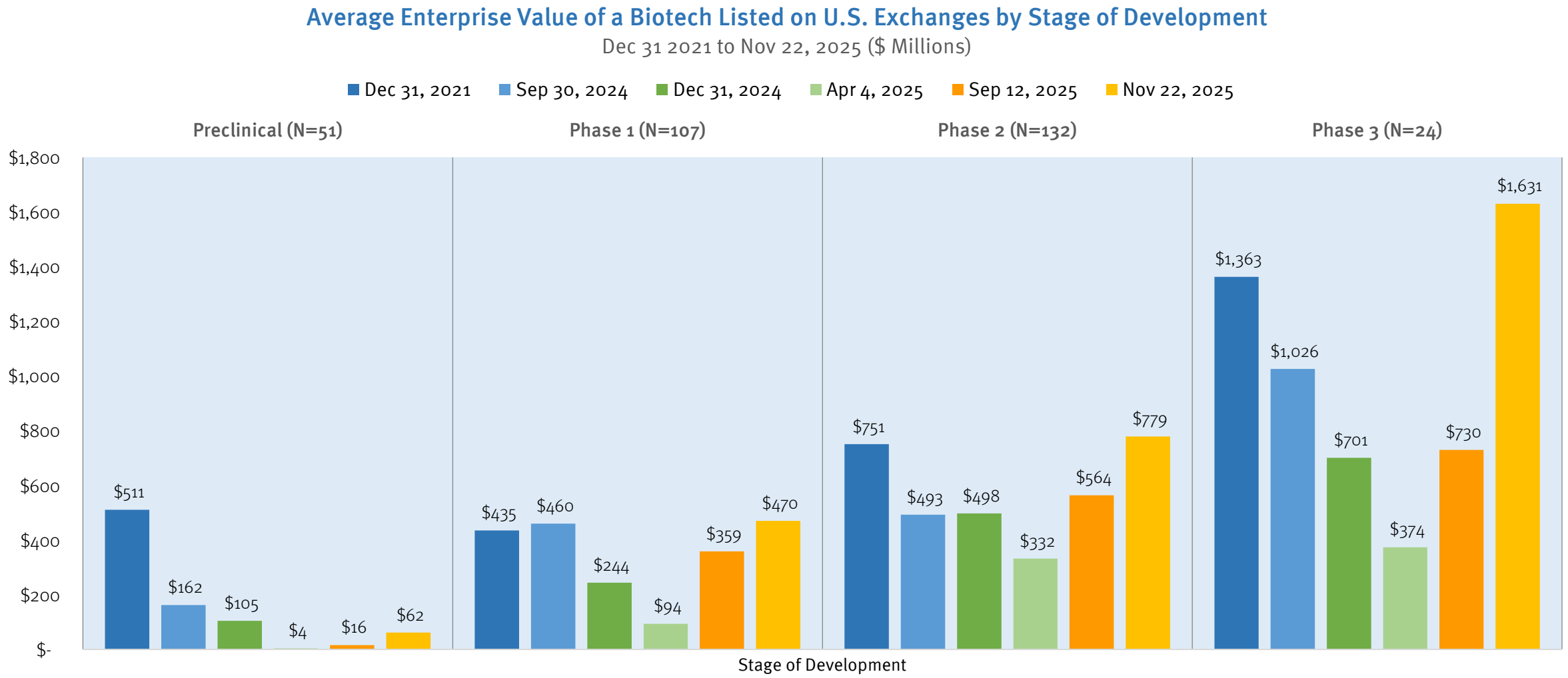


Count of U.S. Public Biotechs, Feb 2022 to Nov 2025



Source: CapitalIQ and Stifel Investment Banking Department Analysis

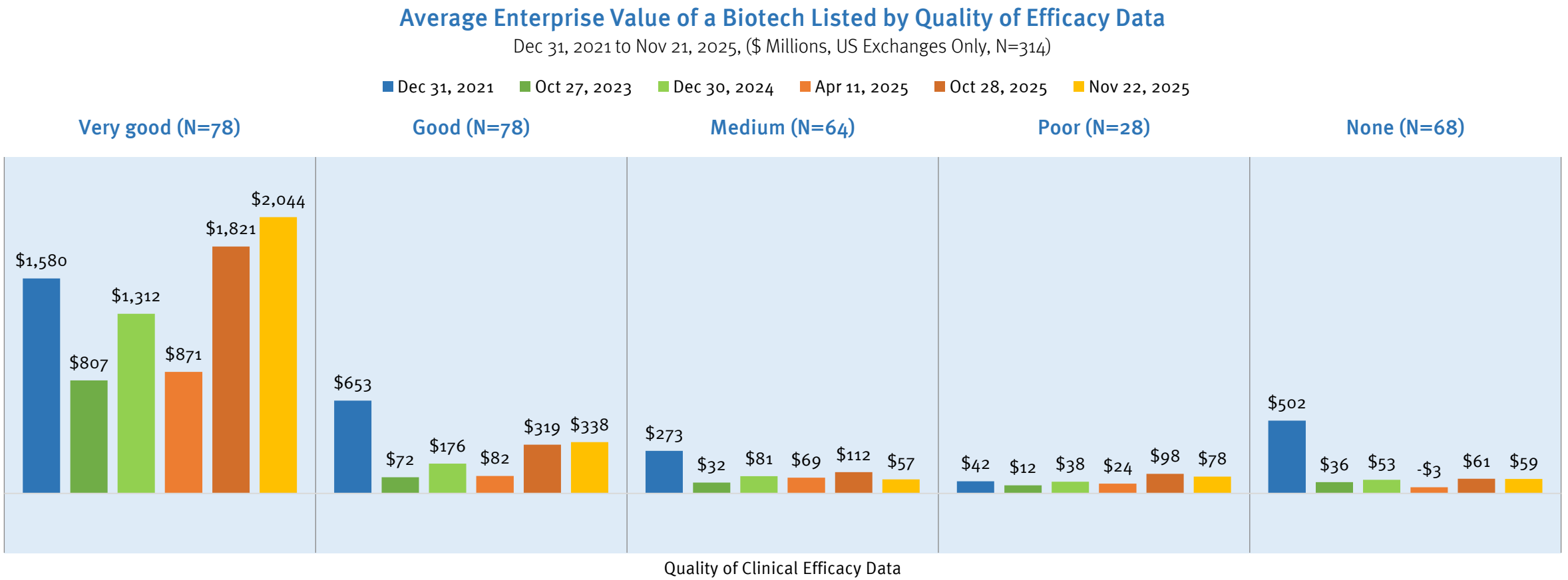
U.S. Phase 1 and 2 Biotechs Back at Last Peak Values. Phase 3's are Beyond Peak Values and Early-Stage Way Below the Last Peak



Source: CapitalIQ and Stifel Investment Banking Department Analysis. Phase of development is defined by release of at least some efficacy data from a given stage of clinical development.

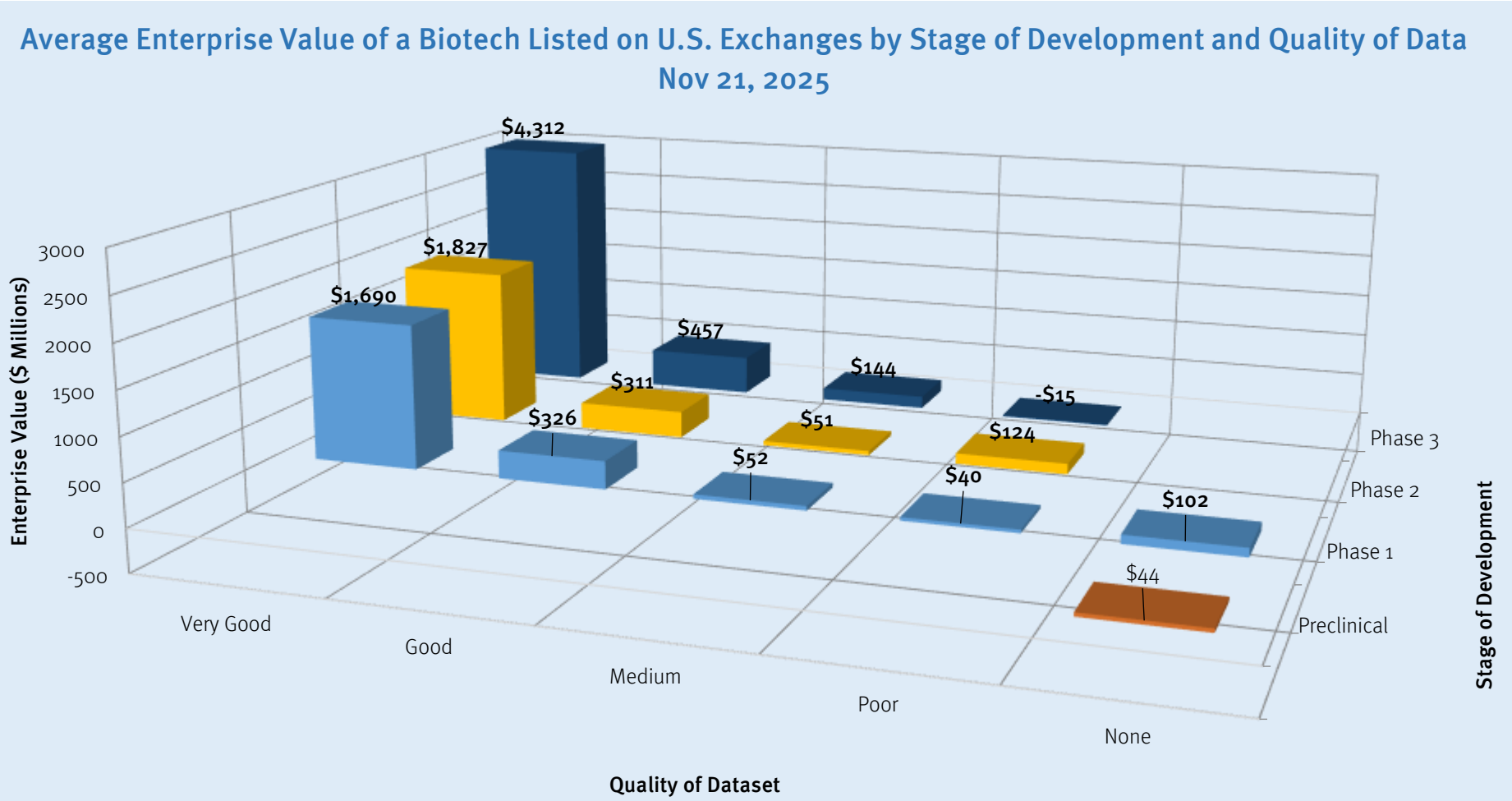
U.S. Market is Putting a Huge Premium on Companies With Very Good Datasets

The market is flocking into biotechs that look like strong M&A targets. Overwhelmingly, these are companies that have very good datasets. There is no rally underway for biotechs that lack very good data.



Source: CapitalIQ and Stifel Investment Banking Department Analysis. Phase of development is defined by release of at least some efficacy data from a given stage of clinical development. . A very good dataset is one where reported efficacy data indicate a strong likelihood that the investigational agent will exceed today's standard of care for the relevant disease. A good dataset is one where there is a reasonable likelihood of matching or slightly beating the standard of care. A medium dataset shows activity but not a good chance of beating the standard of care. A poor dataset is one where the agent clearly will not beat the standard of care, most likely because the agent missed its endpoint in a clinical trial.

Biggest Premium on Companies with High Quality, Late-Stage Data



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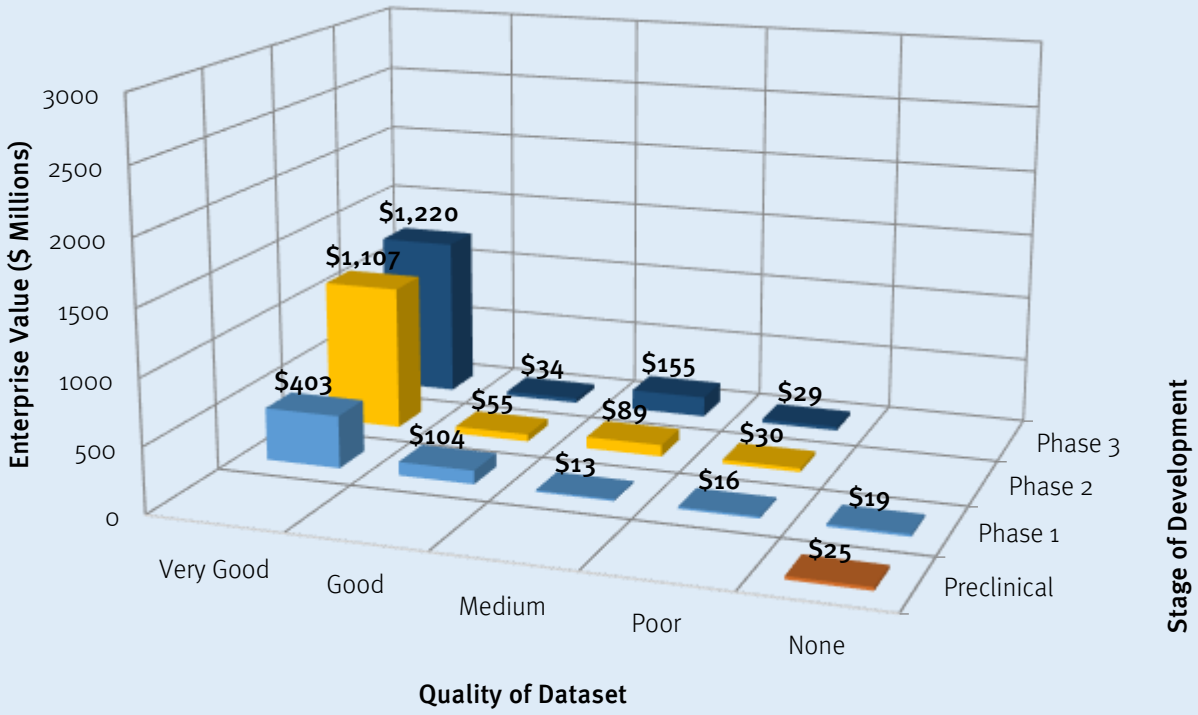
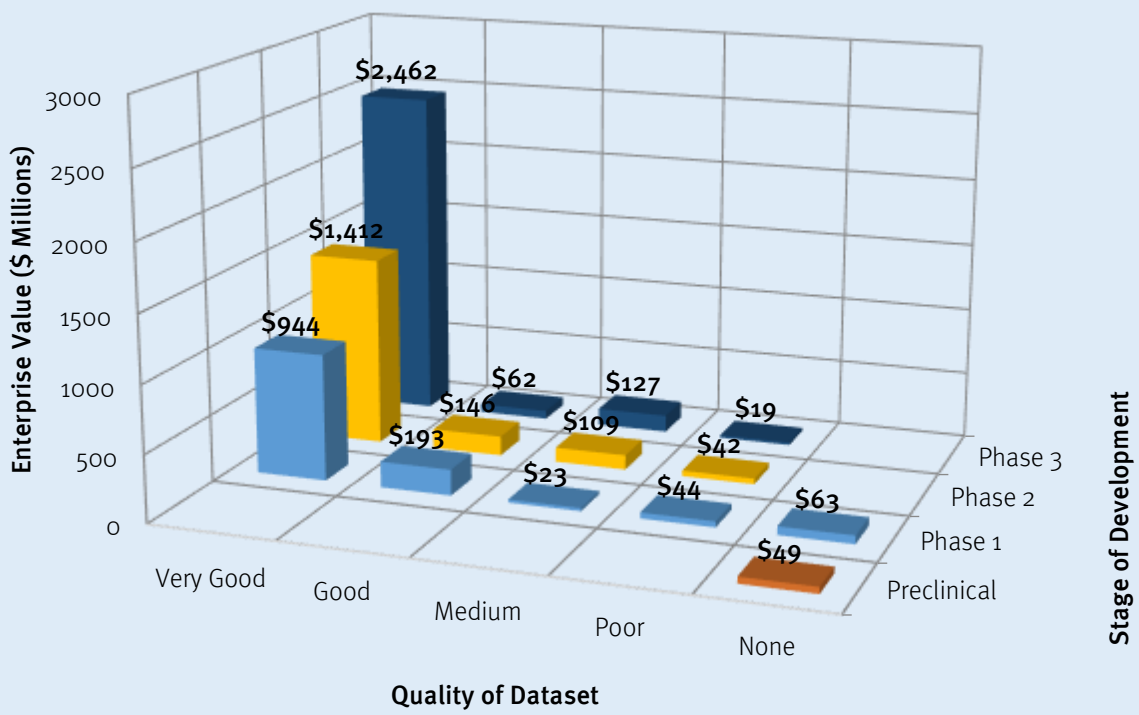
Comparison Points for Previous Page: Dec 2024 and April 2025

Biotech values were slashed across the quality and stage of development spectrum in April. We are now seeing much higher values in the later stage, high quality buckets than at the outset of 2025.

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Apr 11, 2025



Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Dec 31, 2024



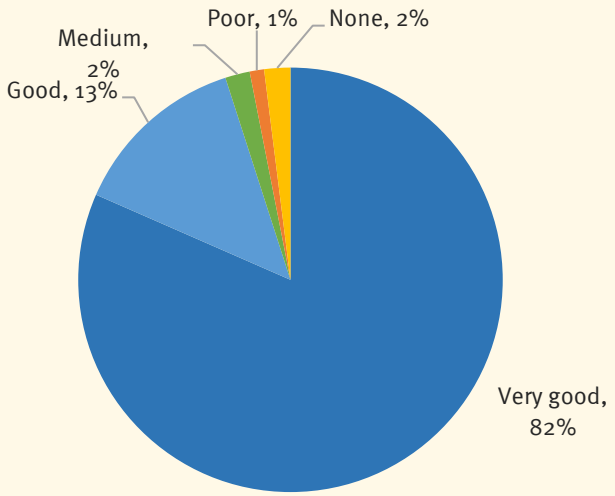
Notes: These data are sourced from CapitalIQ and based on Stifel investment banking analysis of the dataset quality for a company's lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as "very good". We classified "good" data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial. Stage of development refers to the stage of the last completed trial rather than the stage of ongoing clinical trials.

Public Biotech Continues to be a “Show Me” Market

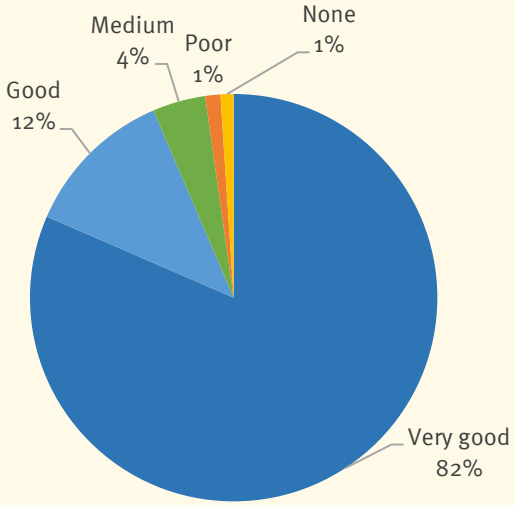
Today, 82% of public U.S. biotech value is held by companies that have a “very good” dataset. Compare this to 77% in 2024 and 47% in 2022. A key driver of this valuation approach is large pharma’s preference to buy companies after they have excellent POC data.

Total Enterprise Value ($ billions) of the U.S. Biotech Sector by Quality of Dataset on Last Completed Stage of Development

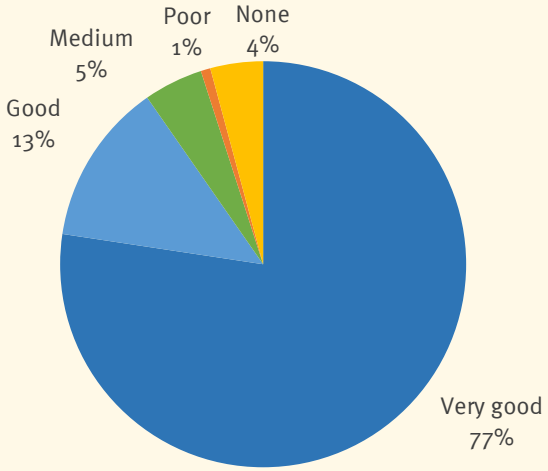
Nov 21, 2025



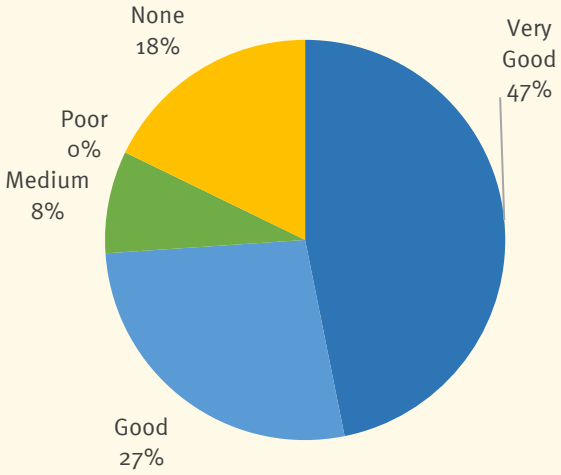
Sep 12, 2025



Dec 31, 2024



Nov 30, 2022



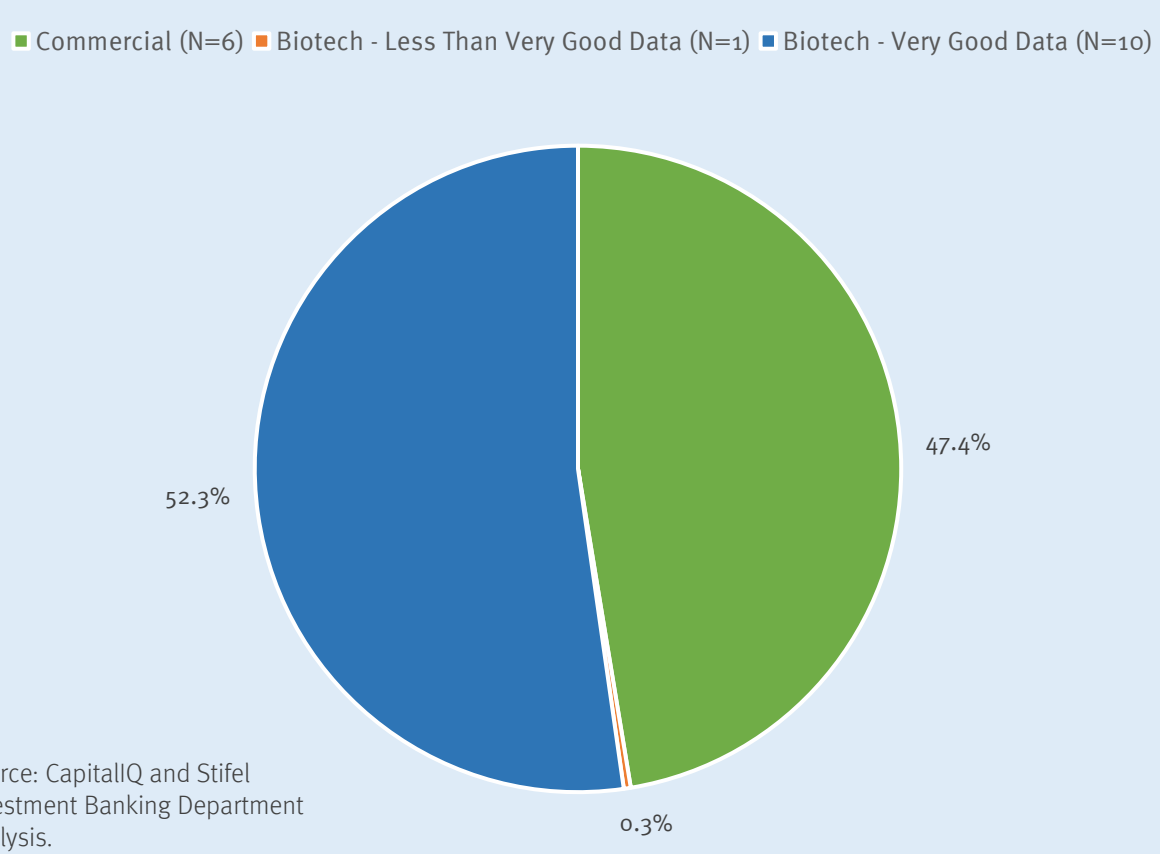
The next page addresses an obvious question: How did changing valuation patterns impact the biotech sector?

Note: These data are sourced from CapitalIQ and based on Stifel investment banking analysis of the dataset quality for a company’s lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as “very good”. We classified “good” data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial.

Investors are Driving Up the Valuations of Large Pharma M&A Targets With Great Data

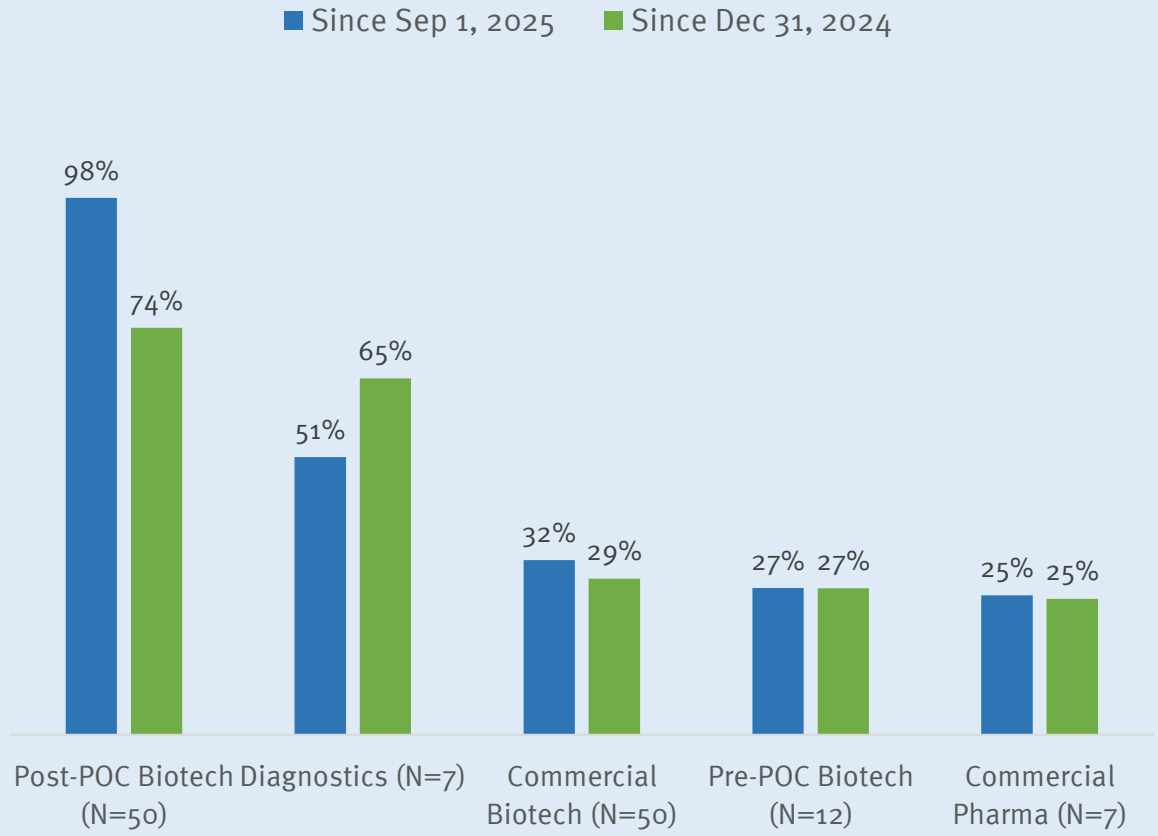
The chart at left shows that large pharma targets are overwhelmingly commercial companies or those that already have very good POC data. The lone exception was Adverum which had some data and promise and was scooped up by Eli Lilly as a bargain play. The chart at right shows that the bull run in biopharma stocks has been strongest among companies with good post-POC data. Diagnostics and commercial biotechs have also performed relatively well. Investors are clearly bidding up the companies that are most likely to be acquired by large pharma.

Large Pharma M&A Deals Thus Far in 2025 by Type of Target (N=17)



Source: CapitalIQ and Stifel Investment Banking Department Analysis.

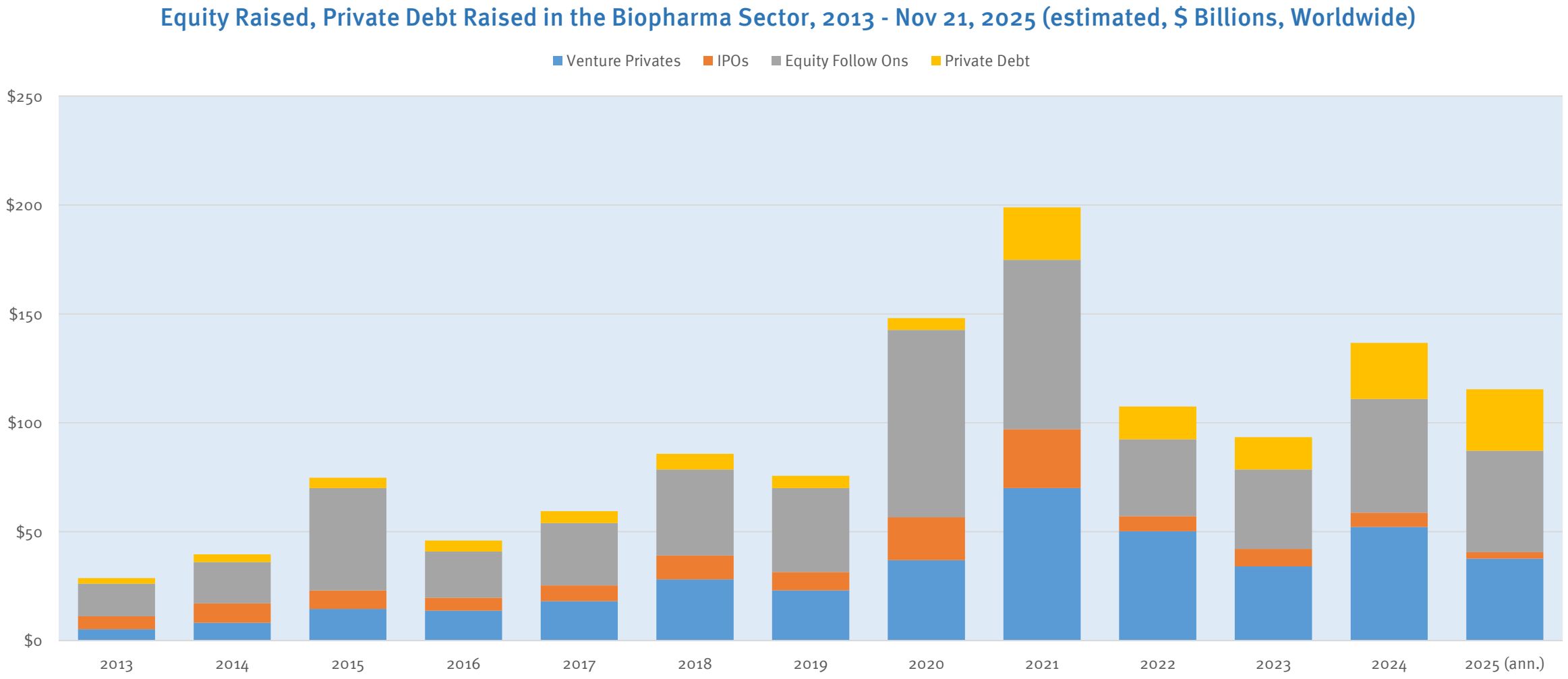
Equal-Weighted Returns on XBI Components, Dec 31, 2024 to Nov 21, 2025 by Company Type



Capital Markets Update

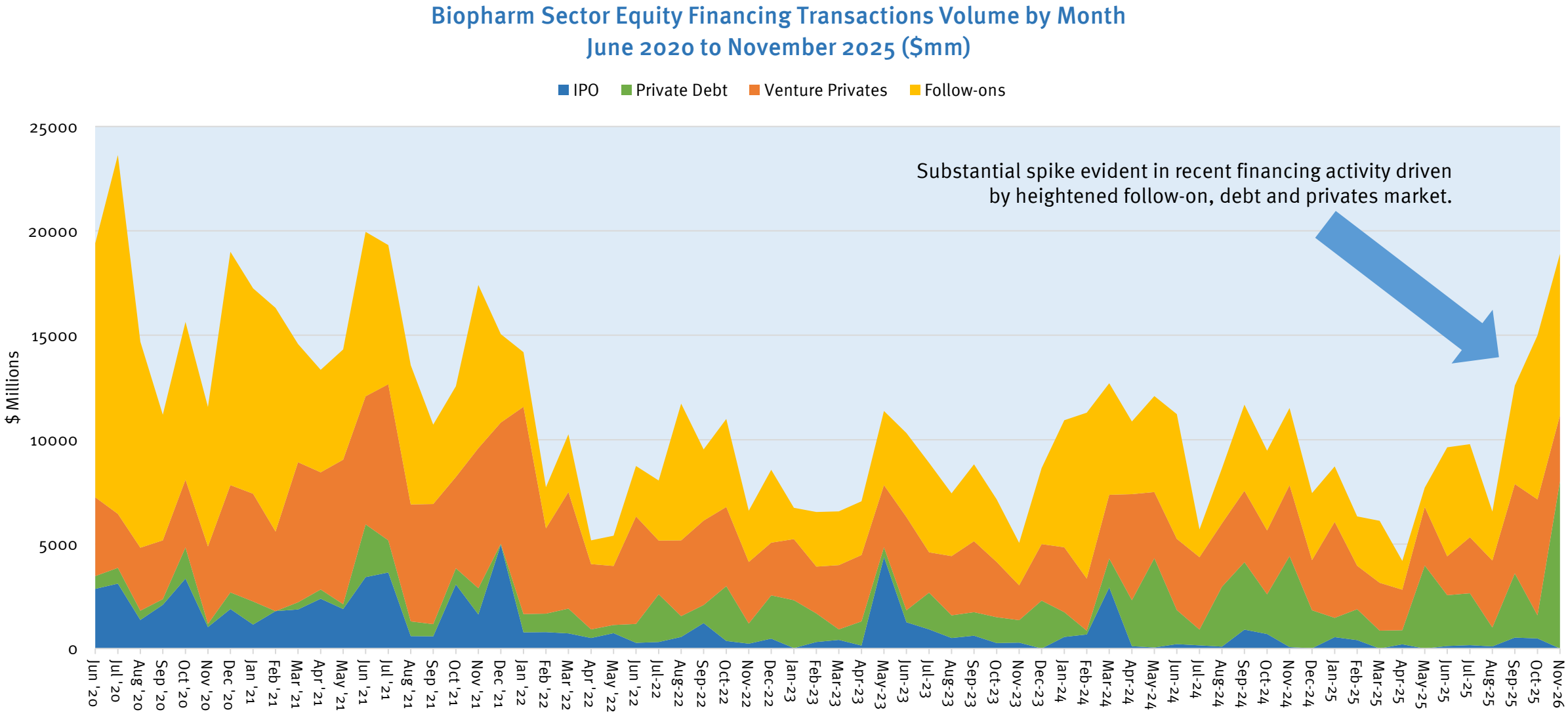
Capital Raising Pace in 2025 Now Ahead of 2023

The rapid pace of financings in the last ten weeks has pushed our estimates of total financing volume for 2025 to be above the levels of 2022 and 2023. There is a reasonable chance that this ends up being the fourth most active financing year on record despite a very slow first half.



Source: Data from CapitalIQ and Crunchbase. Note: Data for 2025 is annualized based on results as of Nov 21, 2025.

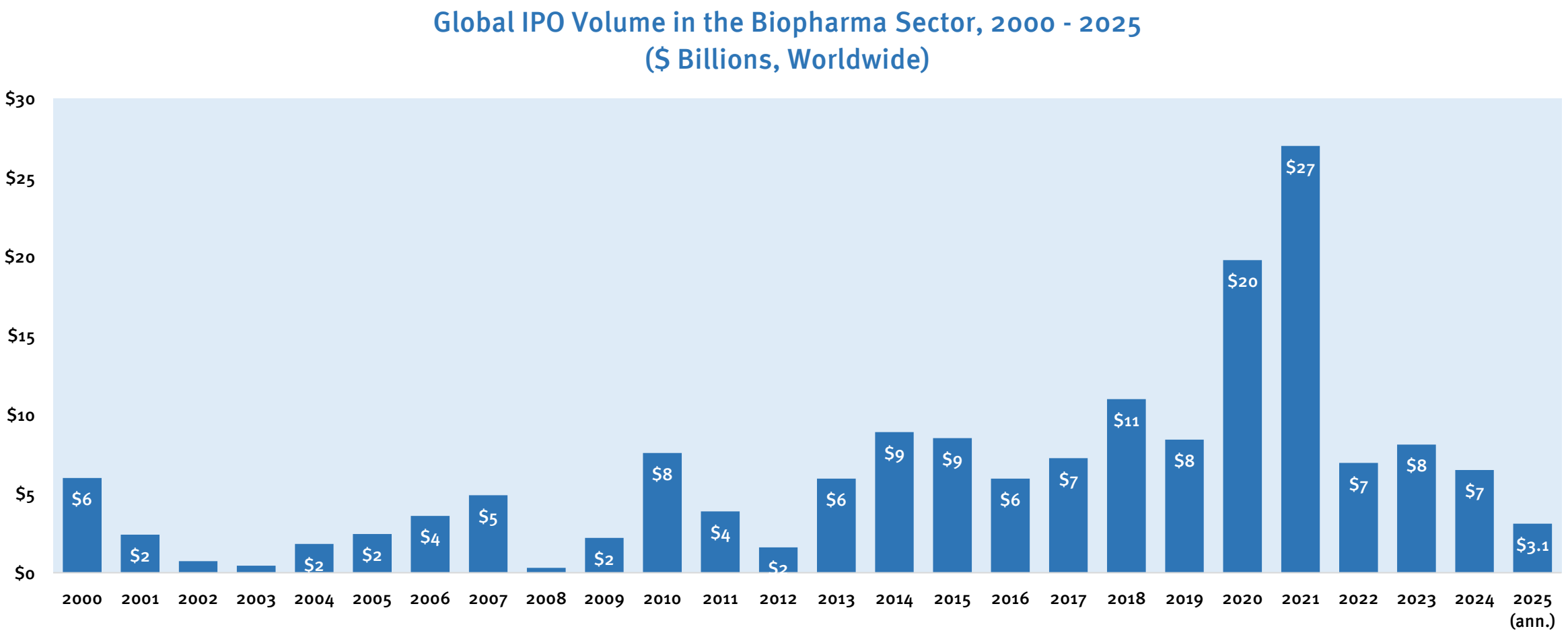
Total Financing Levels in November Closing in on Pandemic Levels



Source: Data from CapitalIQ and Crunchbase.

IPO Market Remains Slow

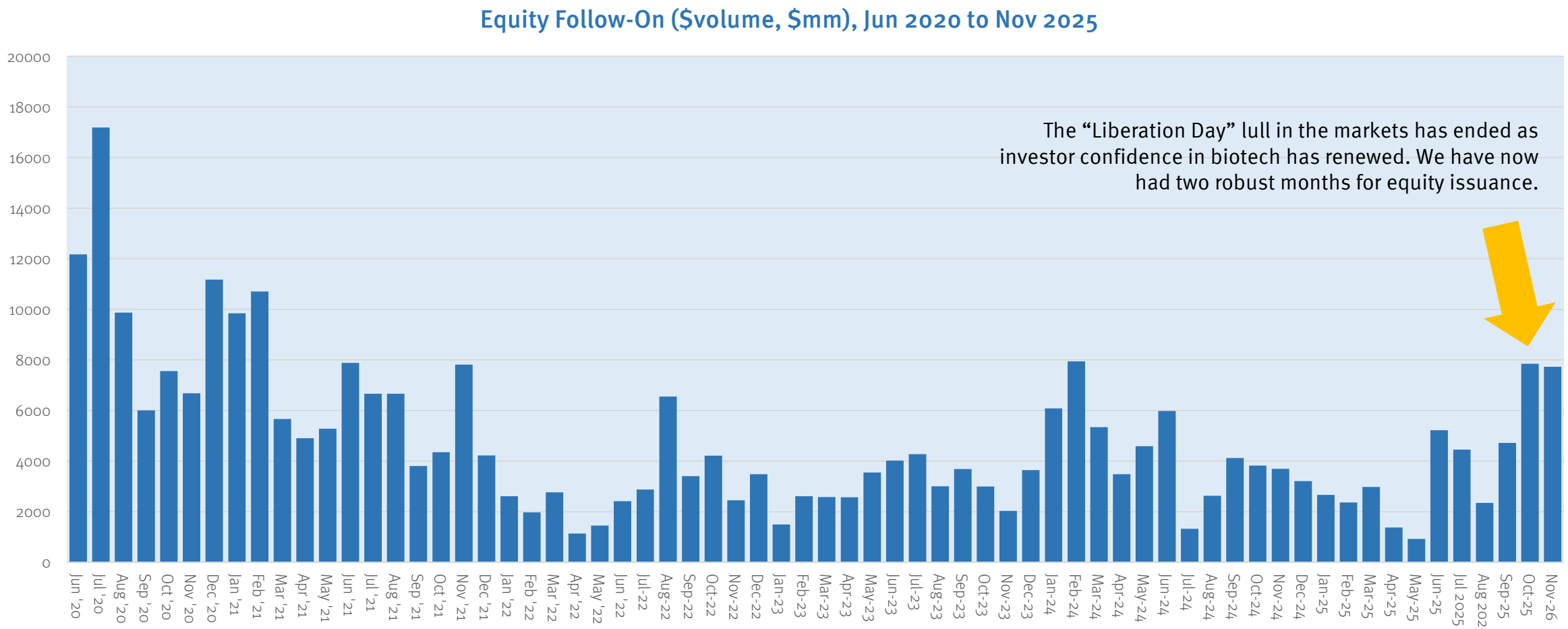
We think that the remainder of 2025 will have a more normal IPO market as the calendar continues to fill in with quality offerings. But the most substantial activity looks likely to us to be coming in 2026 and 2027.



Source: Data from CapitalIQ. Note: Data for 2025 is annualized based on results as of Sep 12, 2025.

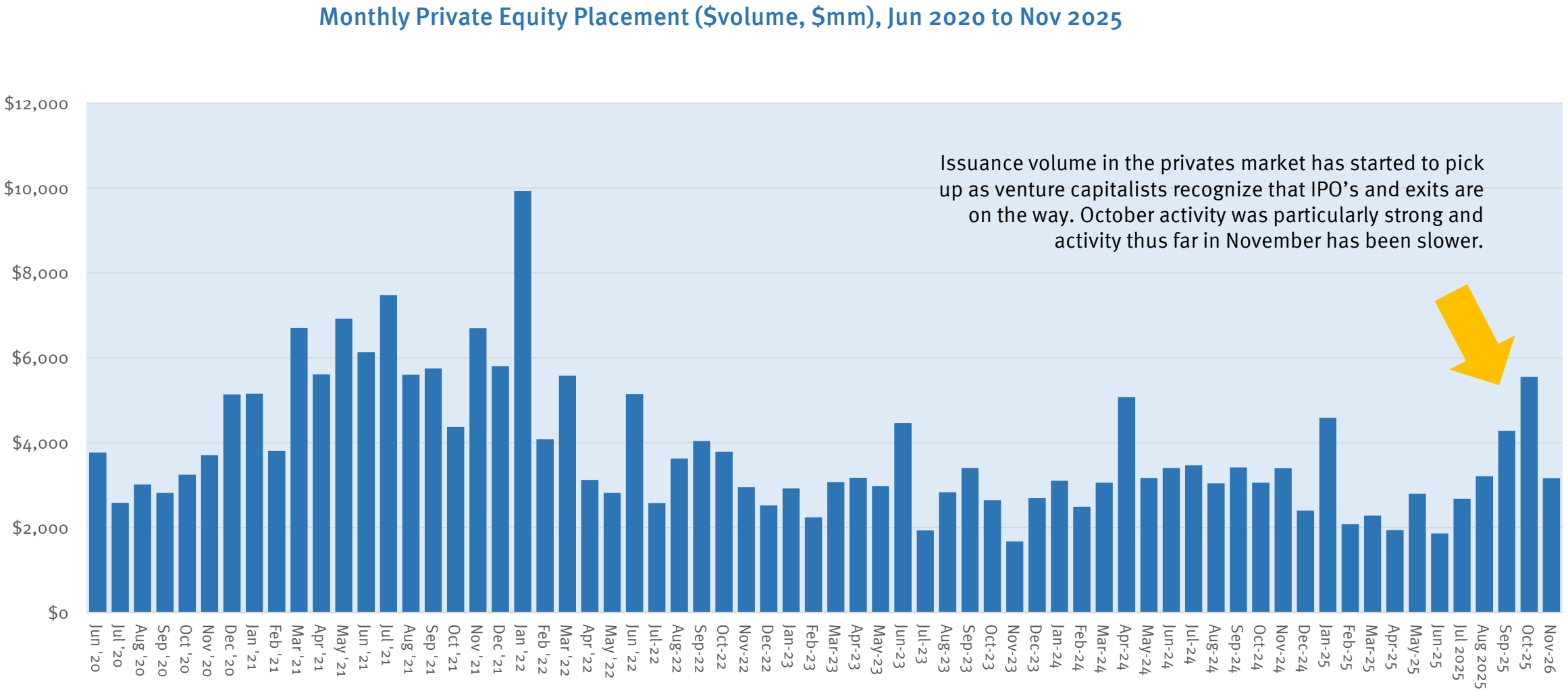
Global Follow-On Market Strong in Last 14 Weeks

The follow-on market has shown a substantial pickup in activity as the XBI has begun to rise and normalization has spread throughout the markets. We have seen more than $6 billion in deals price so far this month and we still have time to go.



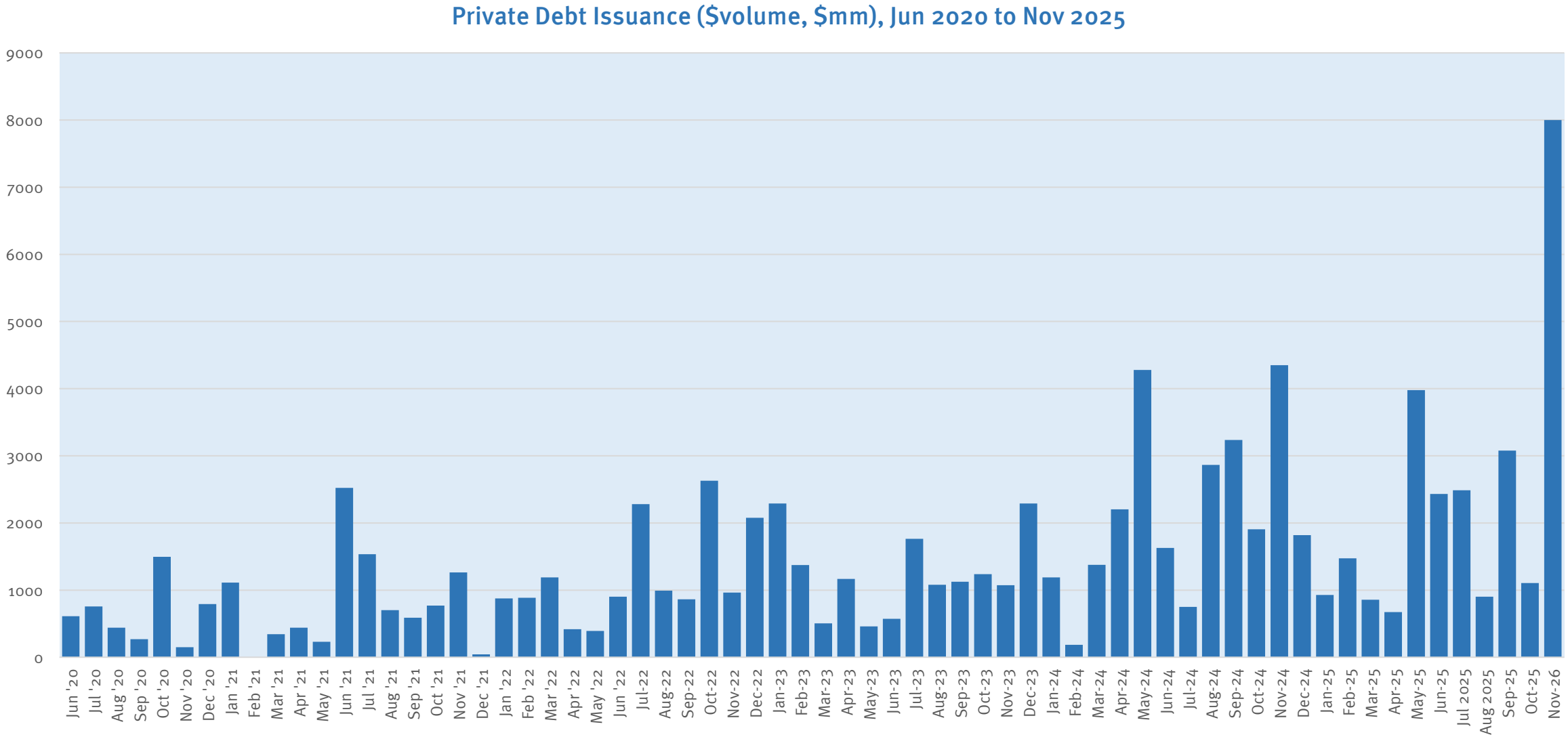
Source: Data from CapitalIQ, Crunchbase. Data for Sep 2025 is extrapolated based on results through July 11th.

Venture Equity Private Deal Pace Showing Strength



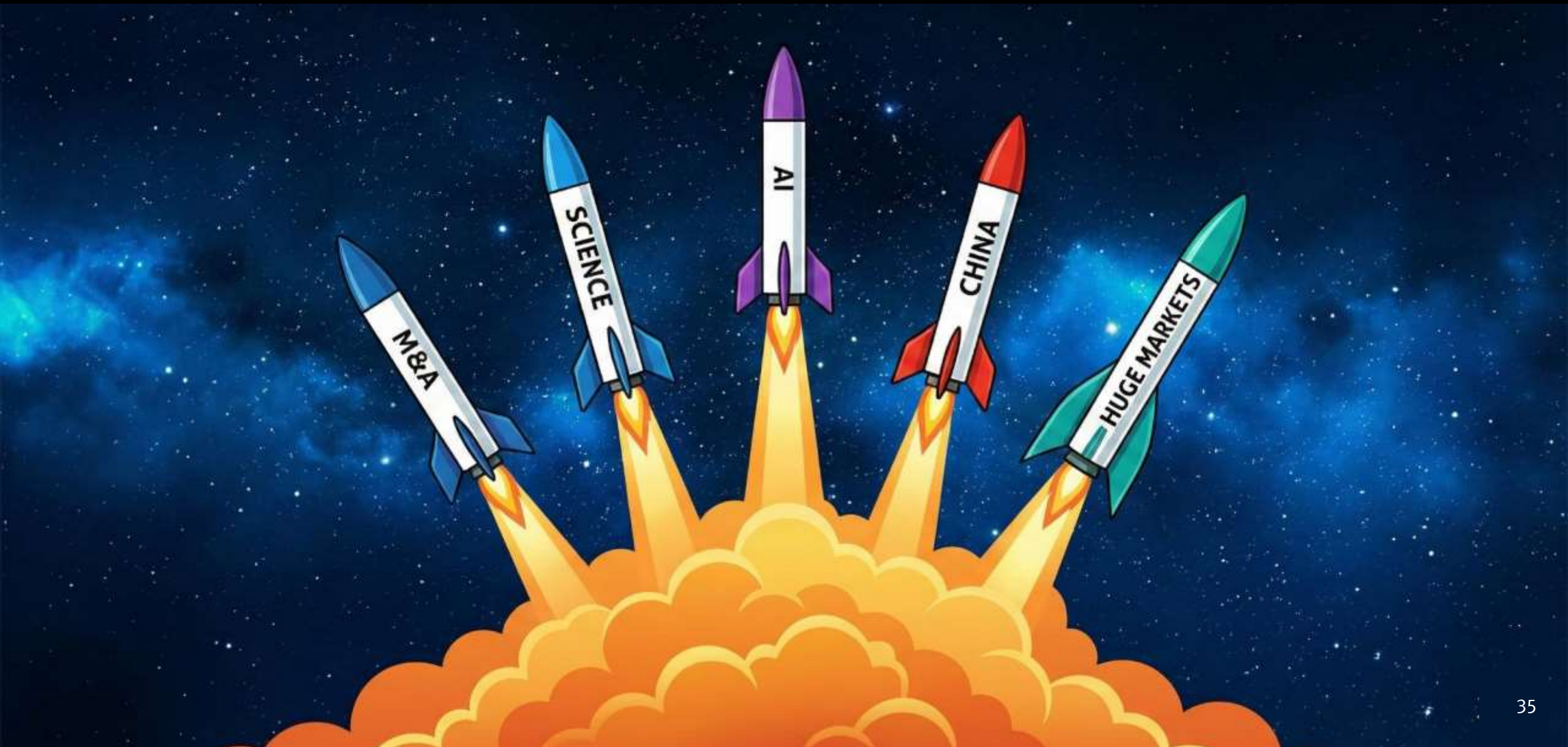
Source: Data from CapitalIQ, Crunchbase. Data for Sep 2025 is extrapolated based on results through August 15th.

Biopharma Private Debt Placement Volume Extraordinary This Month



Source: Data from CapitalIQ, Crunchbase. Data for Nov 2025 is extrapolated based on results through Nov 21st..

Five Trends are Going to Drive Biopharma for the Next Decade



Trends That Will Drive Biopharma in the Decade Ahead

#1 M&A

Pharma must do M&A because of huge upcoming patent cliffs. This is very good for biotech.

#2 Giant Markets

TAM's of pharma will explode, creating above above average returns for years to come.

#3 China Innovation

China has emerged as a true competitor in biosciences and will reshape the industry.

#4 AI Transformation

AI is going to transform the delivery of healthcare. This will impact the ecosystem including pharma.

#5 Incredible Science

Science will continue to reshape the bounds of humanity's ability to conquer disease.

Note: TAM = total addressable market.

First Trend

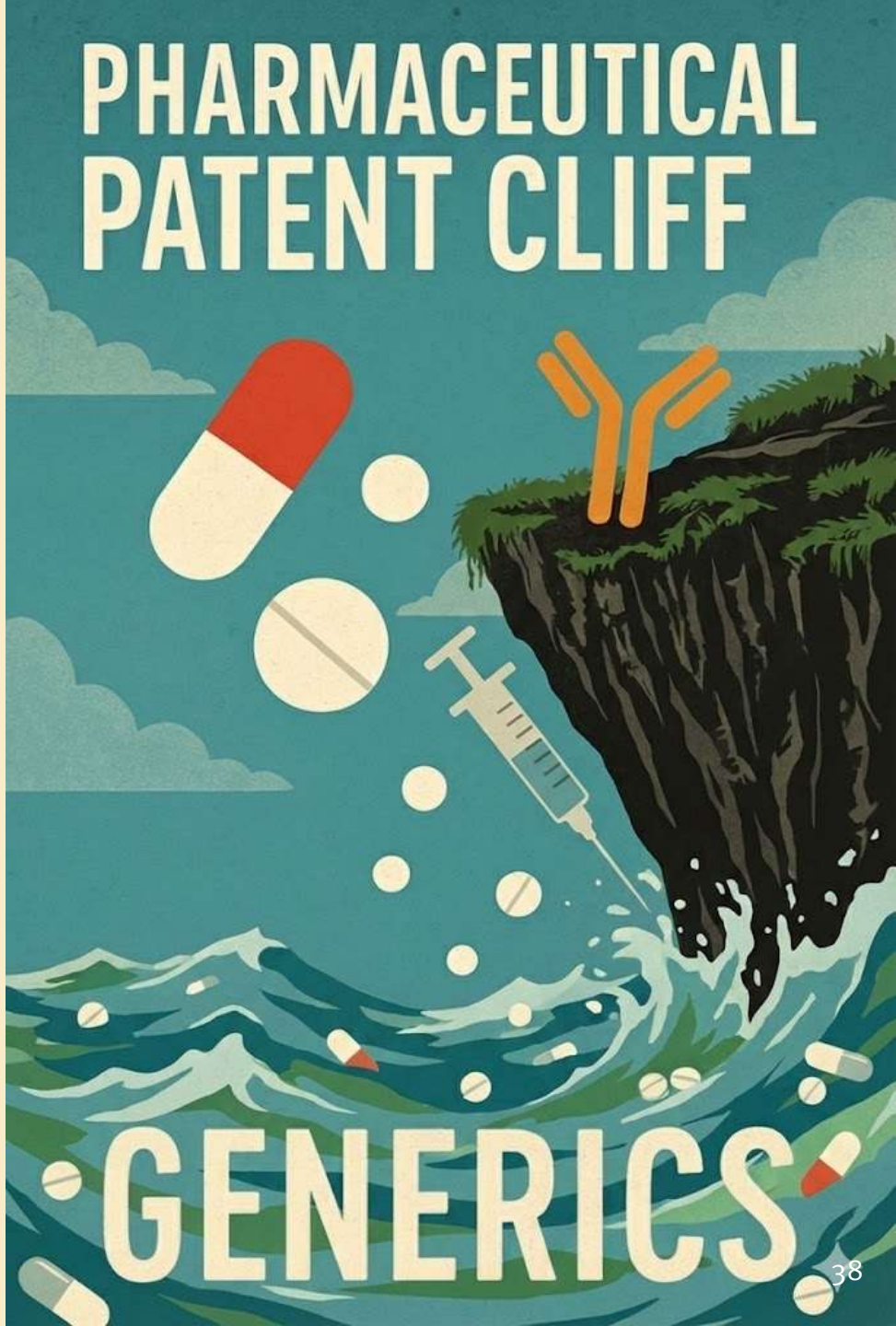
M&A

Massive Pharma Patent Cliffs Ahead

Rosie Bradbury, *Pitchbook*, Sep 12, 2025 (excerpt)

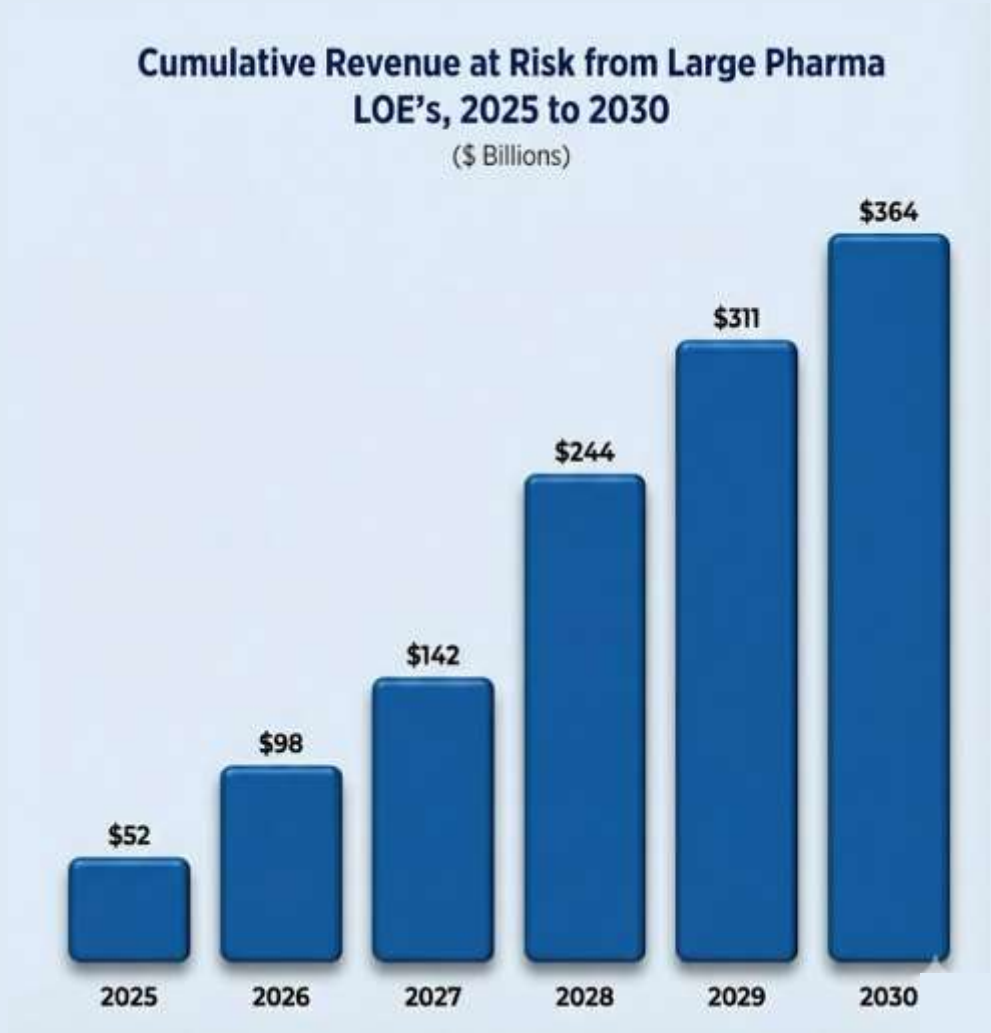
Across the board, from J&J to Pfizer and Eli Lilly, the country's pharmaceutical giants are facing a patent cliff that could spur M&A as they move to fill out their pipelines and close revenue gaps.

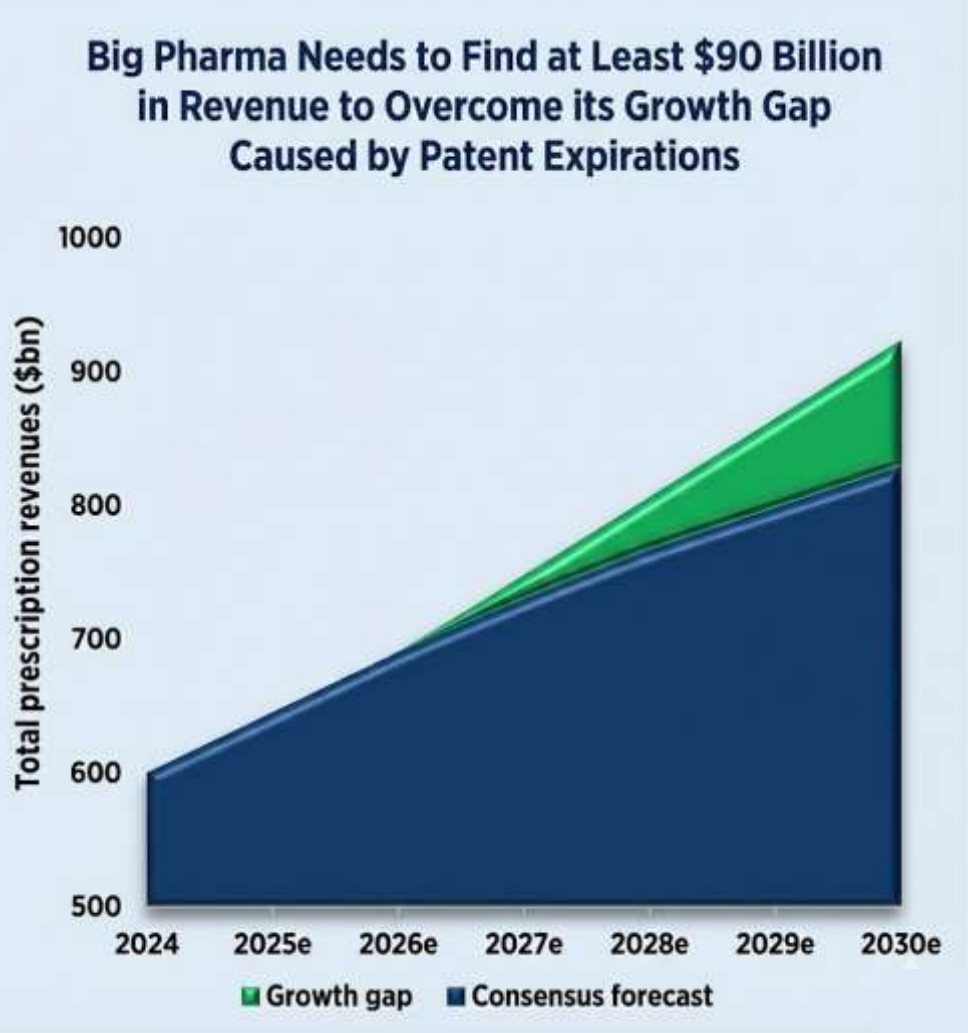
Big Pharma is Facing the Loss of Hundreds of Billions of Revenue. M&A is Pharma's Only Option to Replace the Revenue Losses



Source: https://pitchbook.com/news/articles/as-big-pharmas-next-patent-cliff-looms-biotech-investors-see-dollar-signs

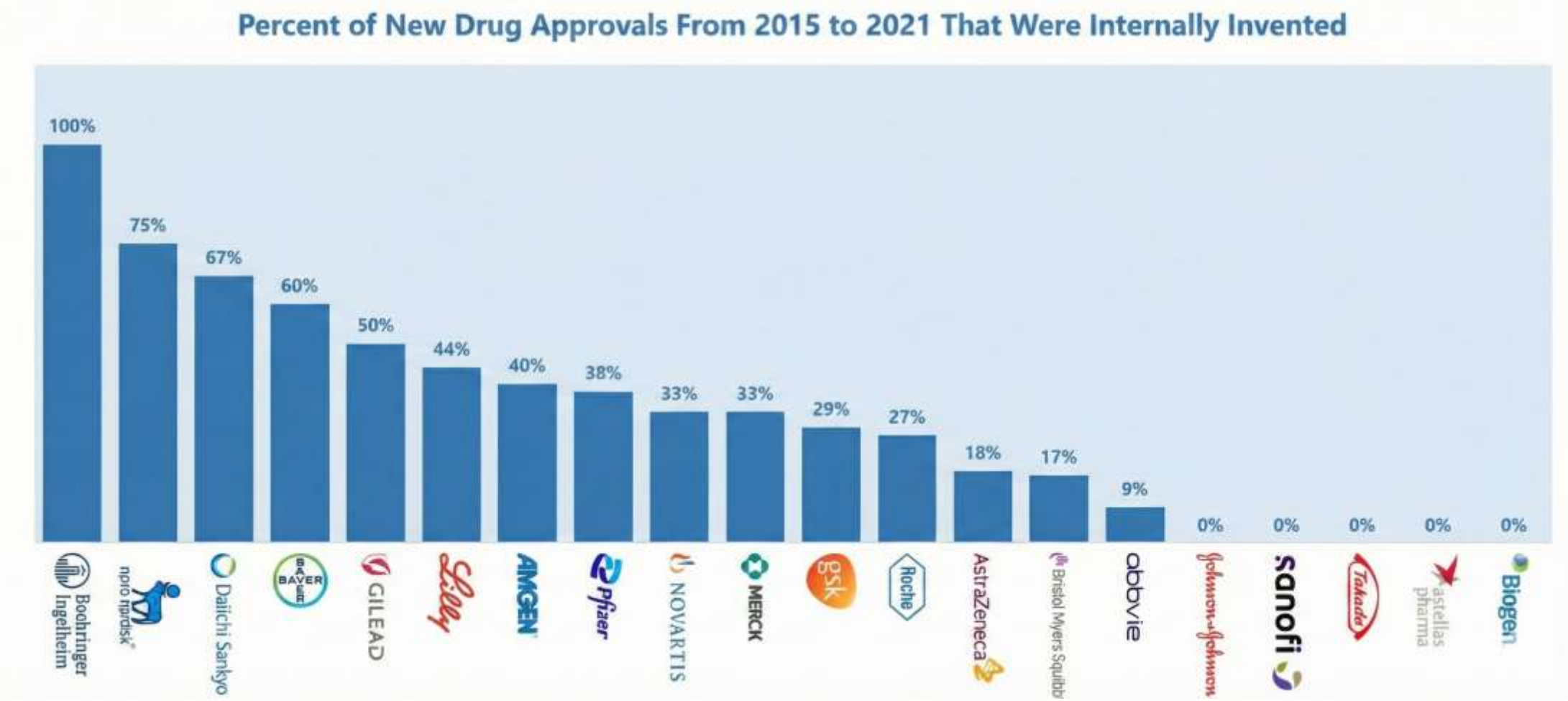
Over 40% of Big Pharma Revenue Faces Patent Expiration in the Next Six Years





Source for both charts: Evaluate Pharma. This is in 2023 sales dollars as per Evaluate Pharma.

Many Pharma Struggle to Replace Drugs That Go Off Patent With New Ones Sourced Internally



Source: https://www.nature.com/articles/d41573-023-00102-z

Top Pharma Have $1.2 Trillion of M&A Firepower Today

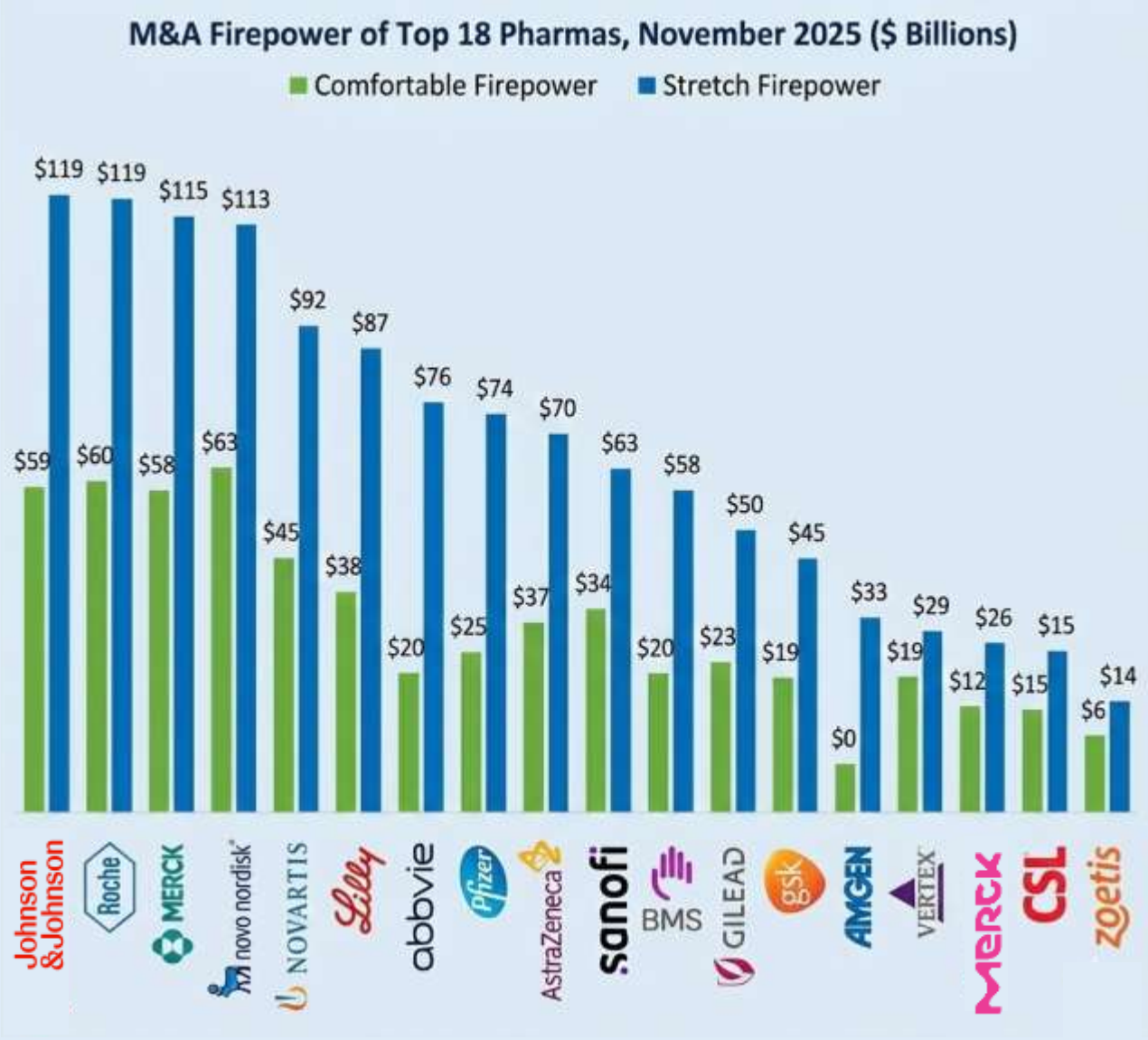
This chart shows M&A firepower of top pharmas. We define comfortable firepower as the amount of debt a company can take on given current EBITDA levels to arrive at a ratio of net debt to EBITDA of 3X.

Stretched firepower would take a company to a ratio of net debt / EBITDA of 5X. Historically, some companies like AZ and Takeda have been willing to go well beyond the 3X net debt / EBITDA comfort levels.

Today, there is $1.2 trillion of stretch firepower and $500+ billion of comfortable firepower among the top 18 companies listed here. This has gone up from 2023 and 2020.

It is important to recognize limits that restrain the use of this firepower, including internal policies on balance sheet strength, credit rating agency requirements, the desire to keep rainy day money and recent commitments to build manufacturing capacity in the U.S.

To illustrate, J&J's Credo speaks of the importance of a strong balance sheet saying, "reserves must be created to provide for adverse times." Wise words. We would be quite surprised to ever see a company like J&J or Roche spend anything like $100 billion in cash on M&A.

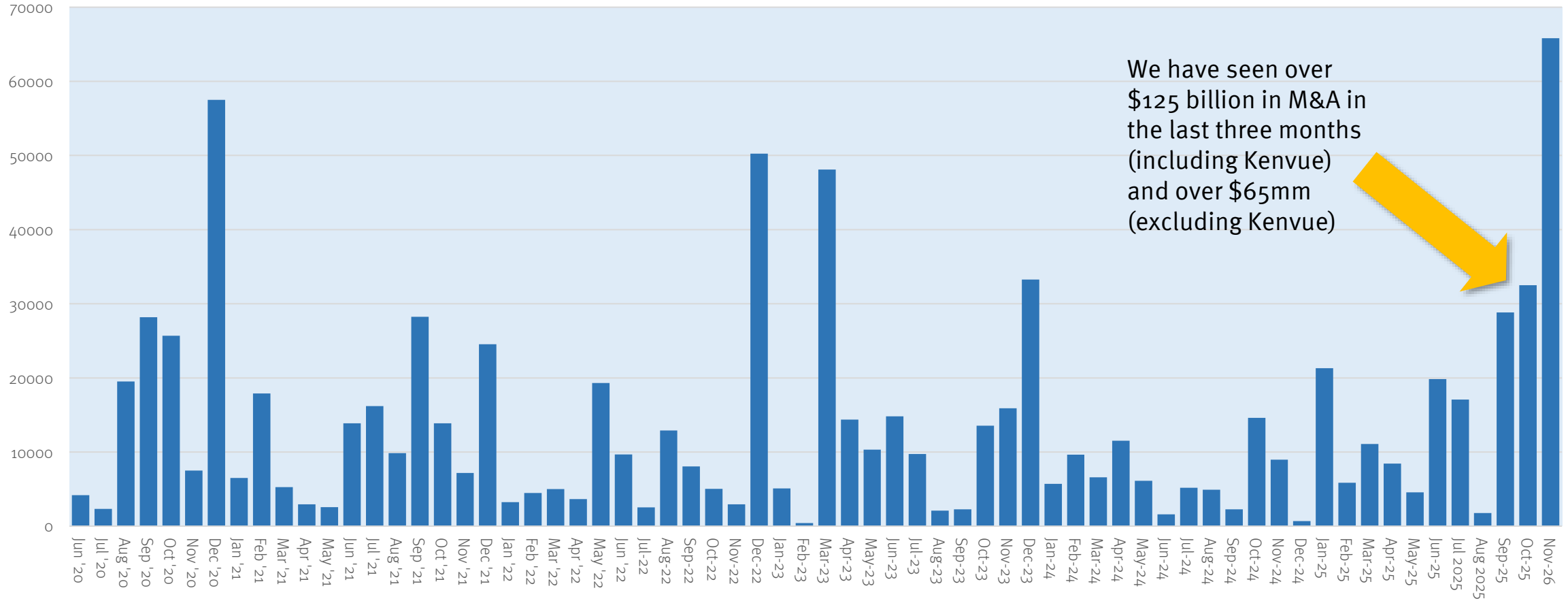


Source: S&P CapitalIQ, Stifel Investment Banking Department Analysis

We are Seeing the M&A Boom Hit Now

We are seeing high volume of biopharma M&A so far in the second half of 2025. We expect this to continue and, if anything, the pace of M&A to pick up in 2026.

Monthly Biopharma M&A Activity ($volume, $mm), June 2020 to November 2025



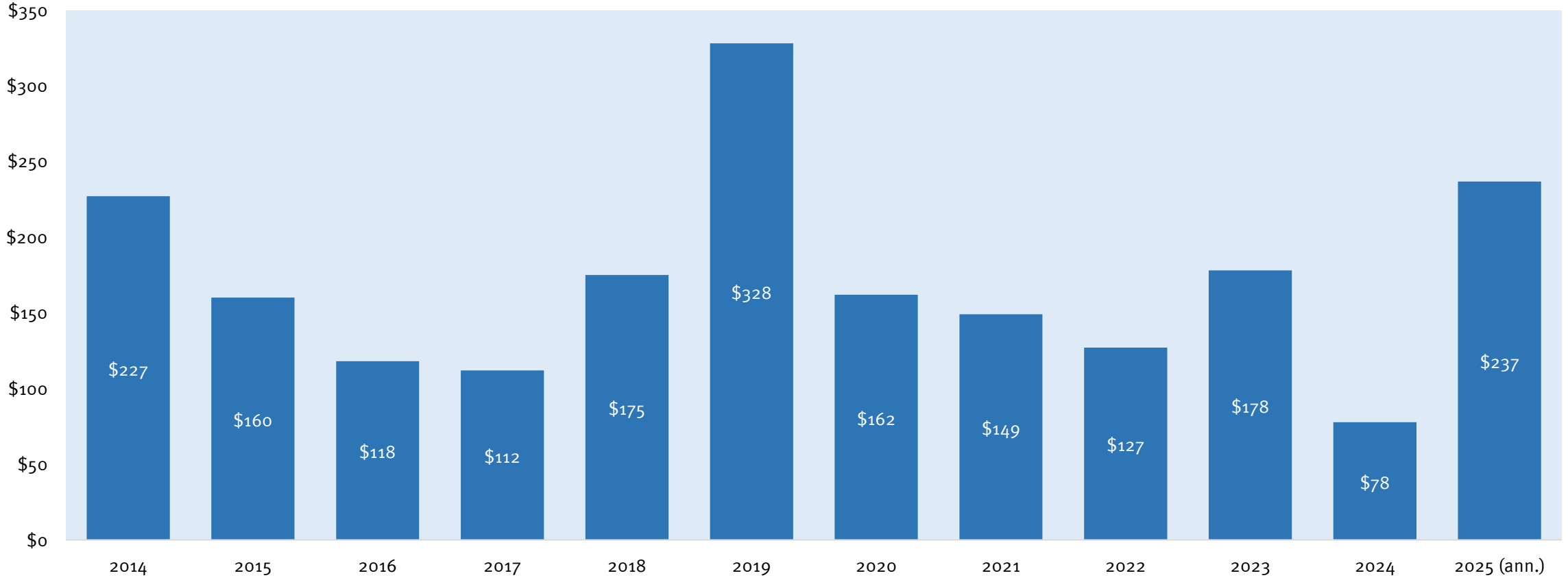
Source: S&P, CapitalIQ.

We are Tracking for the Strongest Year in M&A Since 2019

The recent pace of biopharma M&A is very high – tracking to the be the second most active year for biopharma M&A in history. If the pace of the last three months continued for a year, it would surpass the all-time record of 2019. What is so remarkable this year is that there have been no horizontal mergers between larger pharmas. And we are still running at near record levels.

M&A Volume in the Biopharma Sector, 2014 - 2025

($ Billions, Worldwide)



Source: S&P, CapitalIQ. Note: 2025 data annualized as of Nov 21, 2025.

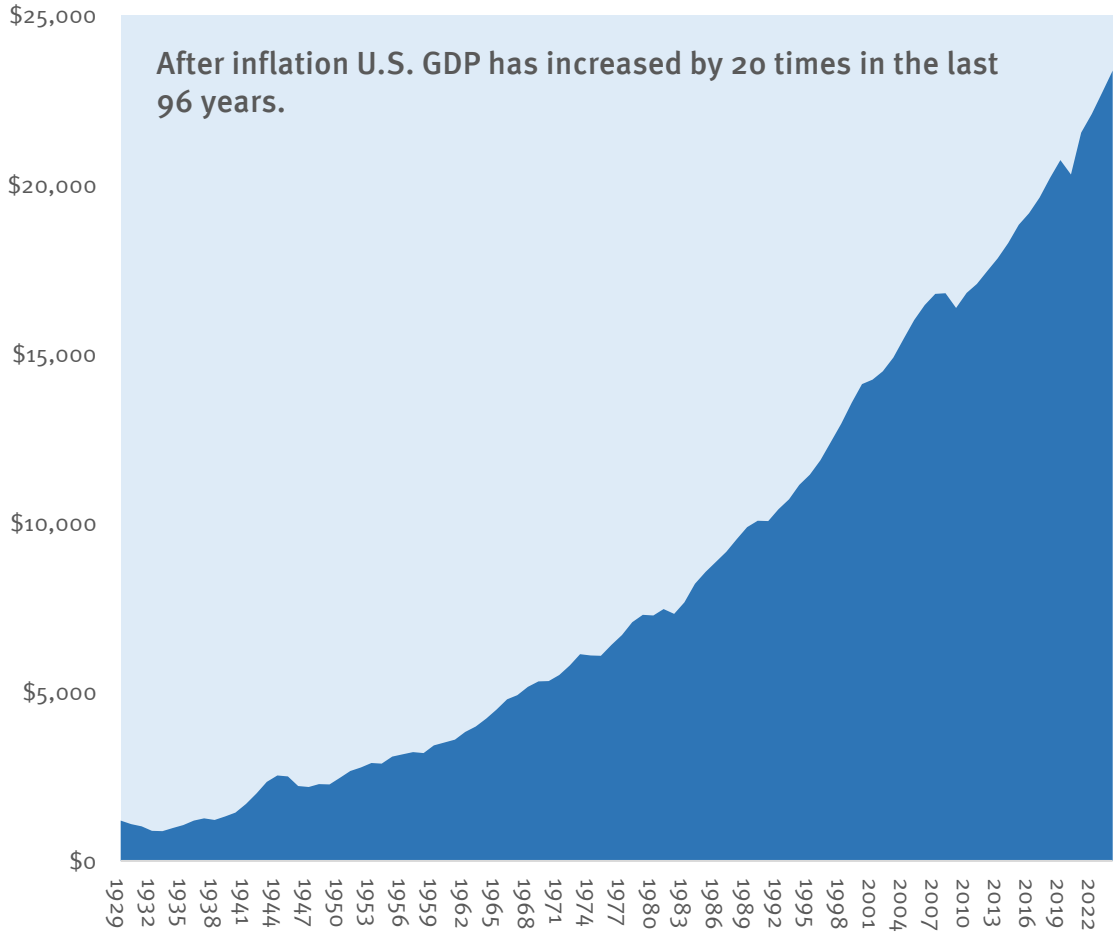
Second Trend

Giant Markets

Real GDP is Up 20-Fold Since 1929. Pharma Spend is Up Much More Since Then

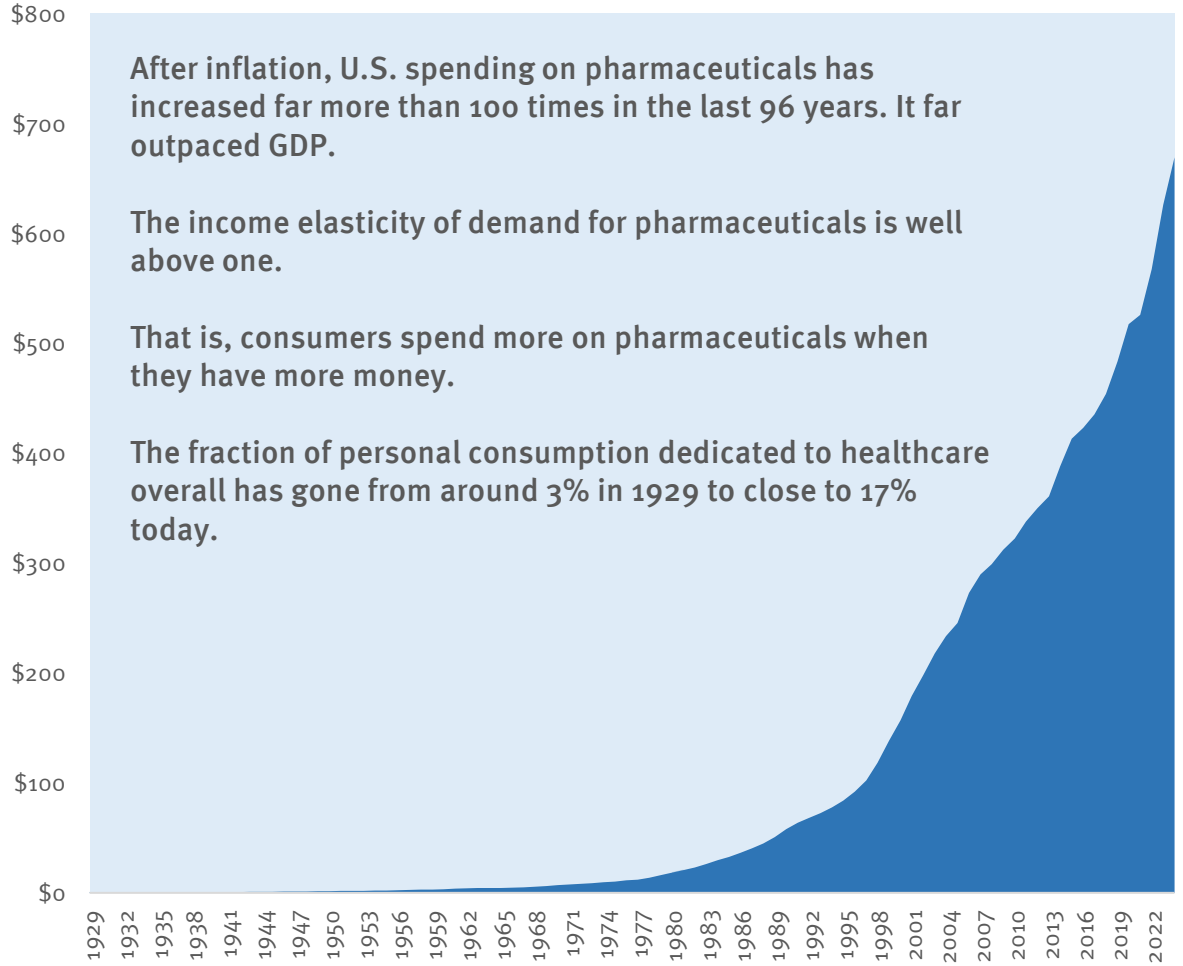
Real Gross Domestic Product in the US

($Billions, 2017 Dollars), 1929 to 2024



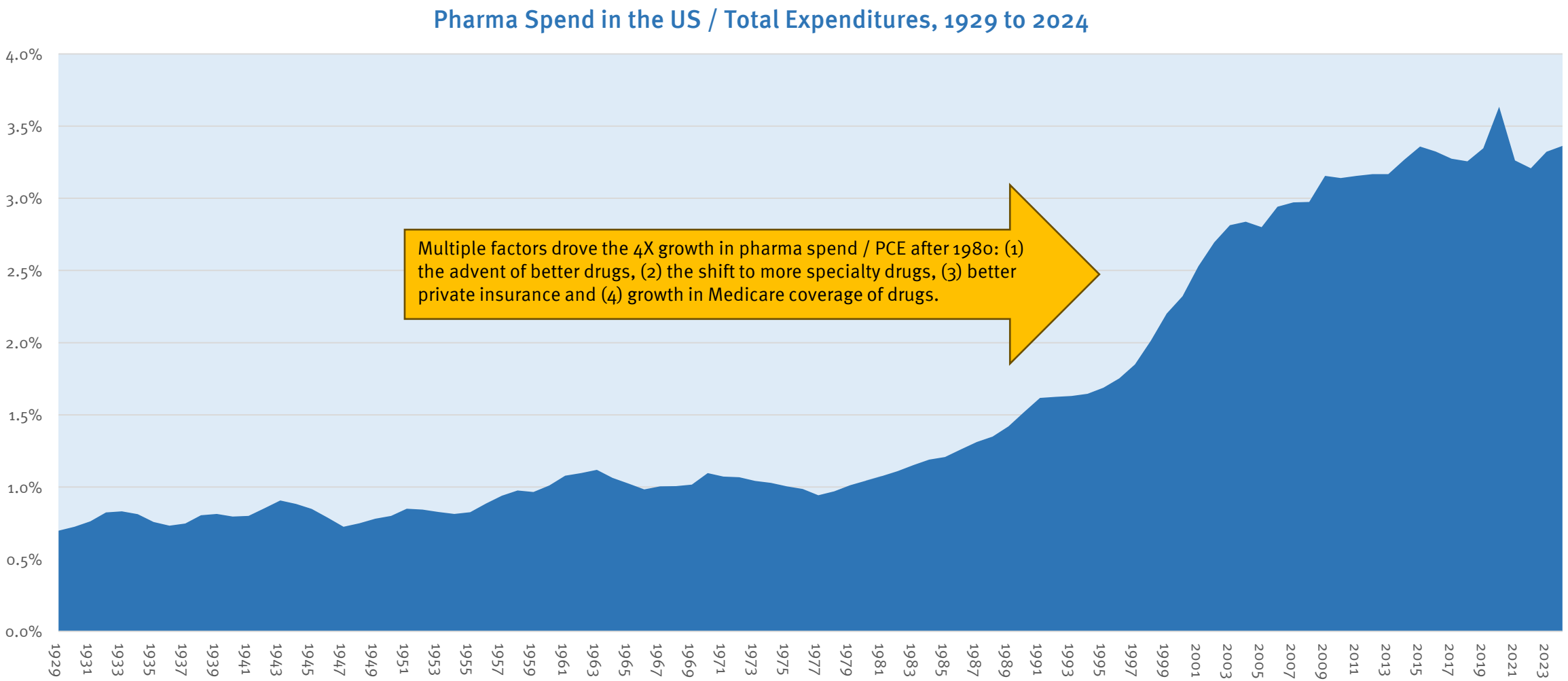
Real Pharmaceuticals Spend in the US

($ Billions, 2017 Dollars), 1929 to 2024



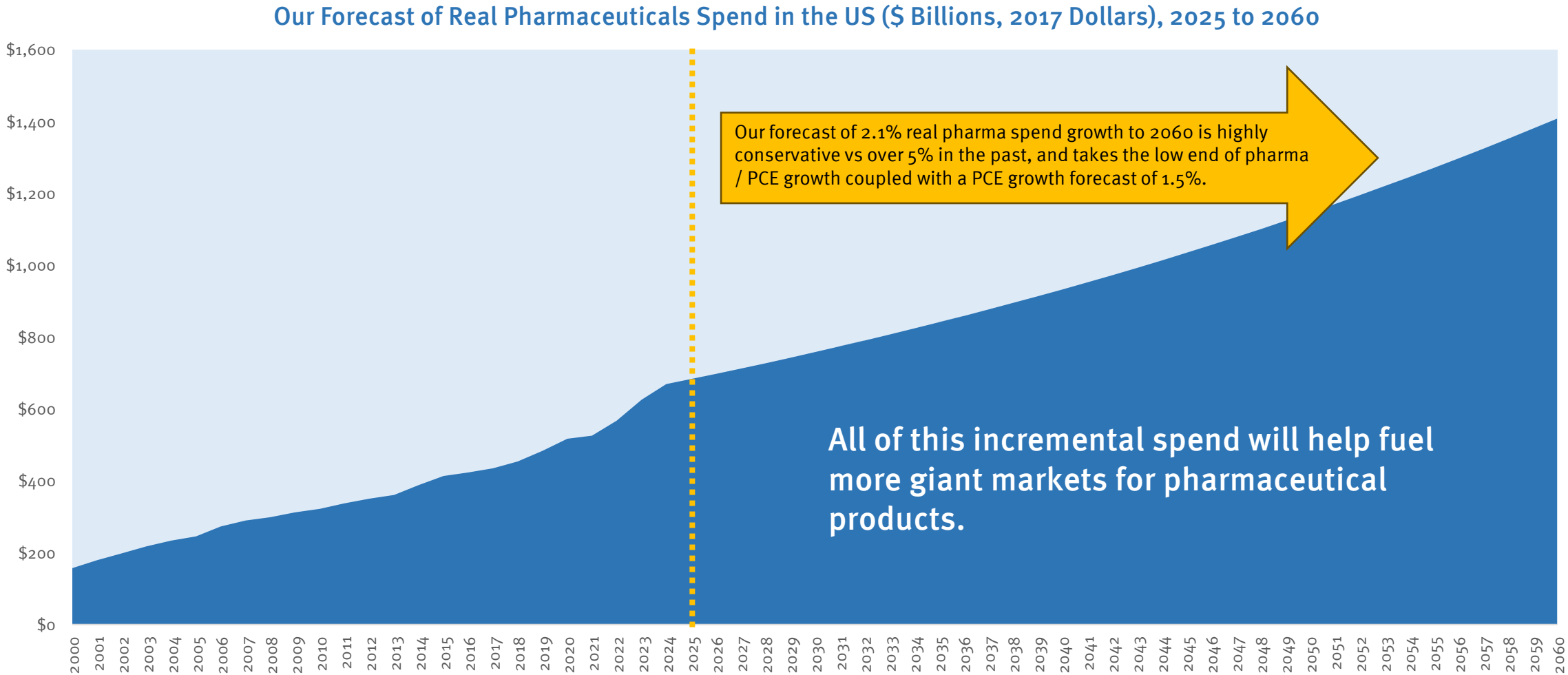
Source: National Income and Product Accounts of the United States, Federal Reserve Bank of St. Louis FRED database.

Pharmaceuticals Today Comprise 3.5% of Total Personal Consumption Expenditures (PCE) in the United States



Source: National Income and Product Accounts of the United States, Federal Reserve Bank of St. Louis FRED database.

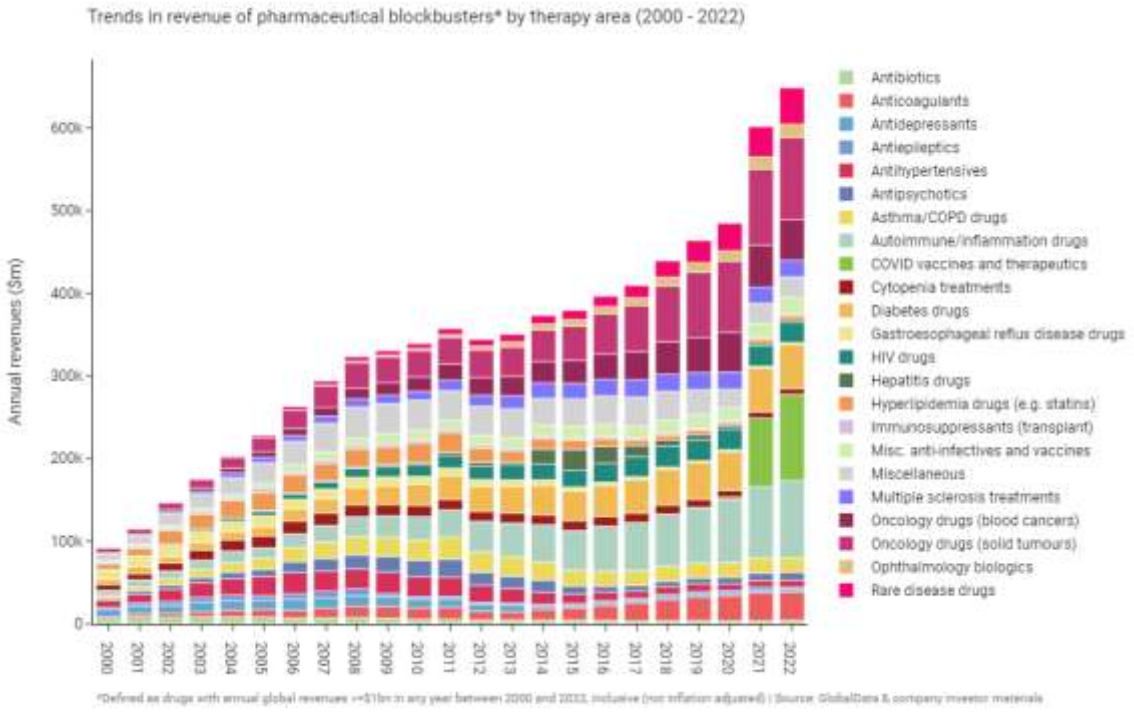
We Forecast That Real Pharma Spend Will at Least Double Over the Next 35 Years Due to Increasing Wealth

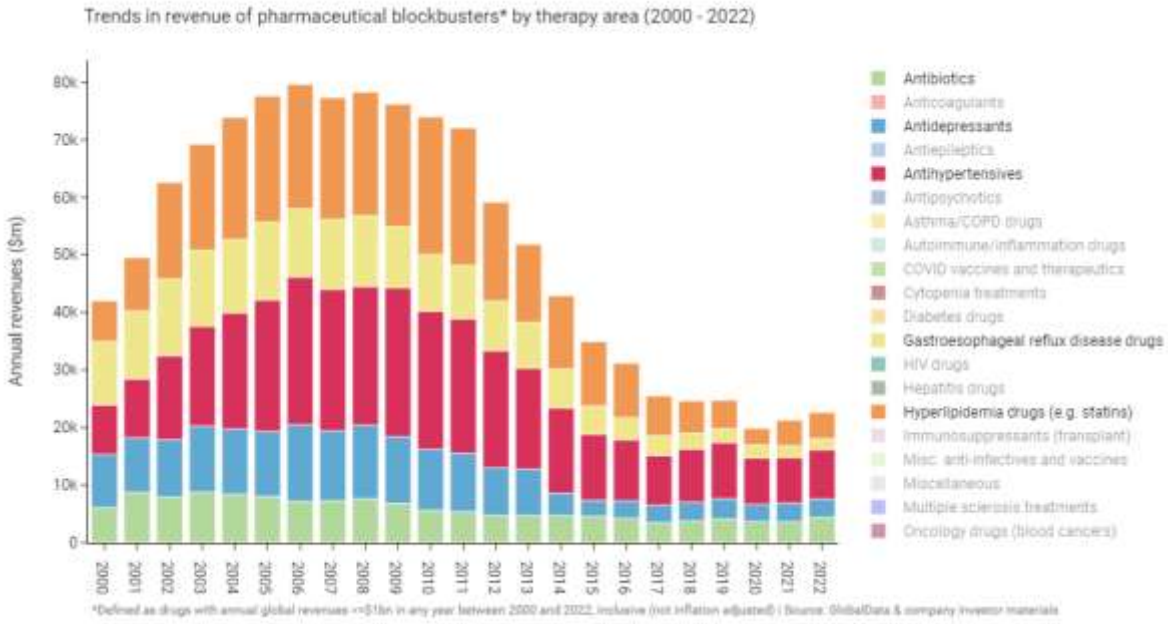


Source: Stifel Investment Banking Department

As Blockbusters Came to Dominate Pharma in 2010+ Era, There Were Far Fewer Big Products for Common Diseases

Alex Telford, Pharmaceutical Blockbusters: the Past, Present, and Future, 2023



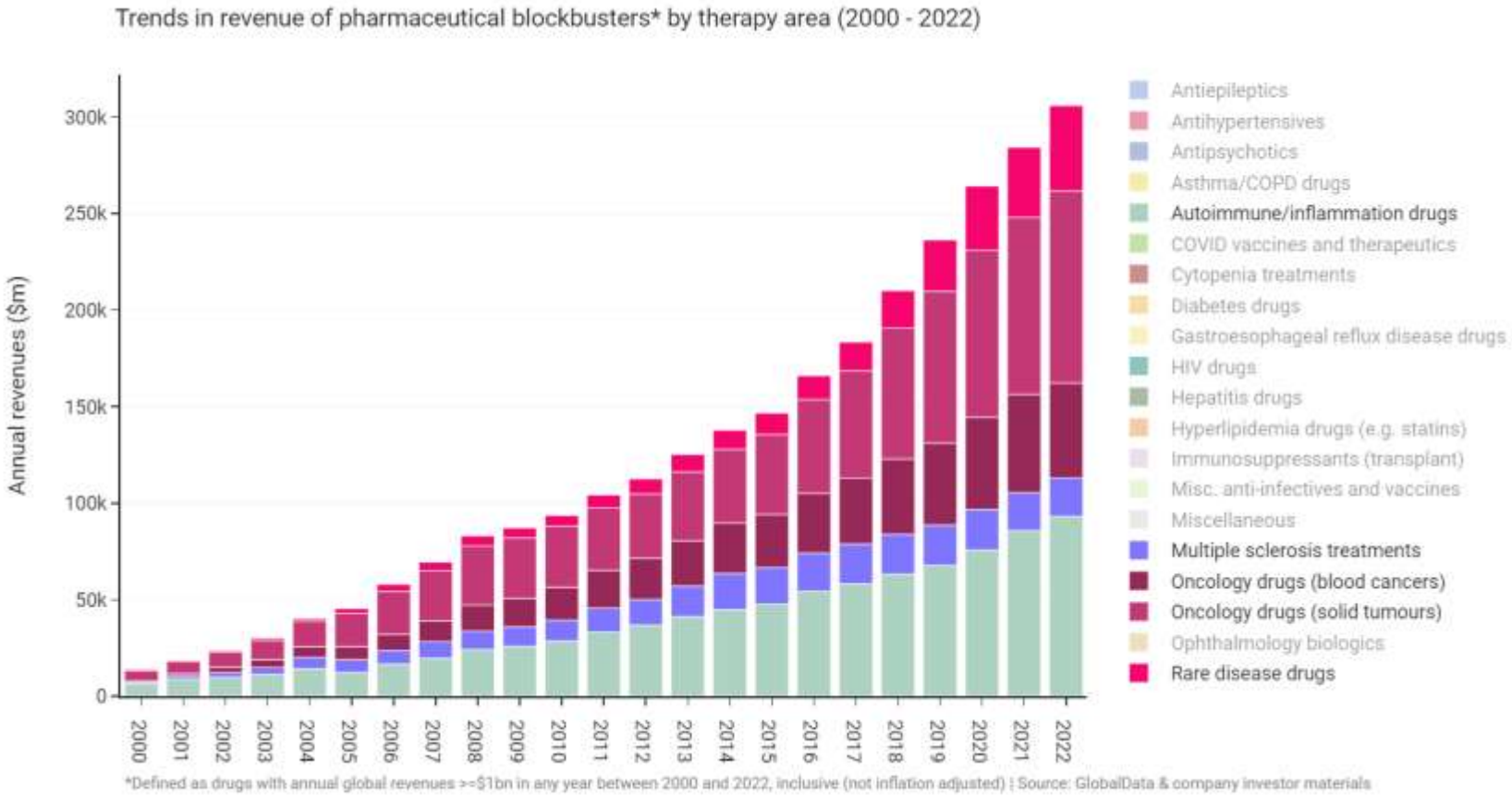


Source: Alex Telford, https://atelfo.github.io/2023/02/26/pharmaceutical-blockbusters-the-past-present-and-future.html

Autoimmune, Cancer and Rare Disease Drugs Blockbusters Drove the Pharma Market in the 2005 to 2022 Period

Alex Telford, Pharmaceutical Blockbusters: the Past, Present, and Future, 2023

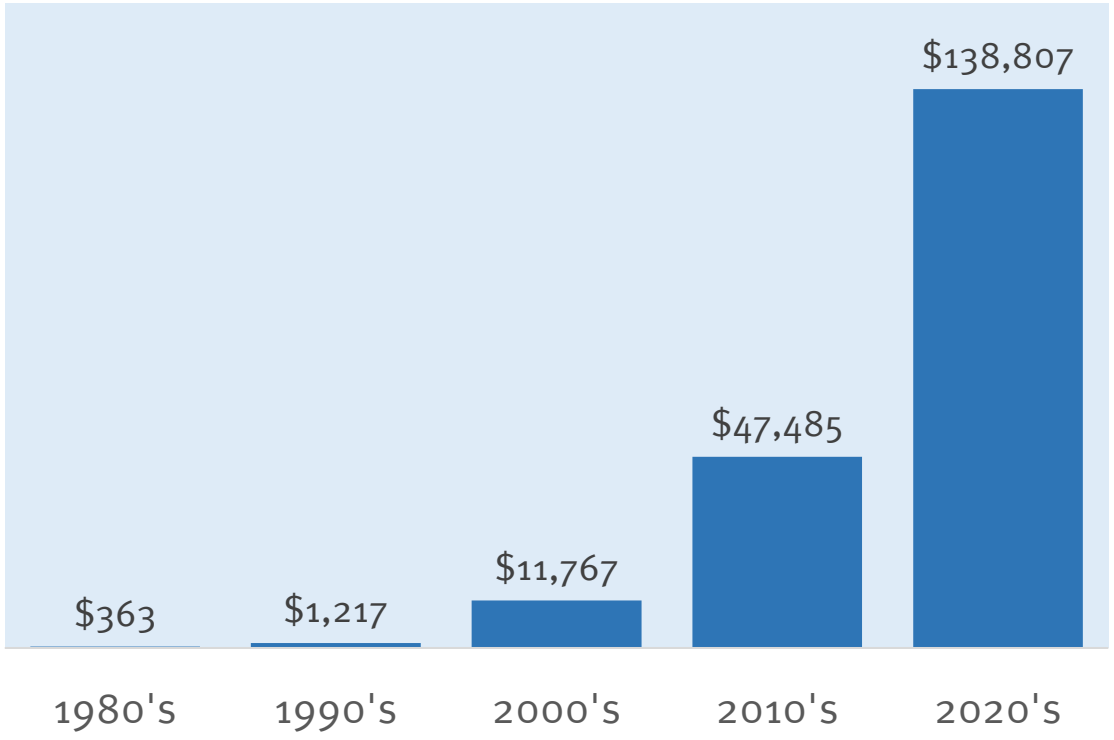
Cancer and rare disease drugs can be thought of as high-cost drugs for narrow markets while autoimmune drugs can generally be thought of as medium cost drugs for large markets.



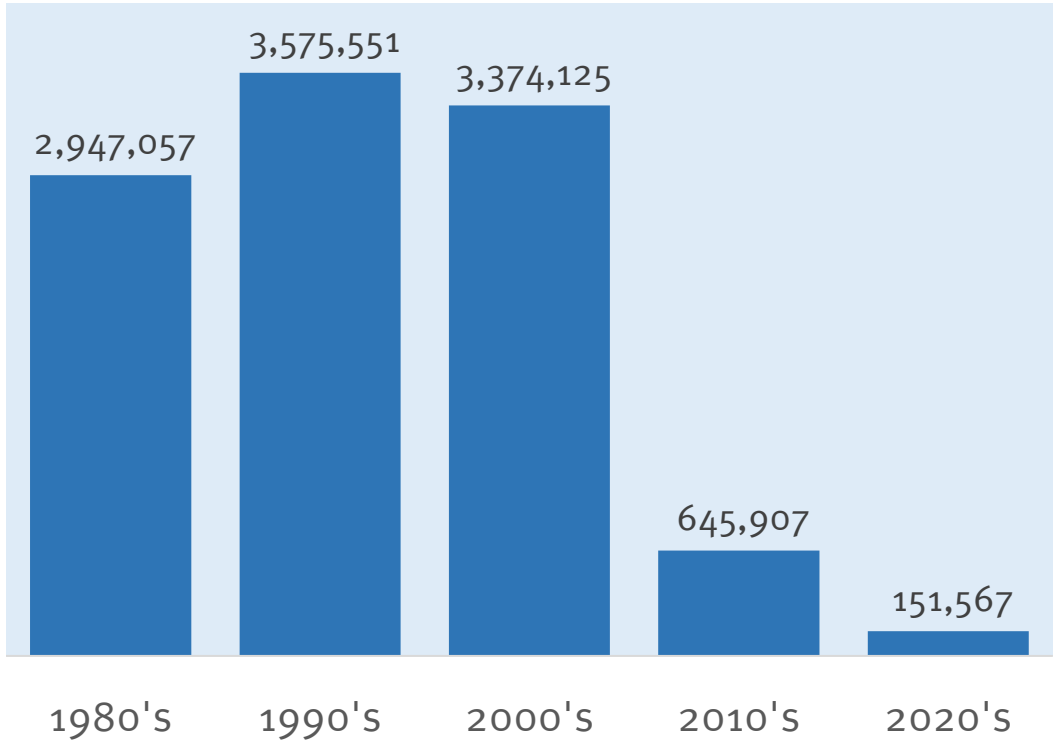
Source: Alex Telford, https://atelfo.github.io/2023/02/26/pharmaceutical-blockbusters-the-past-present-and-future.html

Example of Repricing for Narrower Markets: Cardiovascular Drugs

Average Per Annum Price for U.S. Market at Launch (53 cardiovascular drug approvals), 1980 to 2025



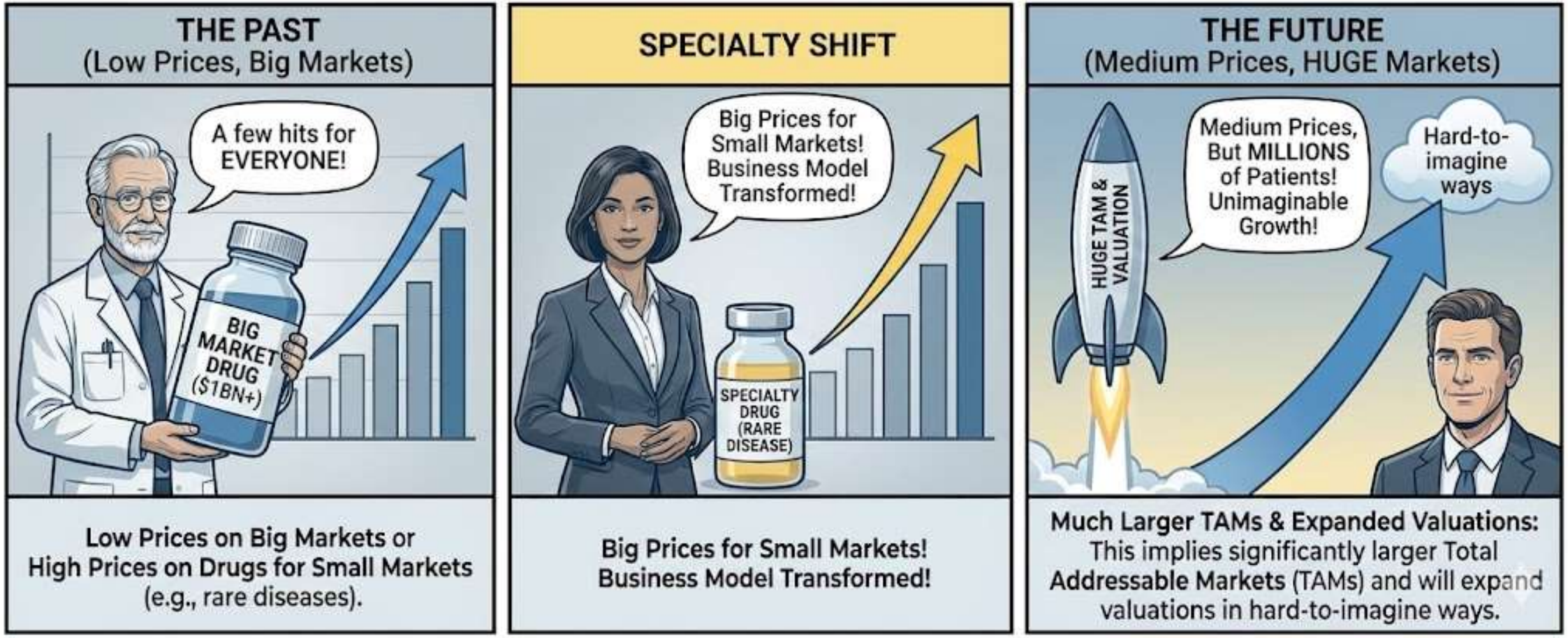
Average Number of Patients in Indication at Launch (53 cardiovascular drug approvals), 1980 to 2025



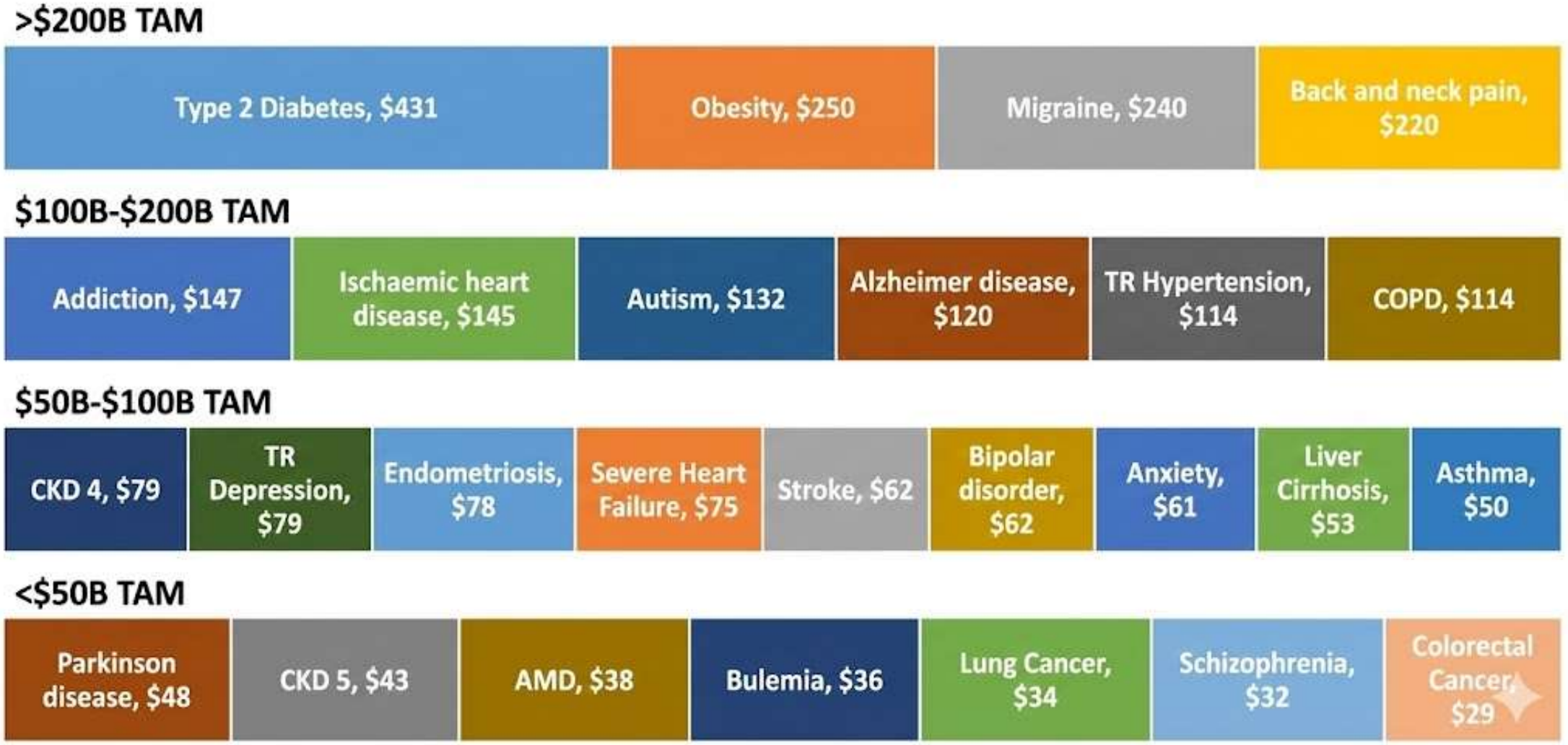
Source: Stifel Investment Banking Department

Higher Societal Wealth Opens the Door to More $50 Billion+ Drugs

We are highly bullish on the biopharma sector because larger social budgets for pharmaceuticals open the door for more drugs like tirzepatide that charge medium prices for large markets and achieve exceptional revenue. This is a big change from the specialty business model which has dominated the pharma industry for the last fifteen years. Think going from a blockbuster in the 1990s ($1 billion in sales) to the mega blockbuster in the 2010's ($10 billion plus in sales) to drugs that routinely do over $50 billion in sales a year in the future. These drugs deliver substantial value to patients and payors across very large markets.



TAM Math for Large Markets If You Apply Appropriate Price Benchmarks Based on Analogous Products

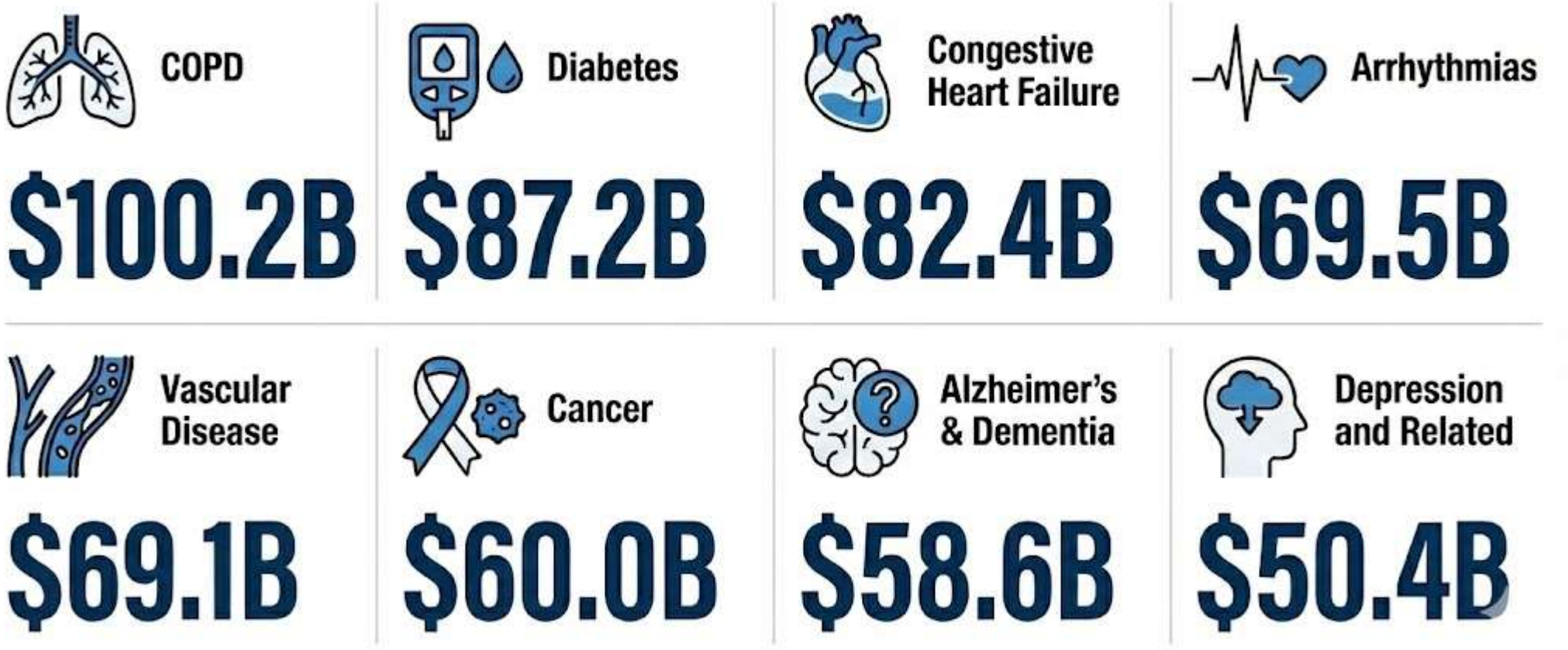


Source: Stifel Investment Banking Department Analysis based on U.S. prevalence and incidence data versus market pricing tolerance using existing benchmarks in the same or similar disease states.

Medicare Advantage Spending by Selected Chronic Diseases

Top Medicare Advantage Expenditures per Annum by Disease

(excluding Rx, paid HCC's only, $ billions, 2021 figures from Medpac)



Note: These figures are estimated by multiplying prevalence estimates from MedPac for key HCC's by average spend per disease state obtained from the literature. Most spend is on individuals with multiple chronic conditions. The numbers shown here overcount actual spend because they are not specific to spend attributable to the single disease. On the hand, note that we have not included atherosclerosis as a disease state as it is not, in general, reimbursed in Medicare Advantage.

Conventional Wisdom Suggests that Large Primary Care Markets are a Very Difficult Place for Pharma to Win

The last 50 years of the pharmaceutical industry has been one where large markets were extremely expensive to cover with giant sales forces, hard to access doctors and tight-fisted payors. This is a key reason pharma shifted resources to specialty drugs. What is changing now is the growing importance of consumer pull in a world of powerful omnichannel marketing.

1980s: The Birth of the Blockbuster → "The Golden Age"

- Huge primary-care sales armies (10,000+ reps at some companies)
- Face-to-face detailing was the dominant marketing channel
- Doctors had broad discretion to prescribe

1980s

1990s: Expansion, DTC Ads, & Managed Care

- DTC became legal in 1997 → huge marketing budgets
- Sales forces grew even larger
- Managed care emerged → formularies started to matter

1990s

2000s: Gigantic Salesforces & Patent Cliffs

- Sales force sizes peaked around 2005. Pfizer, GSK, Merck each had 10k–12k+ reps
- Patent cliffs (e.g., statins, PPIs, SSRIs all losing exclusivity)

2000s

2010s: Rise of Specialty Drugs → Smaller, Expert Sales Models

- Smaller salesforces
- Direct negotiations with payors became much more important

2010s

2020s: Omnichannel Marketing & & Payor Dominance

- Payors dominate
- Consumer pull and DTC ever more important
- Omnichannel approach

2020s

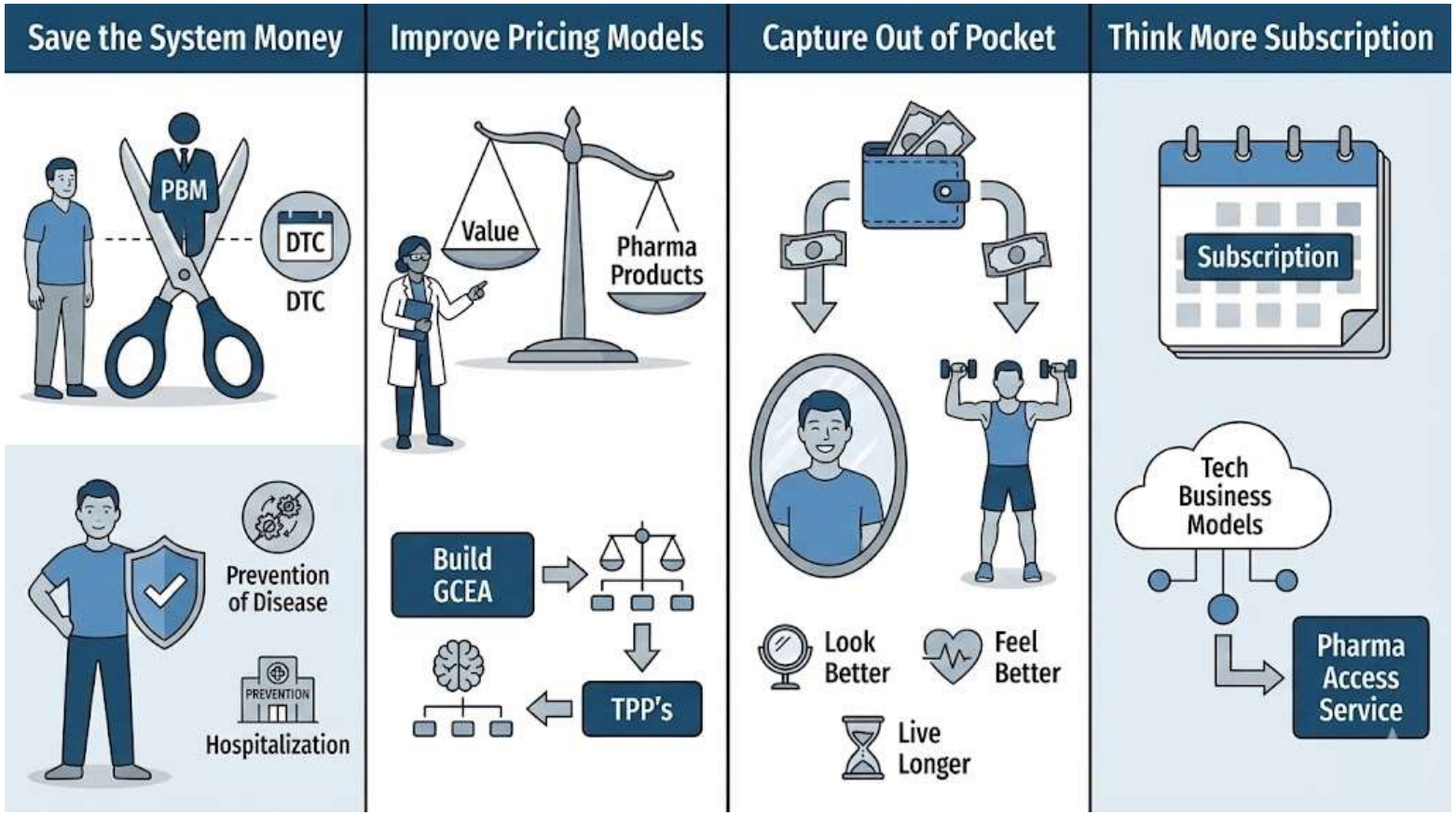
The Road to Higher Spend Per Drug in the Next Few Decades:

Capture Out of Pocket Dollars and Save the System Money

The U.S. redefined what health spending looks like with growing government reimbursement in the 2000's taking total spend up to 17% of GDP. Pharmaceuticals got about a sixth of that pie.

The pharma piece has grown quickly in recent decades mainly because of the specialty drug business model – which has done a good job of tapping into growing insurer and government pharma budgets.

While specialty drugs are not going away anytime soon, we think there are four ways to grow pharma spend beyond the "natural" insurer and government budget constraints. These ideas are illustrated in the chart at right.

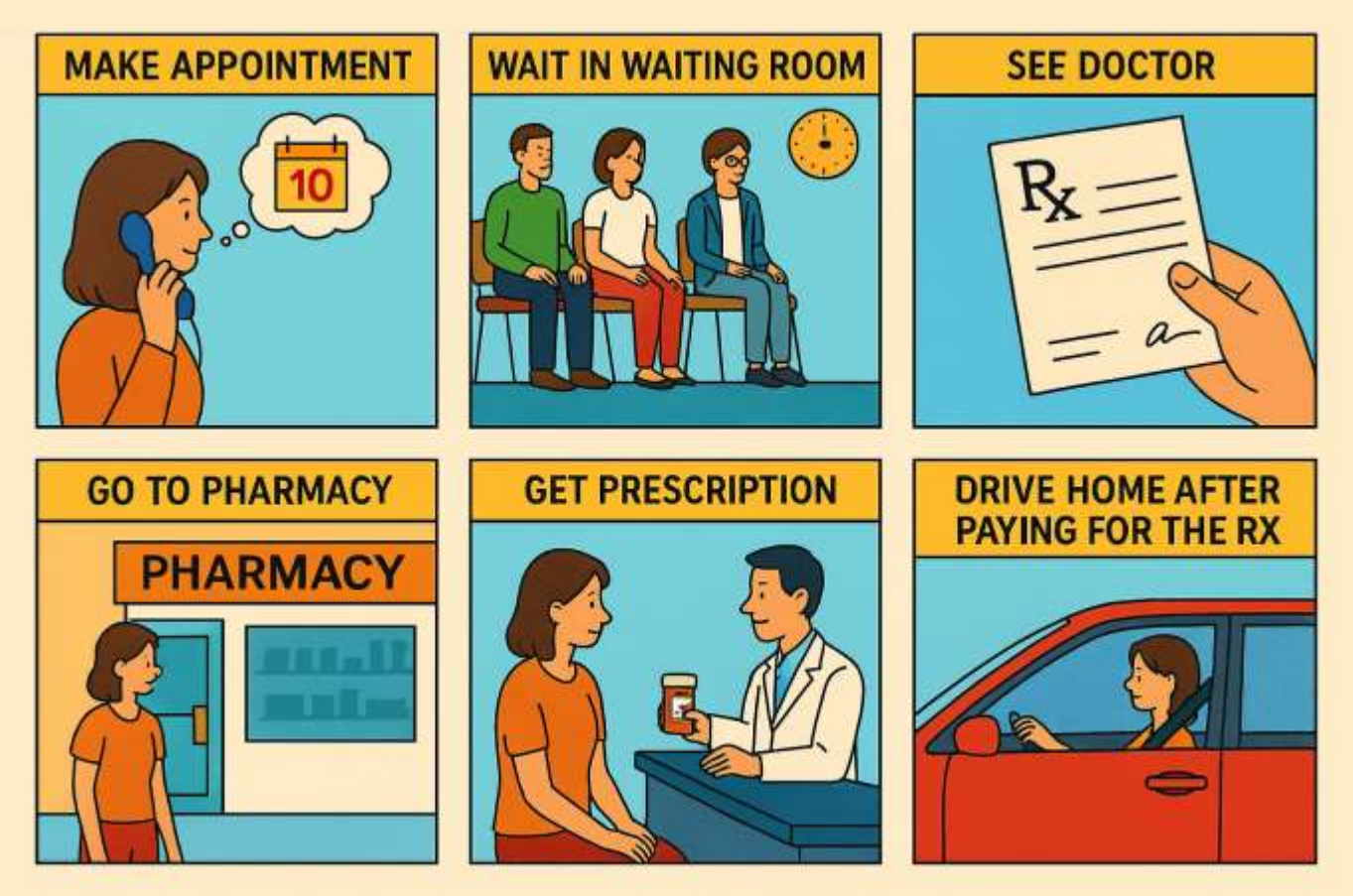


A great place to start it to cut out middlemen as is being done with recent moves to the direct-to-consumer (DTC) platforms by companies like Lilly and Pfizer. There is also a potential win in keeping patients away from expensive hospital procedures with better preventive medicines. Pricing models themselves for drug can be improved, particularly with GCEA (as discussed by us many times) and by building TPP's that reflect value-based factors. The out-of-pocket market is quite large as demonstrated by obesity drugs and could be much bigger still. Finally, tech companies have very skillfully exploited subscription-based business models to elevate revenue. This has not been part of the pharma ecosystem except through health insurance plans whose monthly payments can be thought of, in a way, as subscriptions. We think there is substantial room to create "pharmaceuticals as a service" subscription models for employers and individuals.

DTC: How Patients are Accessing Prescriptions is Changing Rapidly

Online e-prescribing sites in the U.S. like HIMS work *asynchronously*. The consumer provides input to the physician and doesn't have to wait for the physician to react using a traditional appointment format. The physician reads the input later (but, usually within an hour or two) and then dispenses a prescription. The prescription is dispensed much closer to the moment of demand despite the asynchronous nature of the transaction. If urgency is particularly high, it is possible in some locales to have a prescription delivered via a service like Capsule Pharmacy or Uber.

The old way: Getting a prescription is a multi-day process that takes hours.



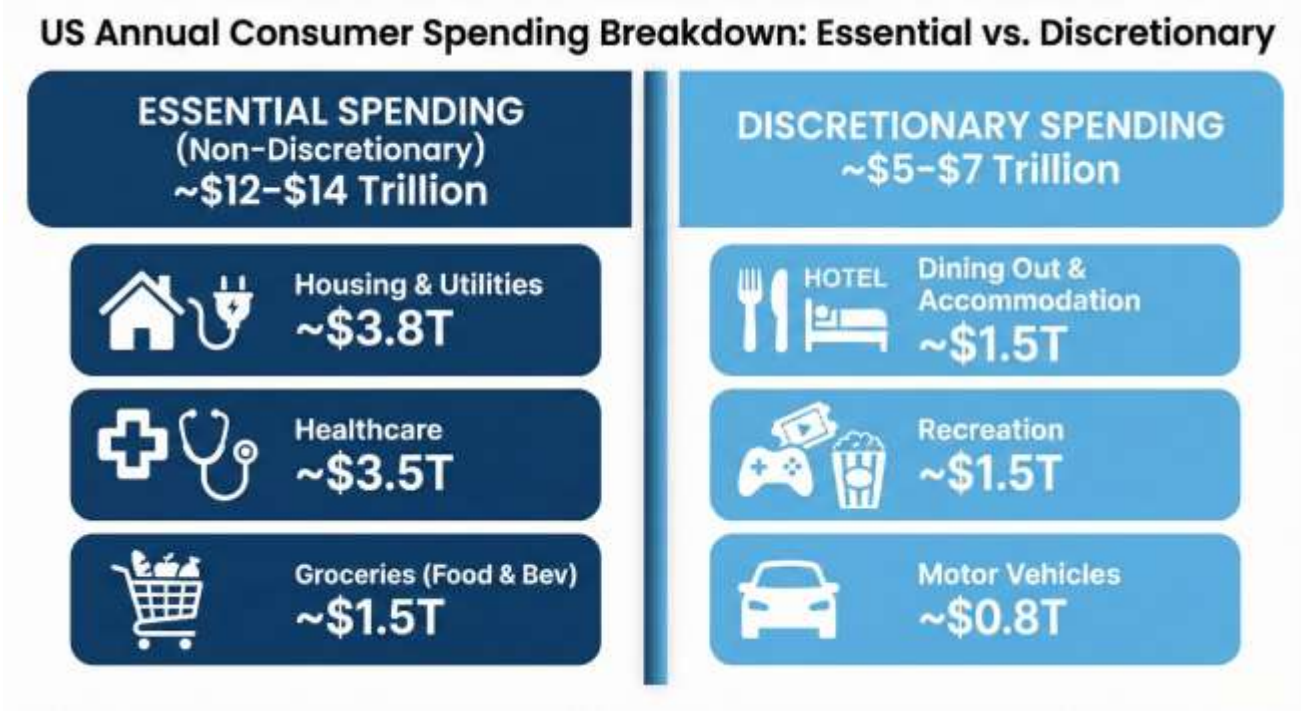
Versus

The new way: Getting a prescription takes less than fifteen minutes.

Huge Untapped Out of Pocket Pharma Opportunity

If there is one thing that the obesity market has taught us in the last few years it is that the out-of-pocket pharmaceutical ("OOP") industry opportunity is far larger than many might have imagined. Pure OOP drugs sidestep the payor and the need to have a huge sales force but require a completely different set of marketing skills (e.g., social media). This takes the industry in a direction that is opposite of where it's been headed: the pursuit of ever more costly specialty medicines for narrow indications.

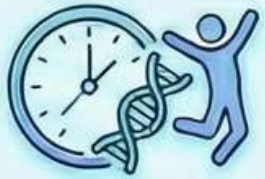
- The average U.S. household spends around $20,000 a year on discretionary items (roughly 30% of spend).
- A top decile U.S. household by wealth spends well over $100,000 a year on discretionary items (50% of spend or more).
- Total U.S. discretionary consumer spending is approximately $5 - 7 trillion per annum –far larger than the pharmaceutical market.
- Obviously, there is substantial room for consumers to substitute spending on restaurants, new cars, entertainment and the like for pharma / wellness if they want to.
- We see no reason why the pharma market couldn't double with discretionary spend if the products were attractive enough.



Illustrative Out-of-Pocket Pharma Spending Opportunities

Aesthetics

Cosmetic treatments, injectables & medical-grade skincare.



Aging

Longevity supplements, hormone therapies & age-management.

Hair Loss

Regrowth foams, serums & oral medications.

Weight Loss

Metabolic health drugs & management programs.

Better Sleep

Sleep aids, circadian rhythm regulators & tech.

Pain Avoidance

Targeted relief patches, topicals & preventative therapies.

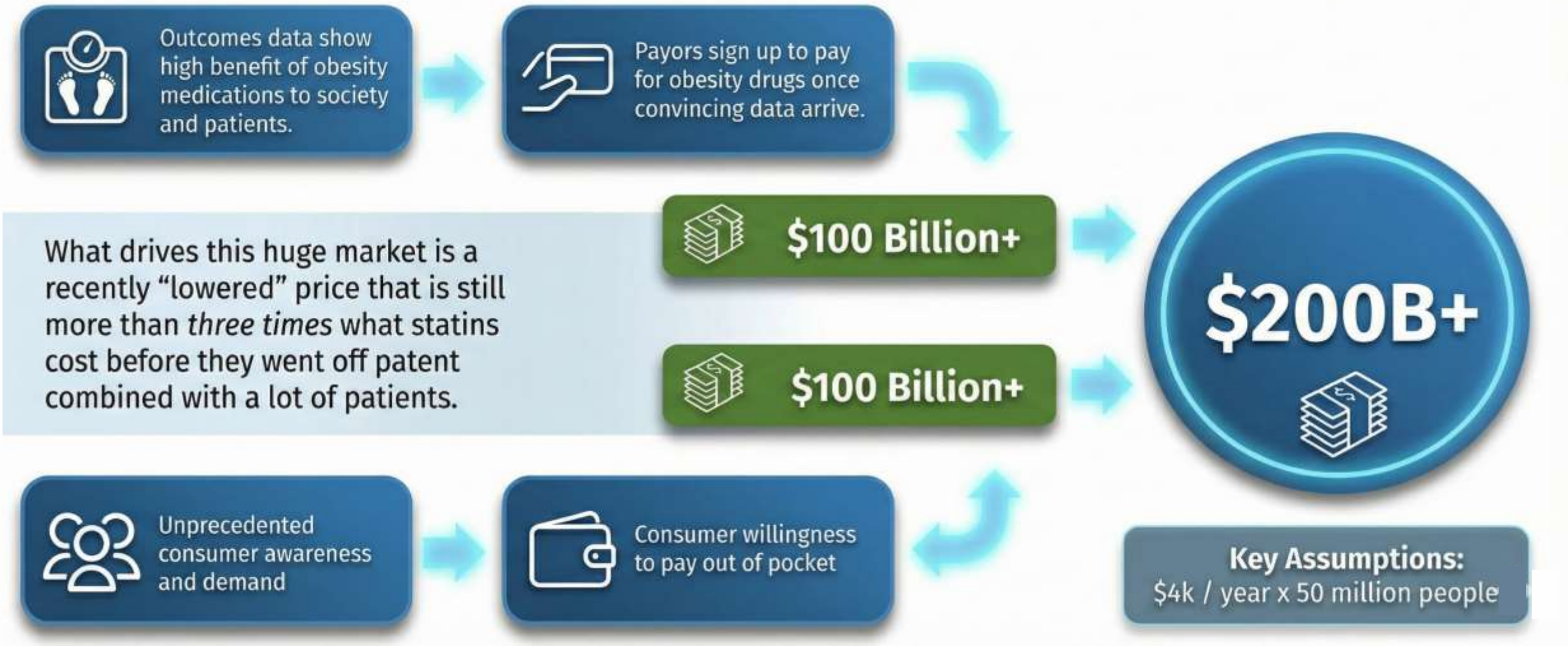
Sexual Health

Performance support, contraceptives & wellness products.

Pleasure Products

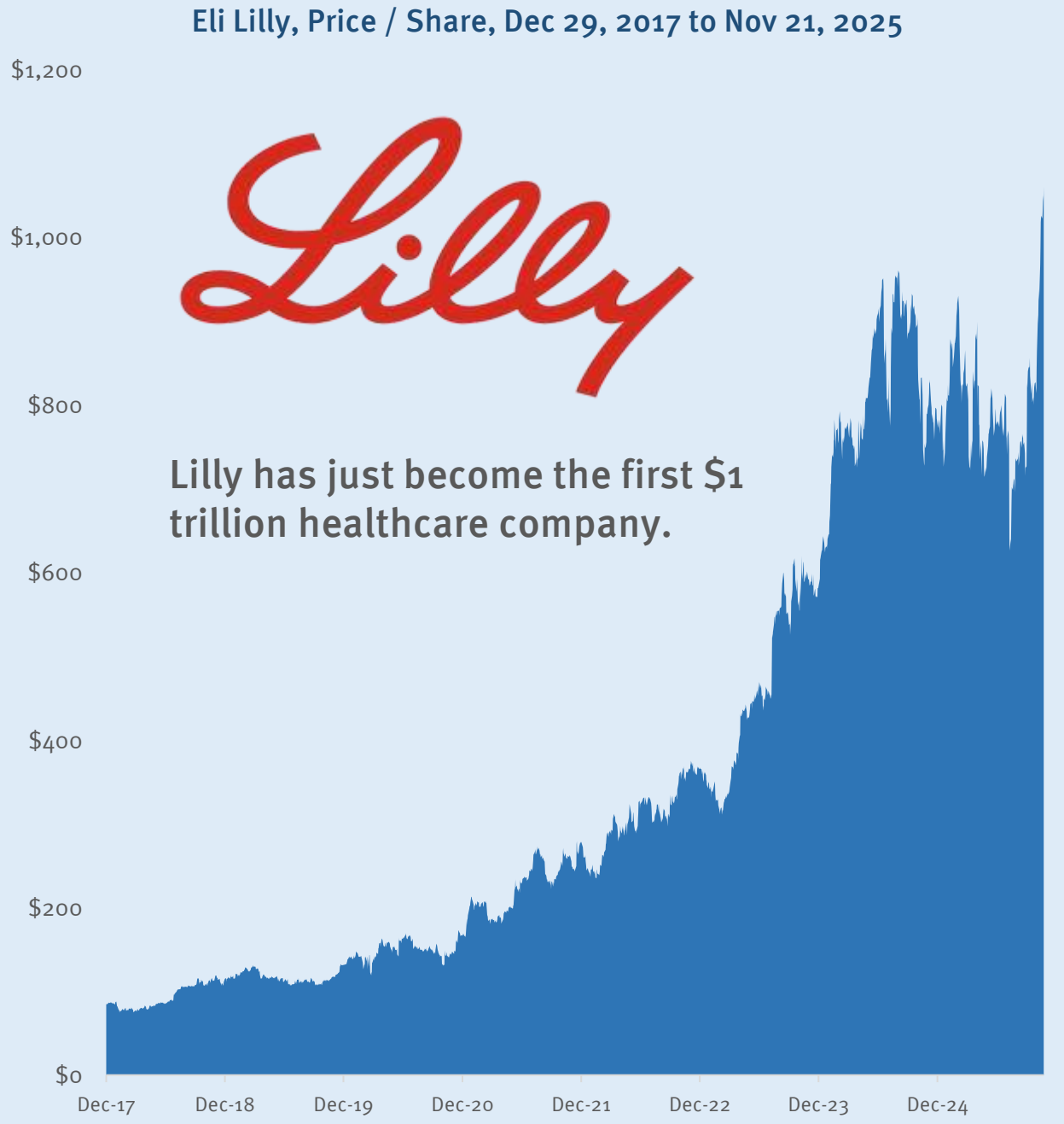
Sensory enhancers, devices & feel good products.

Consumer-Driven Math: The Obesity Drug Market is Going to Be Around $200 Billion in Size -› Driven by Out-of-Pocket Demand



Lilly Has the Largest Drug in History: For Obesity

- Lilly has gone from a $87 billion market cap in 2018 to just over $1 trillion today.
- This has largely been driven by their obesity drug tirzepatide.
- This is a mass market drug with a “real price” – about $6000 a year.
- Under TrumpRx the price is now $4200 – good for Lilly given it comes with broad government reimbursement.
- Tirzepatide just had its first $10 billion quarter – making it the largest drug in history.
- What is so fascinating is that this drug has a first patent expiry after 2035.
- We think this drug easily gets to over $100 billion in market size.



Source: S&P CapitalIQ

The Ultimate Giant Market: Aging Drugs

From Our Nov 21 Report on Aging

- What makes the aging market so interesting from a financial perspective is the confluence of payor incentives and personal incentives.
- The average person would prefer to stay alive longer and would pay for it.
- Similarly, payors have powerful incentives for their insureds to be healthy and long-lived.
- A drug that extends the healthy human lifespan would very likely dwarf the obesity drug market, particularly if chronic use would be required to stay alive.
- Our own view is that revenues in this market could run to $1 trillion or more.

Illustrative Market Sizing Exercise

Imagine a drug that gets you five extra good years of life. Suppose you need to start taking it at age forty and need to take it forever after. Assume that 500 million people take the drug at an average annual cost of $2000.

Revenue = Quantity Sold x Price = 500mm x $2000 = $1 trillion

This would be by far the largest drug product in the history of the world.

Compare this to the car market ($2.4 trillion a year), life insurance ($3 trillion a year in premia paid), residential real estate ($13 trillion a year).

We don't think we are off by an order of magnitude given the value of extra life to the customer.

Key variables that will drive TAM include durability of benefit, safety implications, breadth of benefit (including reduction of aging-related diseases) and regulatory status.

Key Arguments in Our Recent Aging Report

Aging Biology is Understood Well Enough to Support Drug Development

- Advances in the aging biology literature have been stunning in the last decade.
- Aging is a complex area, but genetic and biological insights point to two types of **cell damage** as central causes of aging.
- Even more surprisingly, at least to us, has been the discovery of age-reversal techniques including cell **reprogramming** (initiated by Yamanaka) and strategies to remove senescent cells
- These new techniques give us realistic hope that pharmacological interventions could substantially increase average human lifespans.

Clinical Development of Anti-Aging Drugs is Feasible

- We identify six strategies that can used in a reasonable time frame to run trials on aging drugs at a manageable cost.
- One idea is to focus on **older patients** where the probability of death is high. We believe it would be possible to run a true mortality trial on a drug that worked for less than $100 million.
- An alternative idea is to focus on **biomarkers**. In this report we spend quite a bit of time on this topic, showing that biomarkers are not only predictive of mortality but have specific informative biological context.
- A final idea would be to test aging drugs in **dogs** – which have much shorter lifespans. Loyal, a dog aging company, is doing just this now.

Regulatory Agencies Are Willing to Approve Anti-Aging Drugs

- We have spoken to FDA officials who indicate that the agency is **unequivocally willing to approve drugs for slowing aging.**
- FDA insiders note that the agency already approved the protocol for Nir Barzilai's as yet unfunded **TAME Trial**.
- This trial has a primary endpoint is a composite of events from cardiovascular disease, cancer, cognitive disease, and mortality. All-cause mortality is a secondary endpoint.
- The **Trump Administration** is particularly **receptive** to efforts to extend lifespan (a topic of high interest to HHS Secretary Kennedy).

Source: https://www.stifel.com/newsletters/investmentbanking/bal/marketing/healthcare/biopharma_timopler/2025/BiopharmaMarketUpdate_112125.pdf

Multiple Promising Approaches to Anti-Aging Drugs Available

	Persuasive Biological Rationale	Persuasive Genetic / Cross-Species Data	Persuasive Data in Non-Primate Animals	Persuasive Data in Primates / Humans
Healthspan Impacting (Diseases of Aging)	Diet and Exercise Metformin NAD+	Diet and Exercise mTOR / Rapamycin	Cardiolipin / Elamipretide Diet and Exercise DNMT Modulators mTOR / Rapamycin	Cardiolipin / Elamipretide Diet and Exercise Mesenchymal Cells NAD+
Longevity Impact (Live Within Normal Human Age Boundary)	Caloric Restriction Diet and Exercise DNMT / EZH2 IGF-1/IIS IL-11 Mitochondrial uncouplers NAD+ SIRT1 / SIRT6	Caloric Restriction IGF-1/IIS SIRT1 / SIRT6	Caloric Restriction Diet and Exercise IGF-1// IL-11 Masatinib + Quercetin Mitochondrial Uncouplers mTOR / Rapamycin SGLT2 SIRT6	AMPK Caloric Restriction Diet and Exercise IGF-1/IIS SGLT2
Lifespan Impact (Exceed Normal Human Age Boundary)	Cardiolipin / Elamipretide cGAS / STING D-PUFA's FOXO04 Peptides HSC Cell Reprogramming KCD10 Agonists Mesenchymal Cells Necrosis Inhibitors Partial Reprogramming	cGAS / STING CIRBP Agonism NAD+	BCL-2 inhibitors cGAS / STING CIRBP Agonism FOXO04 Peptides HSP90 Inhibitors NAD+ / SQ1 Heterochronic Parabiosis Partial Reprogramming uPAR CAR-t	

Source: https://www.stifel.com/newsletters/investmentbanking/bal/marketing/healthcare/biopharma_timopler/2025/BiopharmaMarketUpdate_112125.pdf

Deepening Pipeline of Aging Drugs in Development

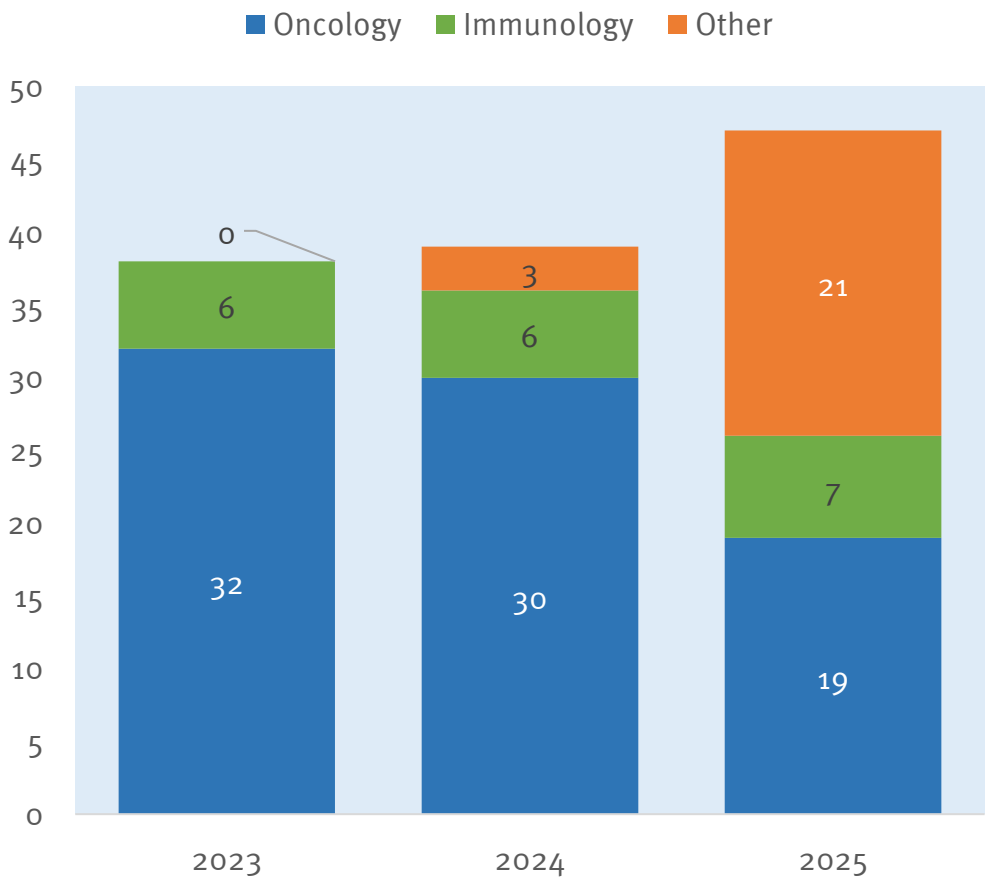
Source: https://www.stifel.com/newsletters/investmentbanking/bal/marketing/healthcare/biopharma_timopler/2025/BiopharmaMarketUpdate_112125.pdf

Third Trend

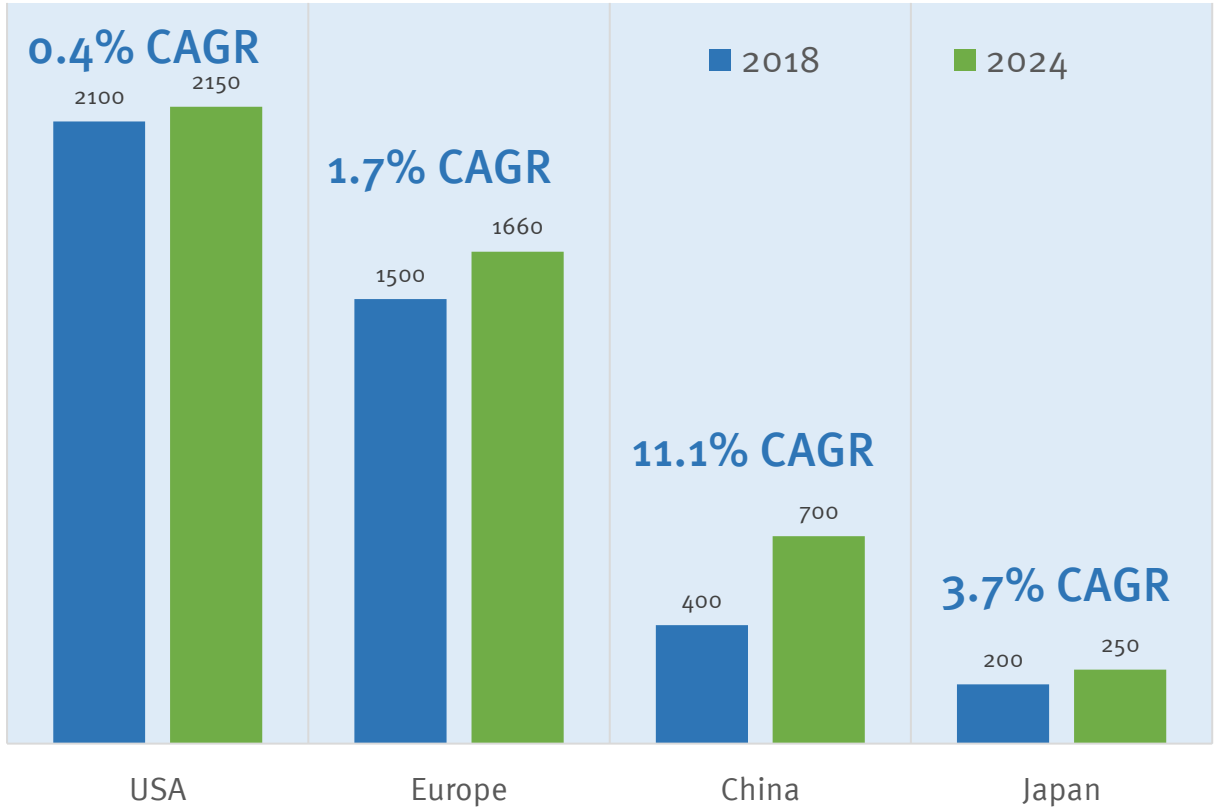
China Innovation

China Innovation Picking Up Substantially

Count of China Originated Global Biopharma License Deals, 2023 to 2025 (YTD)



Count of Biomedical Research Papers in Cell, Nature and Science Journals by Author's Country Affiliations, 2018 to 2024



Source: McKinsey Presentation at BayHelix-BioCentury Conference, Oct 2025

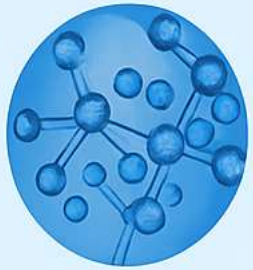
China is Innovating in Pharma Faster and at Lower Cost Than the West

China speed & efficiency

	Discovery	Clinical development
Speed	**2–3x faster** from target nomination to IND submission	**2–5x** faster in patient enrolment
Efficiency	**⅓ to ½ of costs** vs. global best practices*	**<50%** per patient cost of USA/EU

Underlying drivers

Strong macro environment



Scaled end-to-end local ecosystem & infrastructure

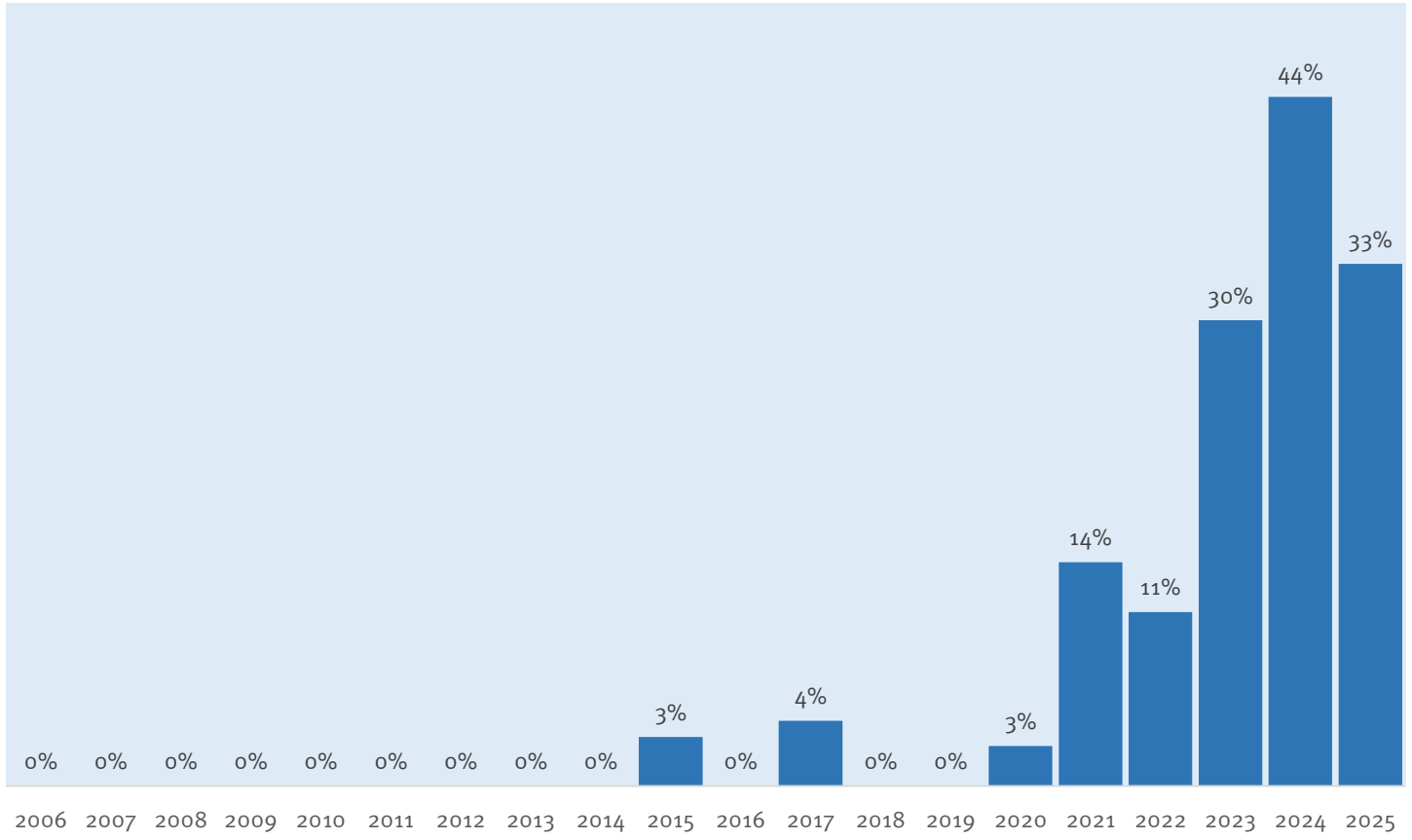
Delivery focused ways of working

Source: McKinsey Presentation at BayHelix-BioCentury Conference, Oct 2025

Ever More Licensed Molecules Going Into Big Pharma Are Coming from China in 2025

Percent of Large Pharma In-license Deals Sourced from China

2006 to 2025 (YTD, Deals of $50mm Upfront or More)



China has become even more important as a source of innovation molecules to big pharma in recent years, although 2025 volume is down a bit.

Source: DealForma, Cutoff for 2025 deals was Nov 21, 2025.

Capital: Funding Sources for China Biotech Diversifying

		Out-licensing	NewCo	M&A	IPO	VC Investment
2025 YTD	# of deals	47	13	5	9	43
	Total amount USD Bn	81	13.9	1.3	1.1	0.9
	Upfront amount USD Bn / Total	3	0.4			
2024	# of deals	42	8	6	4	82
	Total amount USD Bn	40	9	4.4	0.3	1.7
	Upfront amount USD Bn / Total	4	0.3			

Source: McKinsey Analysis, Biocentury China Conference, Oct 24, 2025

Key Trends We are Seeing in the China Biopharma Ecosystem

Global Expansion & Acquisition

Greater willingness to expand globally and to acquire Western molecules.

Government Support

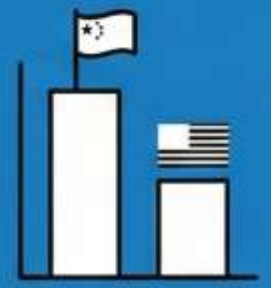
Increasing financial and regulatory support from the Chinese government.

First-in-Class Innovation

Increasing development of first-in-class targets based on new biology.

Efficient Clinical Ecosystem

Much more rapid and efficient use of Chinese clinical trial ecosystem.



Clinical Trial Leadership

Clinical trial starts in China now exceed those in the US.

Chinese Pharma is on the Cusp of Going Global

Economist, Nov 23, 2025 (excerpt)

After America, China is the world's largest developer of new medicines and its companies ran about a third of the planet's clinical trials last year. That is up from just 5% a decade before (see chart 1). It is also rising to the forefront in critical areas of research, such as those relating to cancer. Investors have taken note. Shares in Chinese biotech companies have surged by 110% this year, more than three times as much as their American peers.

Some Chinese firms now want a bigger slice of the pie. A growing model is the "NewCo", under which a biotech company sets up a legally distinct company in America, often backed by foreign investors, and spins off promising assets into it. Chinese pharma looks temptingly cheap to Westerners. The market value of listed Chinese biotech firms is less than 15% that of their American peers. Upfront licensing payments are typically two-thirds lower, and total deal sizes about half, of comparable global transactions.

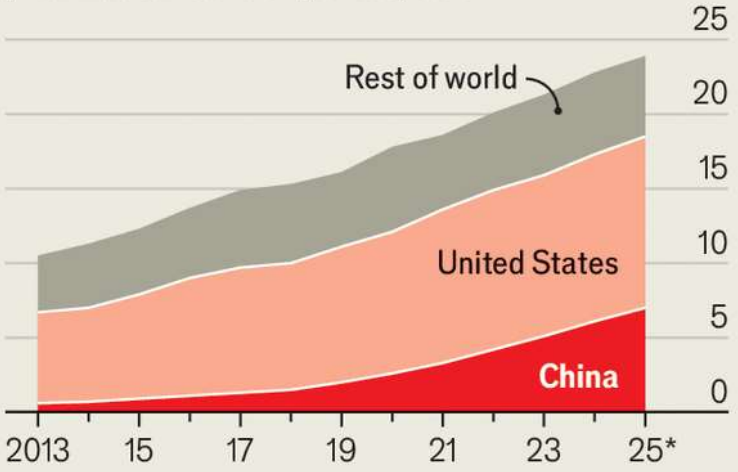
Another advantage of the NewCo model is that it can help mitigate some of the political concerns around Chinese pharma abroad. Others still abound, however, particularly around data privacy. Sharing patient data from clinical trials is complicated by privacy rules and related review processes. And the FDA has taken a strict approach to approving drugs based on trials that have been conducted only in China. In June it halted any new clinical trials that exported Americans' genetic data to China. A report published in April 2025 by a congressional committee that included Eric Schmidt, Google's former boss, warns that China's strength in drug discovery, combined with its advances in artificial intelligence, could soon allow its firms to eclipse America's. He and others fret about the security risks at the junction of pharmaceuticals and biotechnology.

There are reasons for cautious optimism, too. More competition usually means more treatments at lower cost. For patients long denied access to cutting-edge drugs, China's rise could help close the gap. That would particularly matter for those in need of them in poor countries. For Chinese drugmakers, the real test is not only inventing novel therapies that work but breaking into new markets and passing the regulatory hurdles associated with them. Mr Wang notes that most Western giants took a century to reach today's scale. By that measure, he says, China's industry is still "at a very early stage."

Source: https://www.economist.com/china/2025/11/23/chinese-pharma-is-on-the-cusp-of-going-global/

Pilling up 1

Innovative drugs in development by pharmaceutical companies, '000



Clinical-trial starts by company location, %

Sources: Citeline; Iqvia Institute *To January 3rd

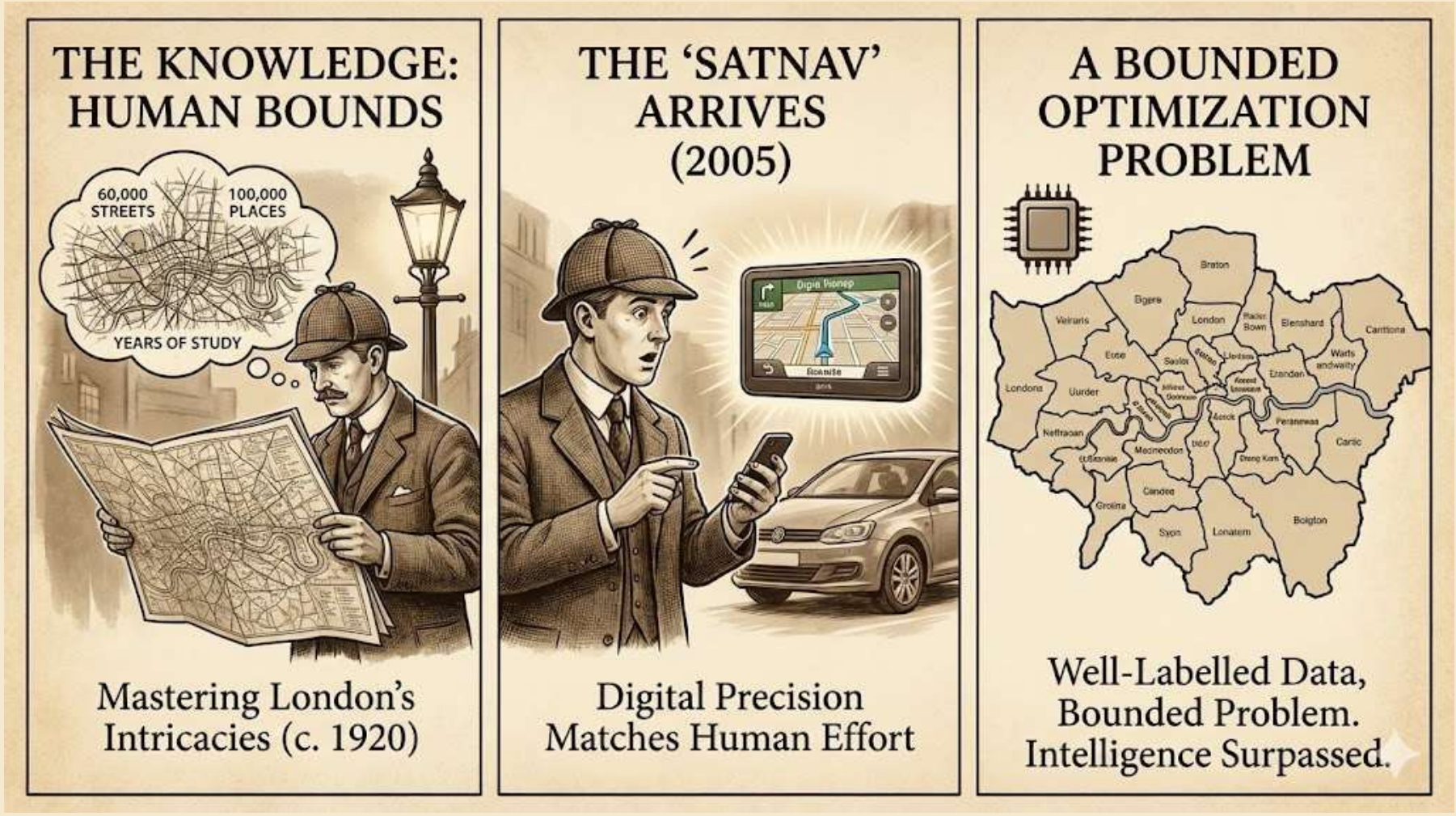
Fourth Driver

AI Reshapes Healthcare

The Power of Machine Learning and AI:

How the “SatNav” Made the London Taxi Driver’s “Knowledge” Obsolete

In the old days a London taxi driver would spend up to four years gaining the “Knowledge” which would allow one to drive efficiently from any one point in the city to another. Then, in 2005 the Garmin could do all of this in seconds because it is working off a well-labelled dataset and a bounded optimization problem. What makes AI work today is the same thing. One needs a good input dataset and a bounded well-defined problem, and the computer will make mincemeat out of human brains.



Three Giant Opportunities in Health and AI

Each these problems is bounded and involves highly contextualized situations where input datasets are good enough that a computer could figure out how to vastly improve on status quo knowledge and decision-making.

1. Foundational Models

Building foundational models in biology and medicine for specific problems like kidney function.

2. AI-Driven Care

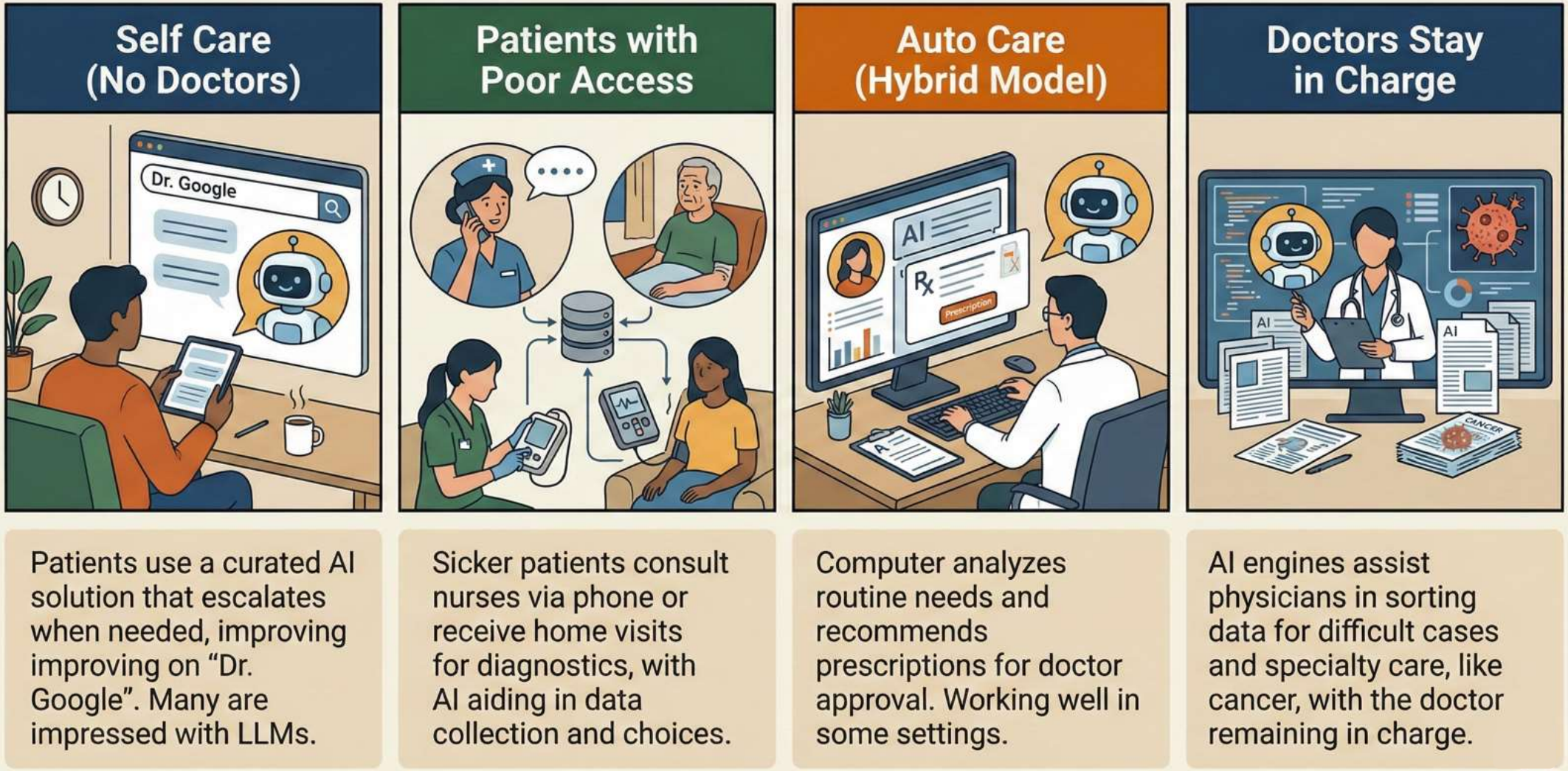
Using AI driven differential diagnosis models and care/outcome prediction models to deliver better care care to those that lack access to good care.

3. Artificial Agents

Artificial agents in the back office for dealing with paperwork, insurance companies and the like.

Scenarios of How AI May Transform the Delivery of Medicine

There are many obvious and interesting applications of AI including (1) doctors hold on to their current role and use AI themselves, (2) patients shift to self-care for routine needs and only see doctors for more severe specialty situations (e.g., heart failure or cancer) or (3) patients shift to a hybrid model where the computer is involved more continually in care but doctors oversee the bots to make sure that the right decisions are getting made. Some of the scenarios are outlined in the illustration below.



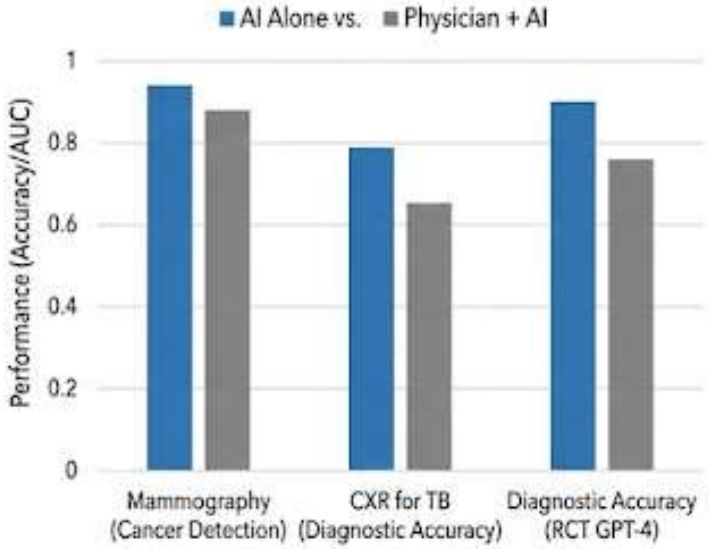
Benchmarking of AI Systems

The MedQA dataset is a widely used biomedical question answering dataset that comprises questions in the style of the US Medical Licensing Exam (USMLE) and is used for evaluation of LLMs' reasoning capabilities. As is evident below, the systems have gotten progressively better to the point that today systems like Grok4 and GPT5 get almost no clinical questions wrong. These systems are far better than average doctors and beat expert doctors. While this may seem amazing, a human that could access all medical knowledge in less than a second with a strong reasoning system should also be able to attain a perfect score.

LLM Performance on Medical Exams (MedQA Benchmark)

LLMs have rapidly improved, achieving near-perfect scores on medical licensing exams.

AI vs. Physician + AI Performance (Limited Value Add)



In key diagnostic and interpretative tasks, AI models often outperform physicians, even when physicians are assisted by AI.

Conclusion: The Future of Autonomous Medical AI

- Extremely high medical knowledge.
- Superior performance in specific tasks.
- Minimal improvement when human oversight is added.
- Potential for autonomous medical decision-making.

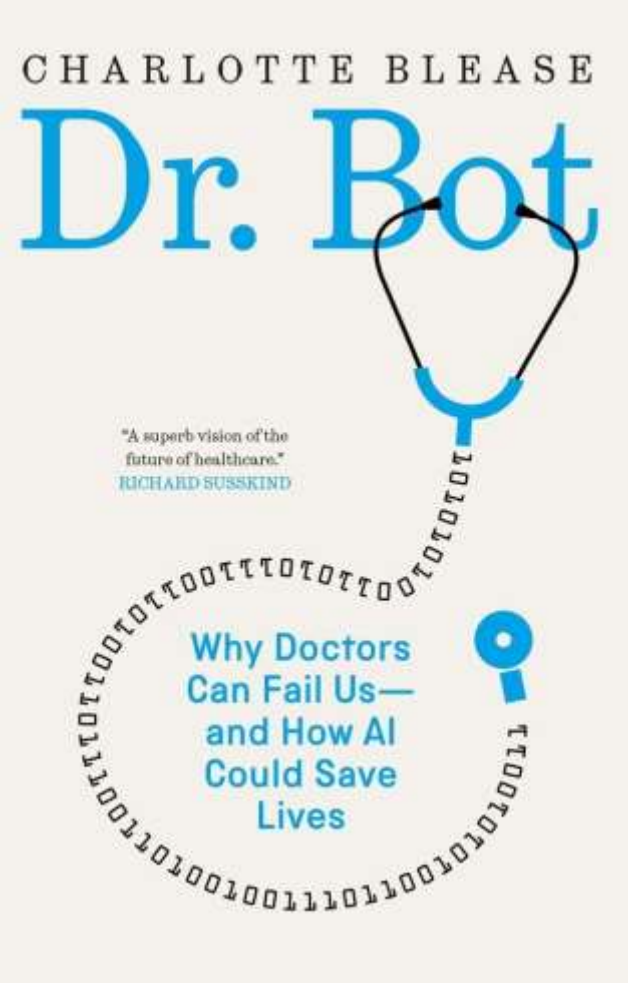
Source: https://erictopol.substack.com/p/when-doctors-with-ai-are-outperformed and Stifel research.

Imperfect or Not, There is Good Reason to Prefer AI over Your Local Doctor

Charlotte Blease, "The Big Idea: why we should embrace AI doctors: People are understandably wary of new technology, but human error is often more lethal," *The Guardian*, August 31, 2025 (excerpt)

Medical knowledge also moves faster than doctors can keep up. By graduation, half of what medical students learn is already outdated. It takes an average of 17 years for research to reach clinical practice, and with a new biomedical article published every 39 seconds, even skimming the abstracts would take about 22 hours a day. There are more than 7,000 rare diseases, with 250 more identified each year.

In contrast, **AI devours medical data at lightning speed, 24/7, with no sleep and no bathroom breaks. Where doctors vary in unwanted ways, AI is consistent.** And while these tools make errors too, it would be churlish to deny how impressive the latest models are, with some studies showing they vastly outperform human doctors in clinical reasoning, including for complex medical conditions.

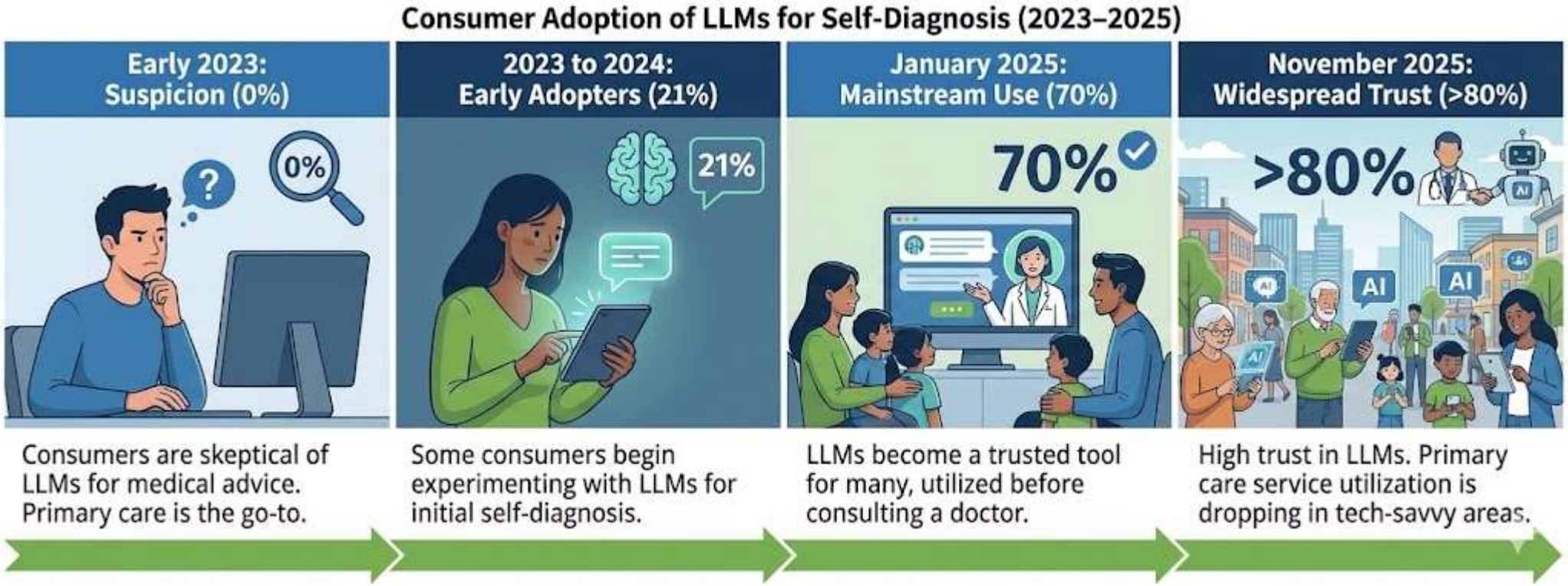


Charlotte Blease's book "Dr. Bot" was released on Sep 9, 2025.

Source: https://www.theguardian.com/books/2025/aug/31/the-big-idea-why-we-should-embrace-ai-doctors

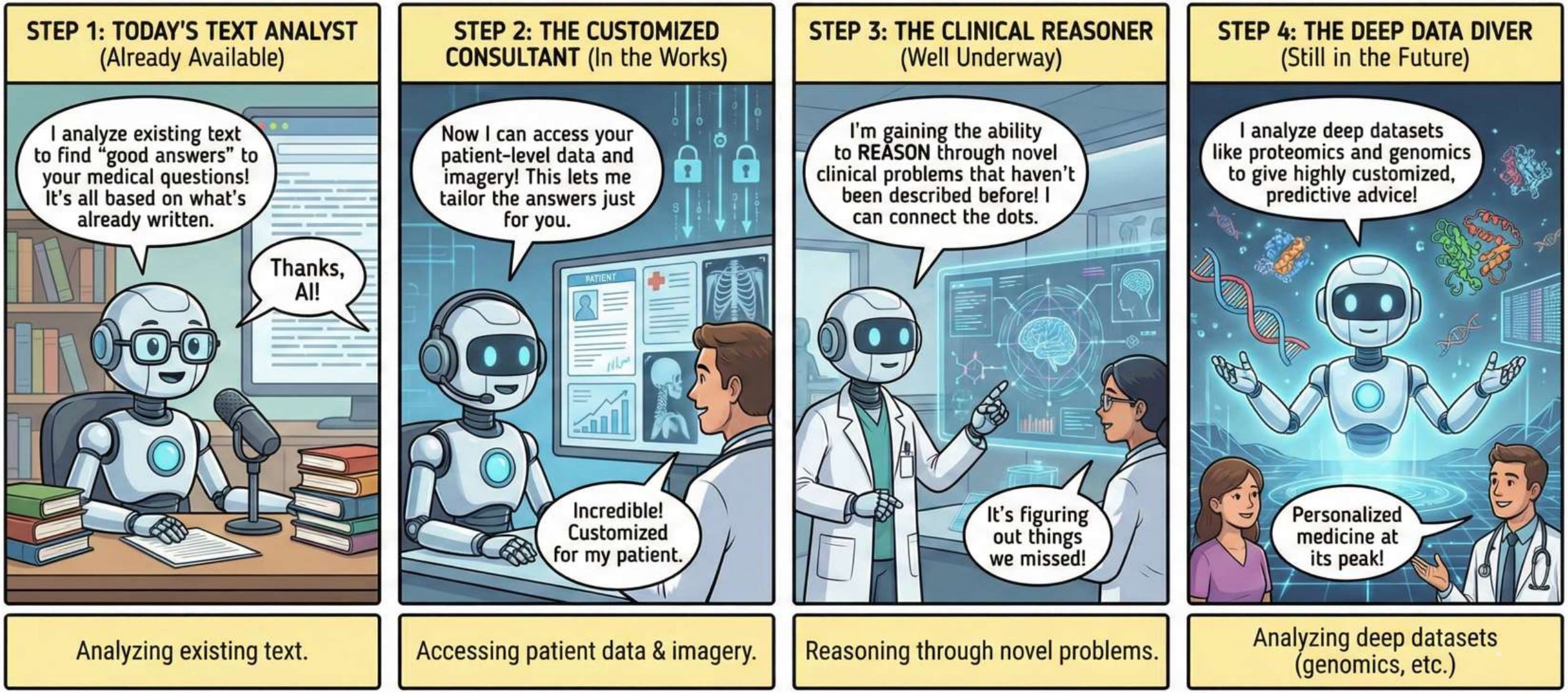
Rapid Consumer Adoption of LLM Guided Self-Care and Self-Diagnosis is Underway

The consumer has gone from being suspicious of LLMs to having similar trust in them as physicians themselves. Our industry conversations indicate that primary care service utilization is dropping rather quickly in some of the more tech-savvy cities in the U.S. as a result.



Sources: (1) 2023 to 2024: https://www.jmir.org/2025/1/e68560, https://www.bain.com/insights/call-the-doctor-are-patients-ready-for-generative-ai-in-healthcare-snap-chart/; (2) January 2025: https://www.bain.com/insights/pharma-commercialization-in-the-age-of-ai-and-active-patients/; (3) September to November 2025, Stifel estimate based on informal survey of a broad set of American people (N=40+).

Today's Text-Analyzing LLM is Just the First Step in Healthcare Transformation



Our View: Hybrid Model Will Evolve From the Status Quo

The use of AI in medicine will not put physicians out of work at all but will increase the premium on knowledge of medicine and diagnostic technologies. We see a world with fewer physicians who oversee AI system and healthcare workers.

MASTER PHYSICIANS

1. Deep clinical experience & bioinformatics/Omics expertise. Diverse background.
2. Review data and appropriateness of algorithmic disease approaches; provide oversight, not sole decision-making.

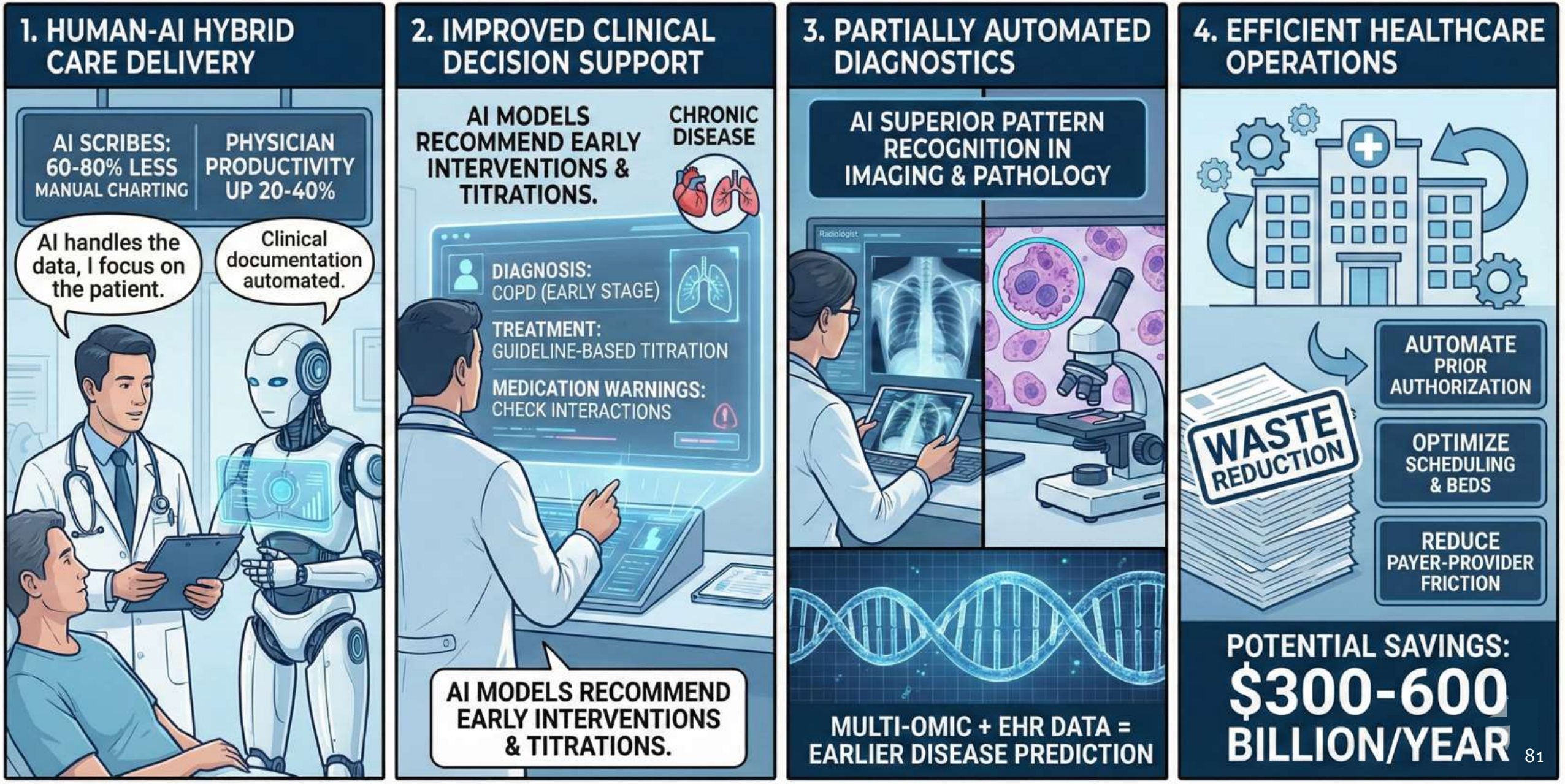
CLINICIANS

1. Includes nurses and physicians.
2. Key focus on positive patient interaction, disease etiology, and treatment understanding.
3. Real-time access to algorithmic/AI advice during patient interactions via tablets.

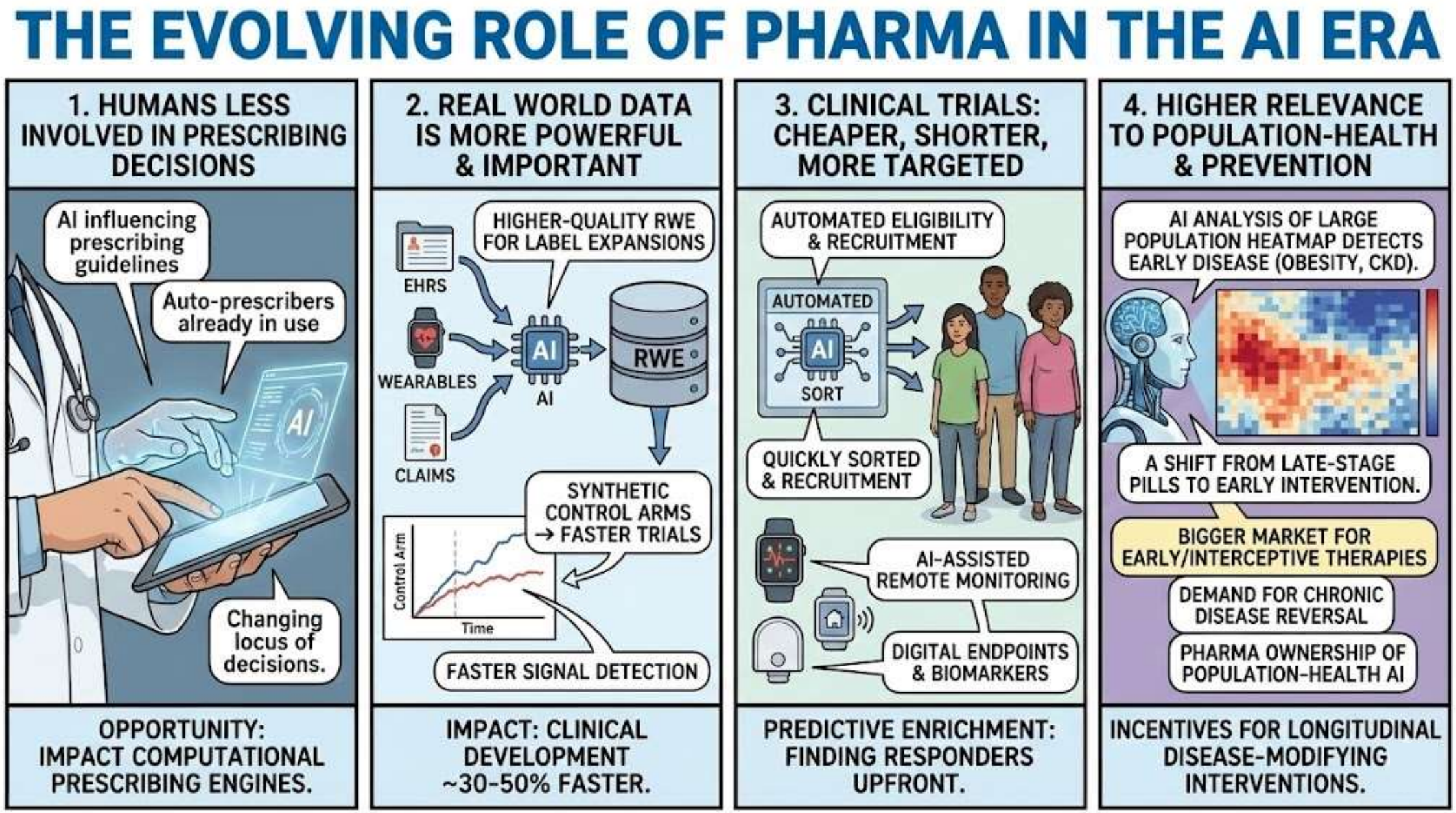
MEDICAL TECHNICIANS

1. First line of patient encounter in ambulatory settings (e.g., urgent care).
2. Well-trained medtechs with LLM-linked iPads achieve significantly more progress than current systems.

The Future of AI in Healthcare



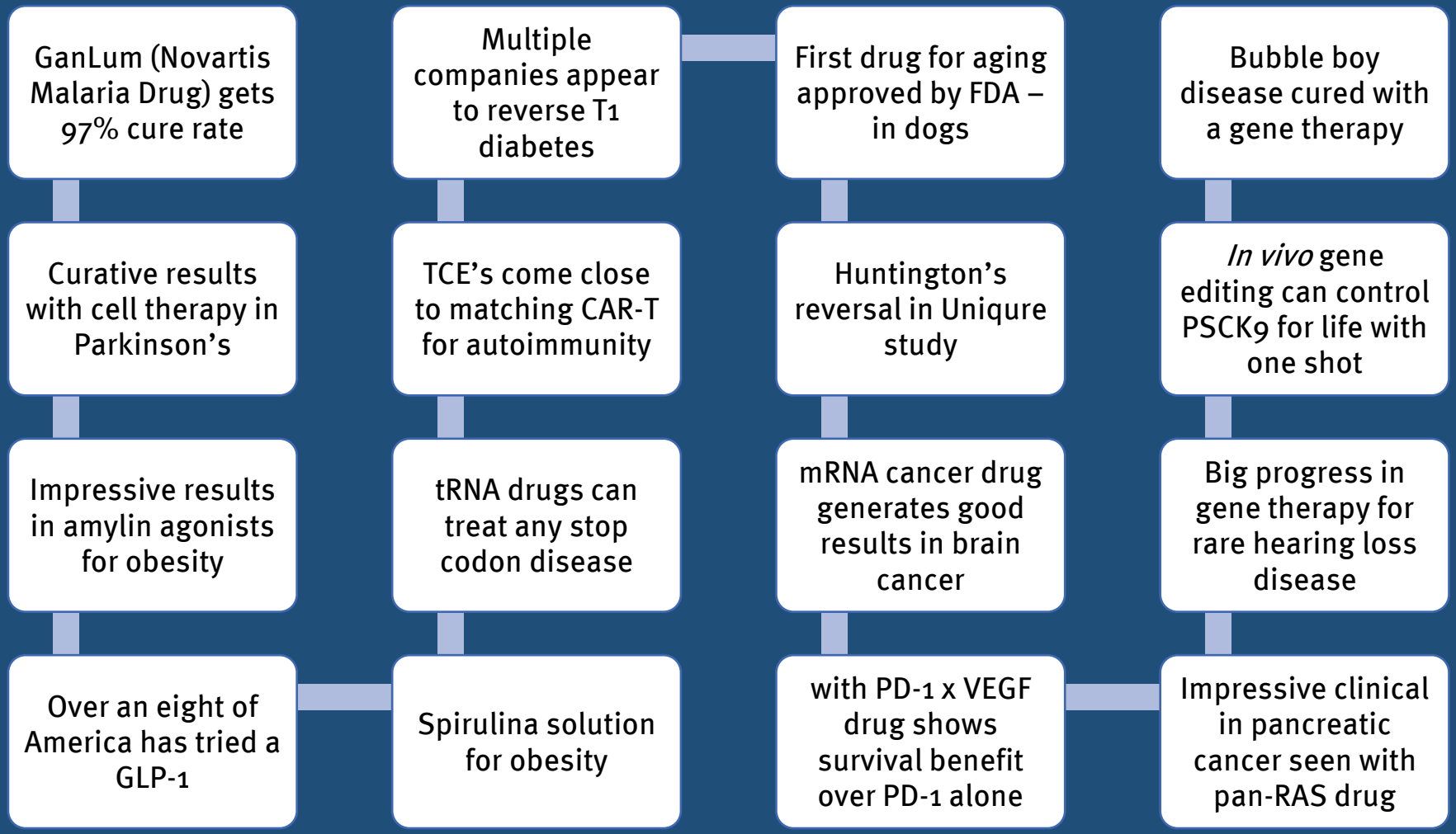
How AI in Healthcare is Going to Impact Biopharma



Fifth Driver

Amazing Science

Many Meaningful Biosciences Advances in 2025



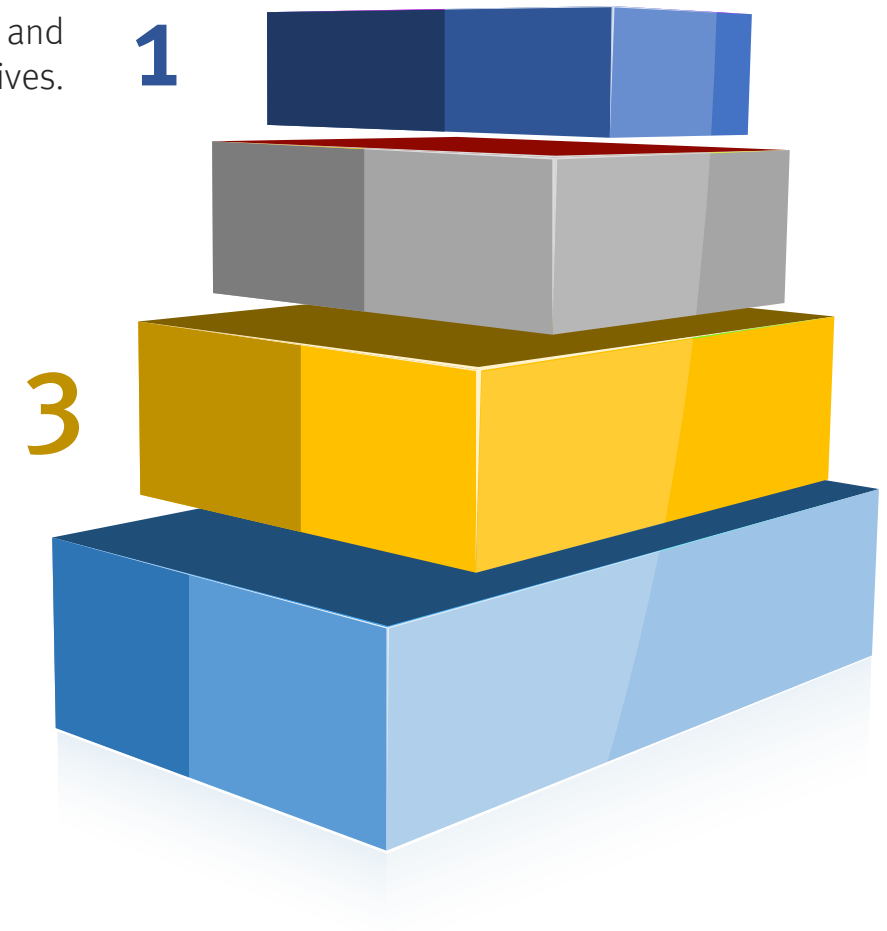
The recent pace of biosciences advances is historic in importance and breathtaking in its speed and breadth.

Biosciences Innovation Importance Pyramid:

Staging Innovation by Its Impact on Disease and Humanity

Every once in a while, an innovation comes up that has the potential to change the course of human civilization.

Incremental. Will impact a disease in an important way and save some lives.



Important. Can Innovation that could substantially improve the human condition by altering the treatment of multiple human organ systems or in making a major difference in a top 5 medical condition (cancer, aging, diabetes, Alzheimers, cardiovascular)

Foundational. Potential to change the entire field of medicine or dramatically improve treatment of disease related to multiple organ systems. Potential to save 10's of millions of lives.

Civilization Changing. Potential to alter the human experience, the fate of civilizations or to save 100's of millions of lives. Potential to extent average human life expectancy by a year or more. Potential to create giant new industries that employ tens of millions of people.

Source: Stifel Investment Banking Department Analysis.

Illustrative Areas of Medical Innovation Importance

Classified by Position

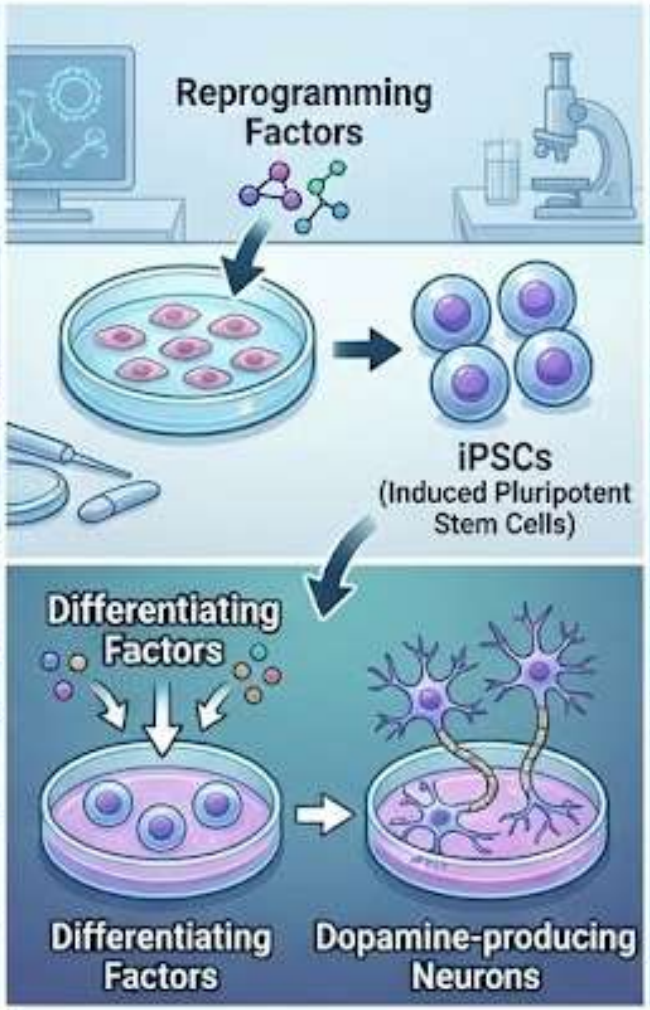
Incremental	Adenosine drugs Antipurinergics APRIL/BAFF CD47 Cytotoxics Diuretics Fertility Drugs FGF21 FGFR system GNRh antagonists HER2 HIF2a IL-6 IL-23 Levothyroxine Metabolomics NLRP3 NRf2 PSMA RIPK1 RORγt SHP2 STAT3 TROP2 TYK2
Important	ARBs ASOs CD19 CAR-T CDK4/6 Ceramide Complement Drugs Degraders ELISA Epigenetics EPO GPCRs HIV Drugs Innate Immunity Ion Channels IVIG JAK KRAS MCR PET Polio Vaccine PPI Statins Steroids TCR drugs TLA1 TNFa TREM2 Thorazine
Foundational	ADCs Amyloid Drugs Anesthesia Antibodies ACE inhibitor Aspirin Base / Prime Editing Ceramides Degraders Epigenetics Epithelial Biology FcRn Drugs Gene Sequencing Gene Therapy IL-4/13 Insulin iPSCs / Parkinson's PD1 Opioids Proteomics RNAi SGLT2 SSRIs T-Cell Engagers
Civilization Changing	Antibiotics / Penicillin Antibodies Aging Biology Bioelectronics Birth Control Pill Discovery of DNA Gene Editing mRNA vaccines Obesity Drugs Precision Medicine and Artificial Intelligence Smallpox Vaccine Synthetic Biology Yamanaka Factors

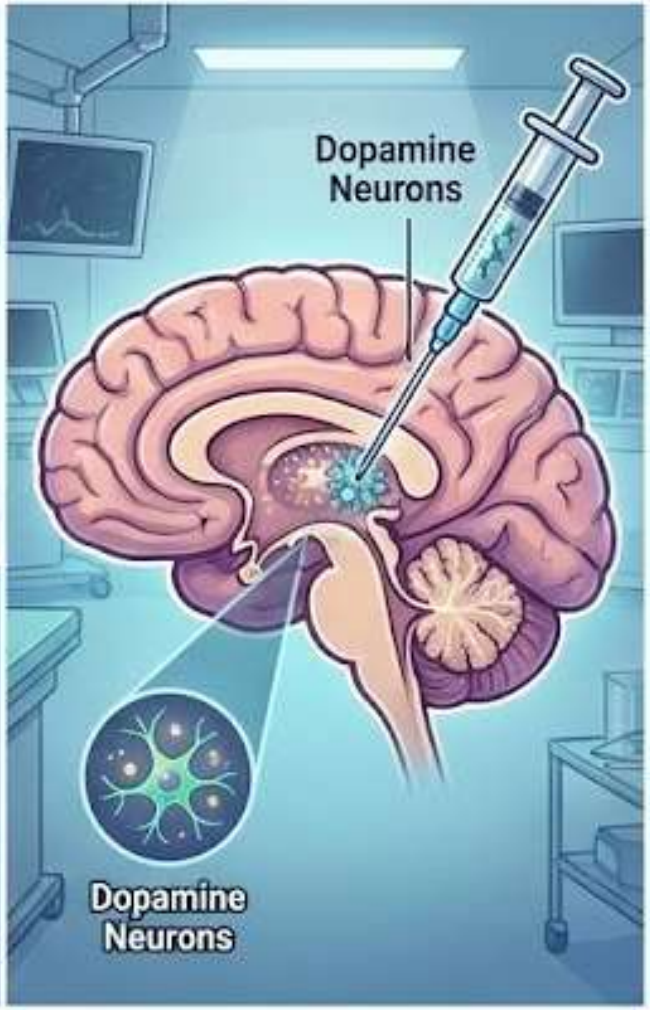
Source: Stifel Investment Banking Department Analysis

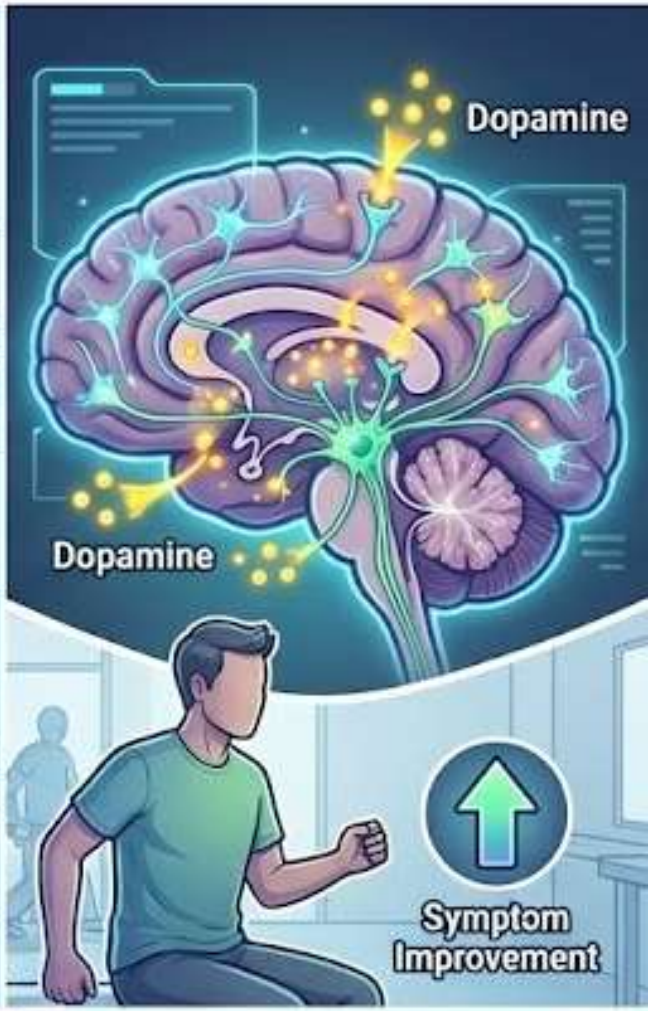
2025 Biosciences Case Study

Cell Therapy for Parkinson’s Disease

MECHANISM OF AUTOLOGOUS CELL THERAPY FOR PARKINSON'S DISEASE







1. Cell Collection

Patient's own somatic cells (e.g., skin or blood) are harvested.

2. Reprogramming & Differentiation

Cells are reprogrammed to iPSCs, then differentiated into functional dopamine neurons in the lab.

3. Precise Transplantation

The healthy, autologous dopamine neurons are surgically implanted into the brain's target area.

4. Functional Restoration

New cells integrate, produce dopamine, and re-establish neural circuits, alleviating motor symptoms.

Parkinson's Cell Therapy Landscape – Clinical Stage

We are seeing multiple companies in this area achieve unprecedented responses in advanced Parkinson's patients. For example, iRegene is seeing improvements of UPDRS scores of 30 points or more in its China study.* This area seems poised for big things if early results replicate.

Cell therapies for Parkinson's disease (PD) aim to restore dopaminergic function by transplanting cells capable of replacing lost or dysfunctional dopamine (DA) neurons. The therapies under investigation, as illustrated in the chart below, range from personalized autologous approaches like those from Oryon Cell and Aspen Neuroscience—using patient-derived iPSCs—to allogeneic products from BlueRock, iRegene, Kenai, and TreeFrog, which use donor-derived cells. These efforts differ in the types of transplanted cells (immature DA neurons vs. progenitors vs. 3D clusters), source material (T-cells, fibroblasts, embryonic stem cells), and development stage (from preclinical to Phase 3). Some, like iRegene and BlueRock, have shown efficacy based on UPDRS scores and demonstrate dose control, but allogeneic therapies typically require immunosuppression. Despite variability in design, most are delivered bilaterally to the brain and rely on iPSC or ESC platforms. The improvements in UPDRS scores that have been seen with several therapies have been quite dramatic and point to curative potential in Parkinson's disease for the first time.

Item	Aspen Neuroscience	BlueRock / Bayer	iRegene	kenai therapeutics	Oryon Cell	S.Biomedics
Product Name	ANPD001	Bemdaneprocel	NouvNeu001	RNDP-001	None	TED-A9
Format of Transplant	Autologous	Allogeneic	Allogeneic	Allogeneic	Autologous	Allogeneic
Phase of Development	Phase 1	Phase 3	Phase 1 (US) / 2 (China)	Phase 1	Phase 1	Phase 2
Efficacy Data (UPDRS)	Yes	Yes	Yes	No	NA	Yes
Immunosuppression	No	Yes	Yes	Yes	No	Yes
Transplanted Cells	DA Progenitors	DA Progenitors	DA Progenitors	DA Progenitors	Immature DA Neurons	DA Progenitors
Type of Injection	Bilateral	Bilateral	Bilateral	Bilateral	Unilateral (Phase 1) / Bilateral (Phase 2)	Bilateral
Type of Cells	iPSC	eSCs	iPSC	iPSC	iPSC	eSC's
Source of Cells	Fibroblasts	Embryonic Stem Cell Line	Unknown	Fibroblasts	T-Cell	Unknown
Dose Control	No	No	No	No	Yes	No
Supportive Primate Data	No	No	No	No	Yes	No

* Note, today's dopamine therapy and DBS treatments get 10 to 15 points improvements in UPDRS, at best.

Source: Stifel Investment Banking Department Analysis of company presentations a

Significant Improvement in Motor Symptoms in the RP2D Cohort (N=5, UPDRS III Off/On)

Aspen Neuroscience Announces 6-Month ASPIRO Phase 1/2a Clinical Trial Results of Personalized Cell Therapy for Parkinson's Disease

SAN DIEGO and NEW YORK, May 7, 2025 /PRNewswire/ — Aspen Neuroscience has released 6-month data from the first three patients dosed in the ASPIRO Phase 1/2a trial of ANPD001, an investigational autologous dopaminergic neuronal precursor cell (DANPC) therapy being studied in patients with moderate to advanced Parkinson's Disease (PD).

"In this first-of-its-kind study, we are seeing clinician-reported and patient-reported improvements as well as a strong safety and tolerability profile at six months. Importantly, ANPD001 has the unique advantage of not requiring immunosuppression," said Edward Wirth III, MD, PhD, Chief Medical Officer of Aspen Neuroscience.

Administration of the DANPCs into the posterior putamen was performed with participants under general anesthesia. Precision dosing of the intended target was enabled using gadoteridol-enhanced intraoperative MRI. These three patients received five million DANPCs per putamen in a single surgical procedure using a custom syringe and cannula.

No hemorrhages nor serious intra-operative or post-operative complications were observed. No graft-induced dyskinesia have been observed. The most common adverse events in the first three patients were incision pain and tongue swelling, the latter of which is related to the prone position during surgery.

At six months there was an average improvement of 45% in the physician-reported MDS-Unified Parkinsons Disease Part III "off" score compared to baseline, and an average improvement of 71% in patient-reported MDS-UPDRS Part II scores. There was an average reduction of 2.0 hours in adjusted "off time," and a 1.5-hour average increase in adjusted "good on" time.

Source: https://aspenneuroscience.com/aspen-neuroscience-announces-6-month-aspiro-phase-1-2a-clinical-trial-results-of-personalized-cell-therapy-for-parkinsons-disease/

Aspen Neuro Results on the First Three Patients Treated with Their Autologous Low Dose Therapy

Parkinsonism and Related Disorders 134 (2025) 107356

Background: About one million Americans are living with Parkinson's Disease (PD), and about 60,000 are newly diagnosed annually. Current therapies address symptoms of PD, but do not address loss of dopaminergic neurons.
Methods: A first-in-human, open-label, phase 1/2a trial evaluating safety, tolerability, and efficacy of intracranial implantation of two escalating doses of autologous induced pluripotent stem cell (iPSC)-derived dopaminergic neuronal precursor cells (DANPC's) in subjects with moderate to advanced PD. The primary study objective is to assess safety and tolerability of bilateral administration of autologous DANPC's into the posterior putamen. A secondary objective is to evaluate clinical efficacy of DANPC administration as measured by change from baseline in multiple patient- and clinician-reported PD-specific outcome measures.

Mean drop at 6 months in UPDRS III Off Score of 19.6 points at low dose.

(Baseline → 6mo)	Patient 1	Patient 2	Patient 3	Average
MDS-UPDRS III OFF score	49 → 33 (33% improvement)	42 → 19 (55% improvement)	42 → 22 (48% improvement)	45.3 % improvement
MDS-UPDRS II	15 → 1 (93% improvement)	17 → 10 (41% improvement)	15 → 2 (80% improvement)	71.3 % improvement
Adjusted change in OFF Time	4.1→1.8 hrs (2.3 hr improvement)	2.3 → 2.5	6.7 → 2.7 (4 hr improvement)	2 hr off time reduction
Adjusted change in "good" ON Time	11.9 → 14.2 (2.3 hr improvement)	13.4 → 12.9	8.4 → 11.1 (2.7 hr improvement)	1.5 hr increase in good on time

Conclusions: Early data from three patients show that precision intracranial delivery of DANPCs was safe and well-tolerated. Both patient reported and clinician reported outcomes show early signs of efficacy, and continued follow up and evaluation of a higher-dose cohort is ongoing.

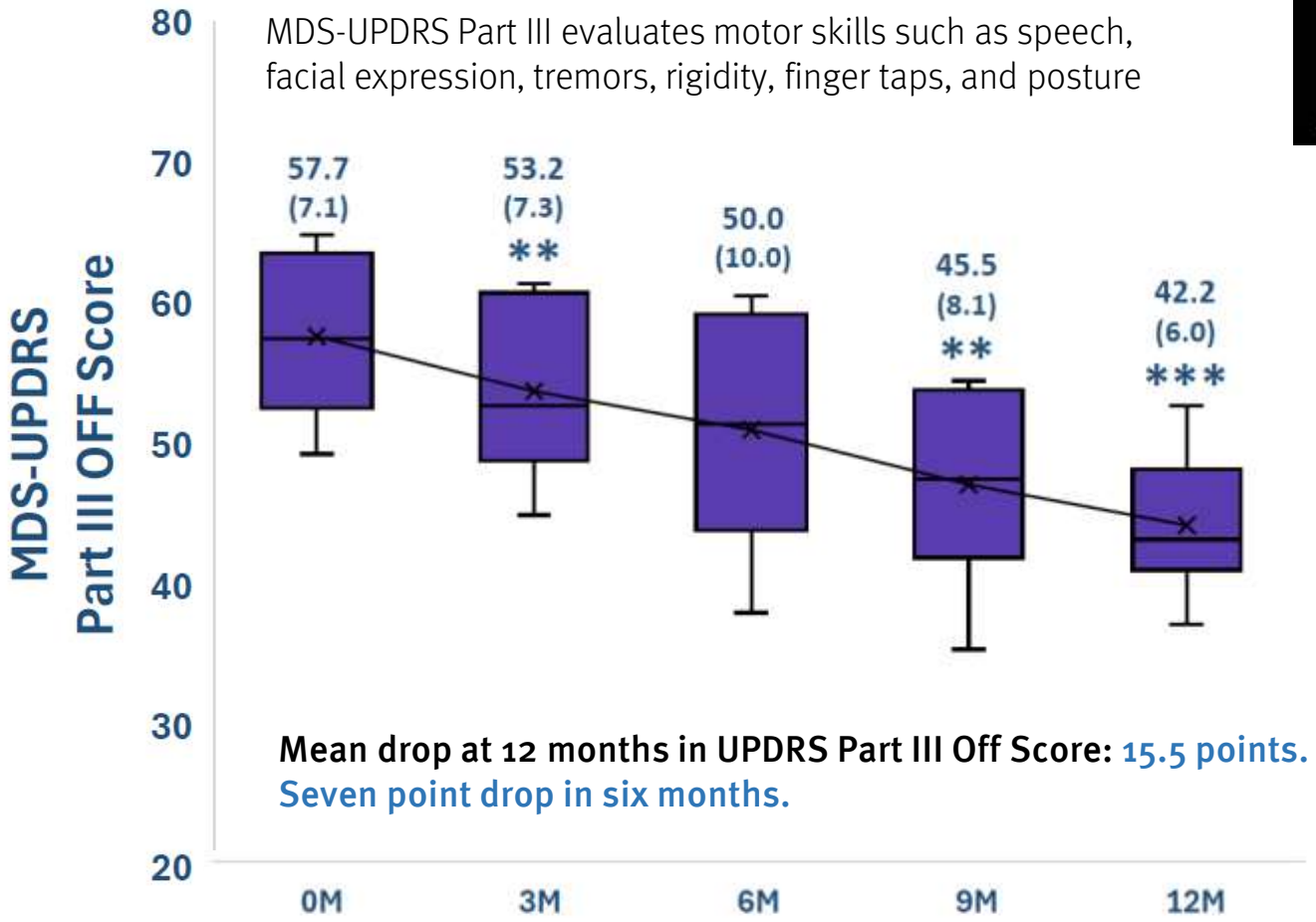
Aspen has not released more recent data from patients that received a higher dose of their therapy. However, Aspen announced a $115 million raise last week that was based on recently obtained data. PR: "It is significant to see a private financing of this quality. Securing this round is a testament to how this team is rising above with innovation in product characterization, manufacturing automation, and **positive clinical results**," said Faheem Hasnain, Board Chairman of Aspen Neuroscience.

Source: https://c212.net/c/link/?t=0&l=en&o=4421807-1&h=758033246&u=https%3A%2F%2Fwww.prd-journal.com%2Farticle%2FS1353-8020(25)00371-2%2Ffulltext&a=Parkinsonism+and+Related+Disorders

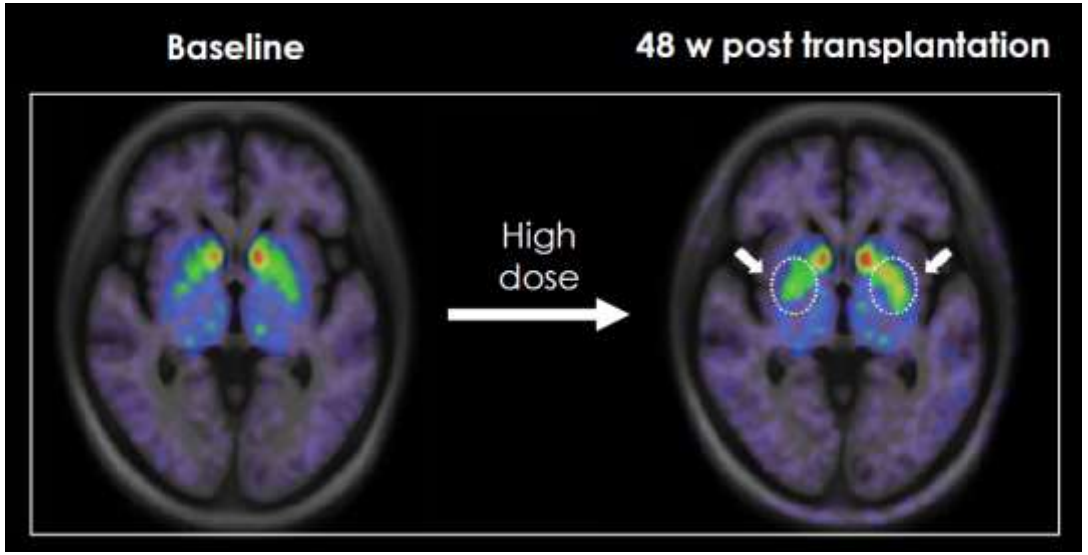
S.BIOMEDICS

MDS-UPDRS PART III Off Score (N=6, High Dose) Following Allogeneic Transplantation of Dopaminergic Cells

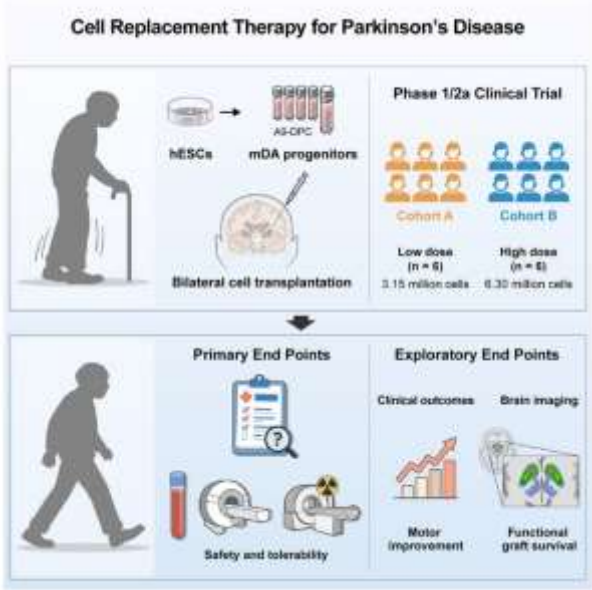
MDS-UPDRS Part III evaluates motor skills such as speech, facial expression, tremors, rigidity, finger taps, and posture



Mean drop at 12 months in UPDRS Part III Off Score: 15.5 points. Seven point drop in six months.



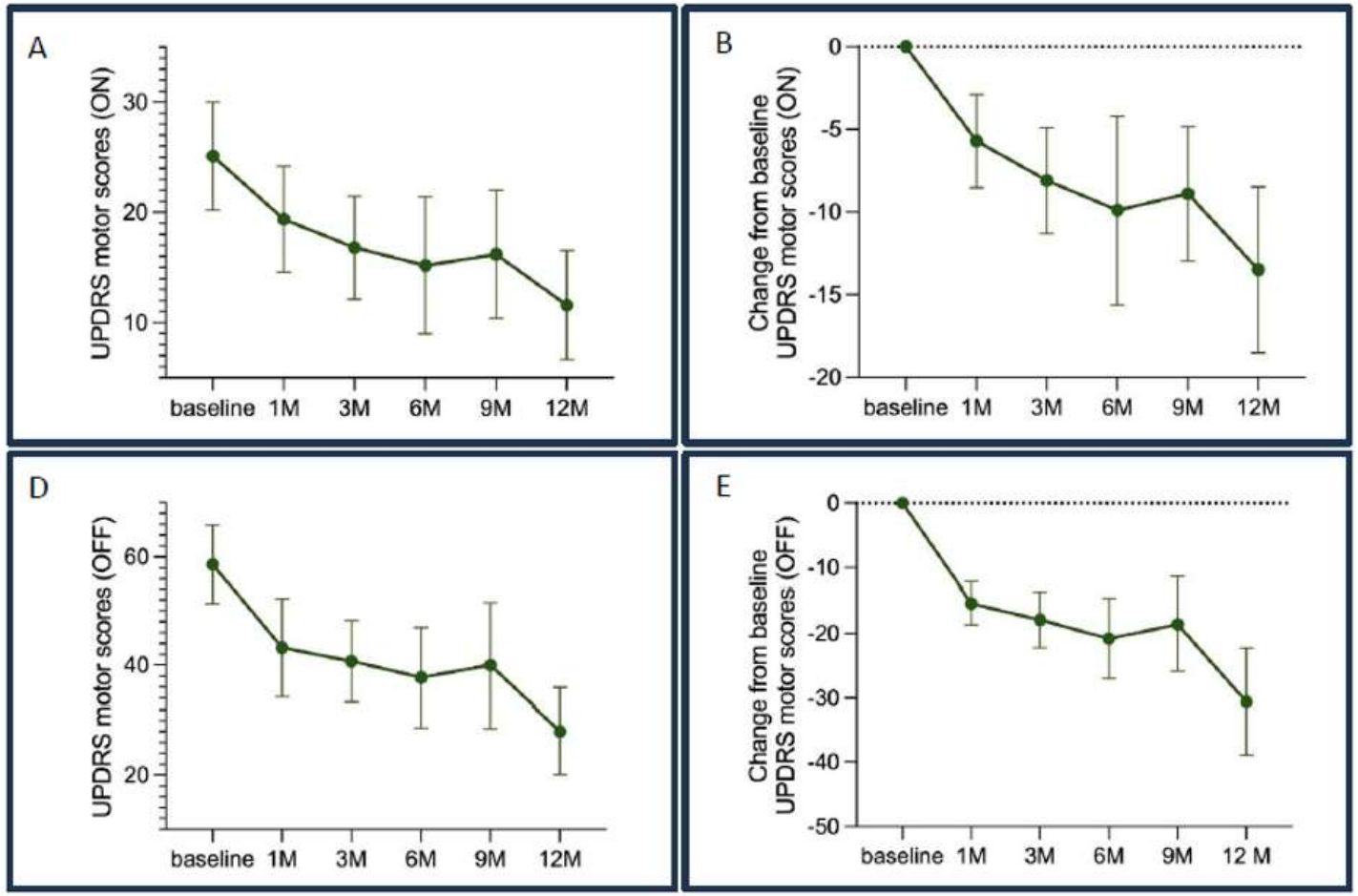
Engraftment of TED-A9 showed enhanced dopamine activity
Engrafted TED-A9 survived and expressed DAT (dopamine transporter) which indicates that synapses were formed



Source: Corporate Presentation. Also see Oct 13, 2025 article in cell.

Significant Improvement in Motor Symptoms in the RP2D Cohort (N=5, UPDRS III Off/On)

Mean drop in UPDRS Part III Off Score: 30.6 points



Total UPDRS score drop of 43 points is getting close to a curative result.

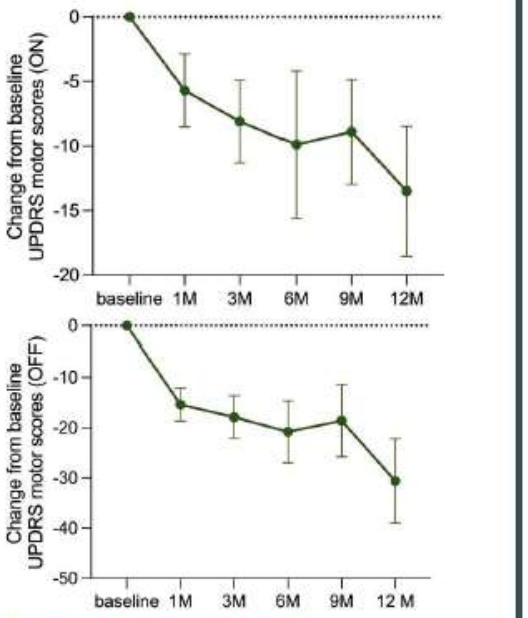
Far better than is possible with today's best therapy which is deep brain stimulation.

Source: Corporate Presentation. Also see https://www.biospace.com/press-releases/iregene-therapeutics-announced-promising-nouvneu001-phase-i-clinical-data

Comparison of iRegene Therapeutic Effect to MeiraGTx and AbbVie

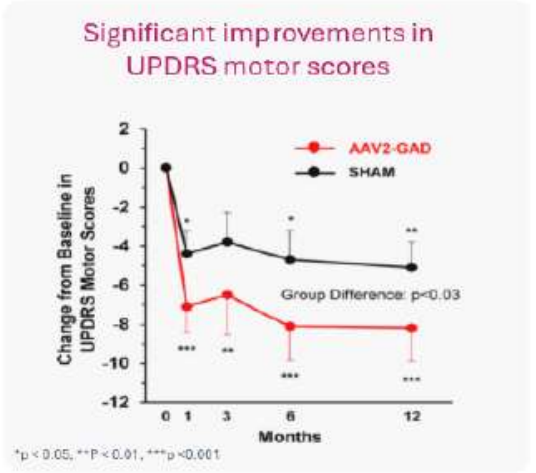
In the RP2D cohort, the 12-month measurement of the effects of NouvNeu001 on motor symptoms using MDS-UPDRS Part III measured showed a mean reduction of 30.6 points in the “OFF”-medication state, and 12.9 points in the “ON”-medication state compared with baseline. Compare this to a 7 point reduction in UPDRS scores with the MeiraGTX gene therapy and a 9-point reduction in UPDRS scores with AbbVie’s Tavapadon.

iRegene



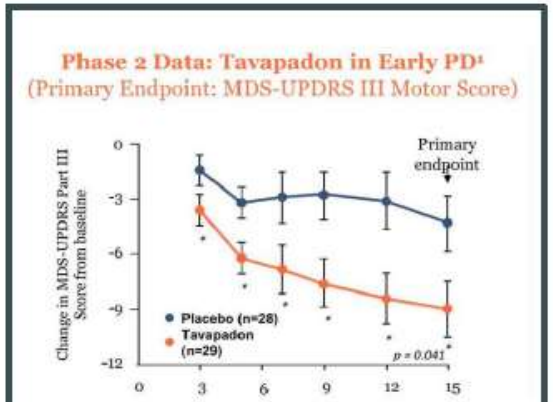
- Only ONE administration
- On going trial show effectiveness after 48 weeks post-transplantation

MeiraGTX



- Met primary outcome measure: improvement in UPDRS 3 motor scores vs. sham at 6 months
- Improvements in the AAV-GAD group were observed at all time points

AbbVie



- D1/D5R, adjunct to levodopa
- Daily oral administration
- Early PD patient
- 15 weeks observation

Source: Iregene Corporate Presentation, September 2025

2025 Biosciences Case Study

Suppressor tRNAs to Read Through Nonsense Mutations

New Gene Editing Technique Can Correct About a Quarter of Gene Mutations By Avoiding Stop Codon Nonsense Mutations

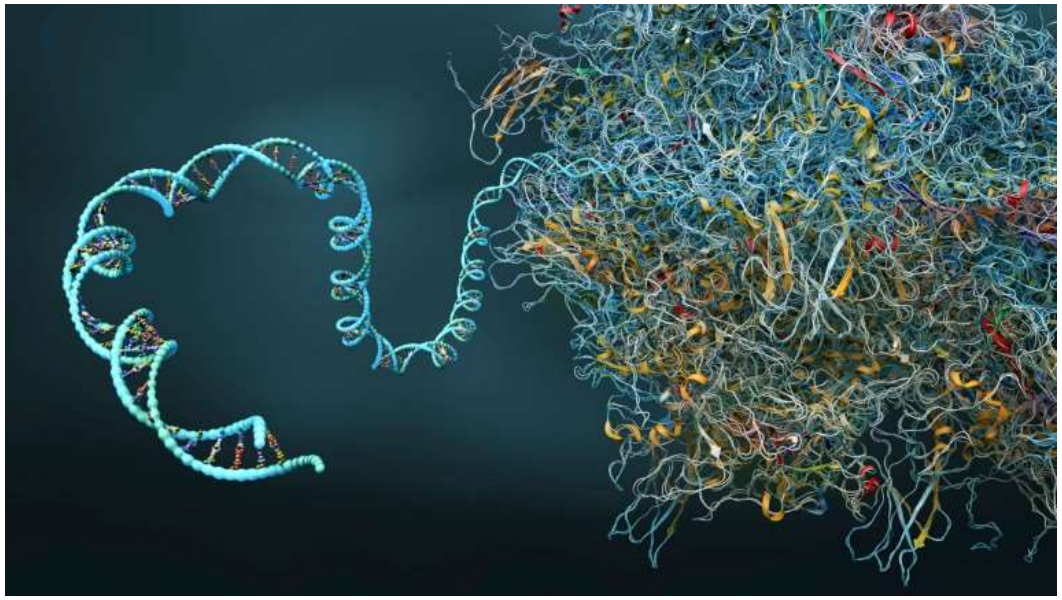
Heidi Ledford, *Nature*, Nov 19, 2025

A single multipurpose gene-editing tool can correct several genetic conditions by restoring proteins that have been truncated by disease-causing mutations. The method might one day overcome a key stumbling block faced by gene-editing therapies: the need to design a bespoke treatment for each disease.

The new approach, called PERT, combines gene editing with engineered RNA molecules that allow protein synthesis to continue even when a mutation in the DNA tells it to stop prematurely. Such mutations are called nonsense mutations, and they comprise nearly one-quarter of known disease-causing DNA variants.

So far, PERT has overcome disease-linked nonsense mutations in mice and in human cells grown in culture, but further testing and refinement are needed before the approach can be studied in people, says David Liu, a chemical biologist at the Broad Institute in Cambridge, Massachusetts, and a co-author of a paper about the technique.

If it does prove effective in humans, PERT could drive down the cost and speed up the development of gene-editing therapies for many conditions. “Disease-agnostic approaches like this raise a possibility that, I think, would be incredibly exciting for patients,” says Liu. He and his colleagues published their results on 19 November in Nature.



A cell’s protein-making machinery (artist’s illustration) can be instructed to ignore mutations that would otherwise result in shortened proteins.

Quite a few rare diseases like Duchenne’s Muscular Dystrophy involve quite a few different types of mutations, requiring one to develop individual therapies for each mutation type. In practice more than 90% of missense mutations lead to diseases then that are simply not accessible because there are just too many mutation types. This new tRNA approach can make it possible to drug many types of mutations in a single gene. This is a major breakthrough in gene therapy.

The New Approach Works by Creating a Transfer RNA that Just Skips Over the Mutated Part of the Gene in the Transcriptional Process

This approach converts a redundant endogenous tRNA into an optimized suppressor tRNA, enabling a single prime edit to rescue premature stop codons across different diseases.

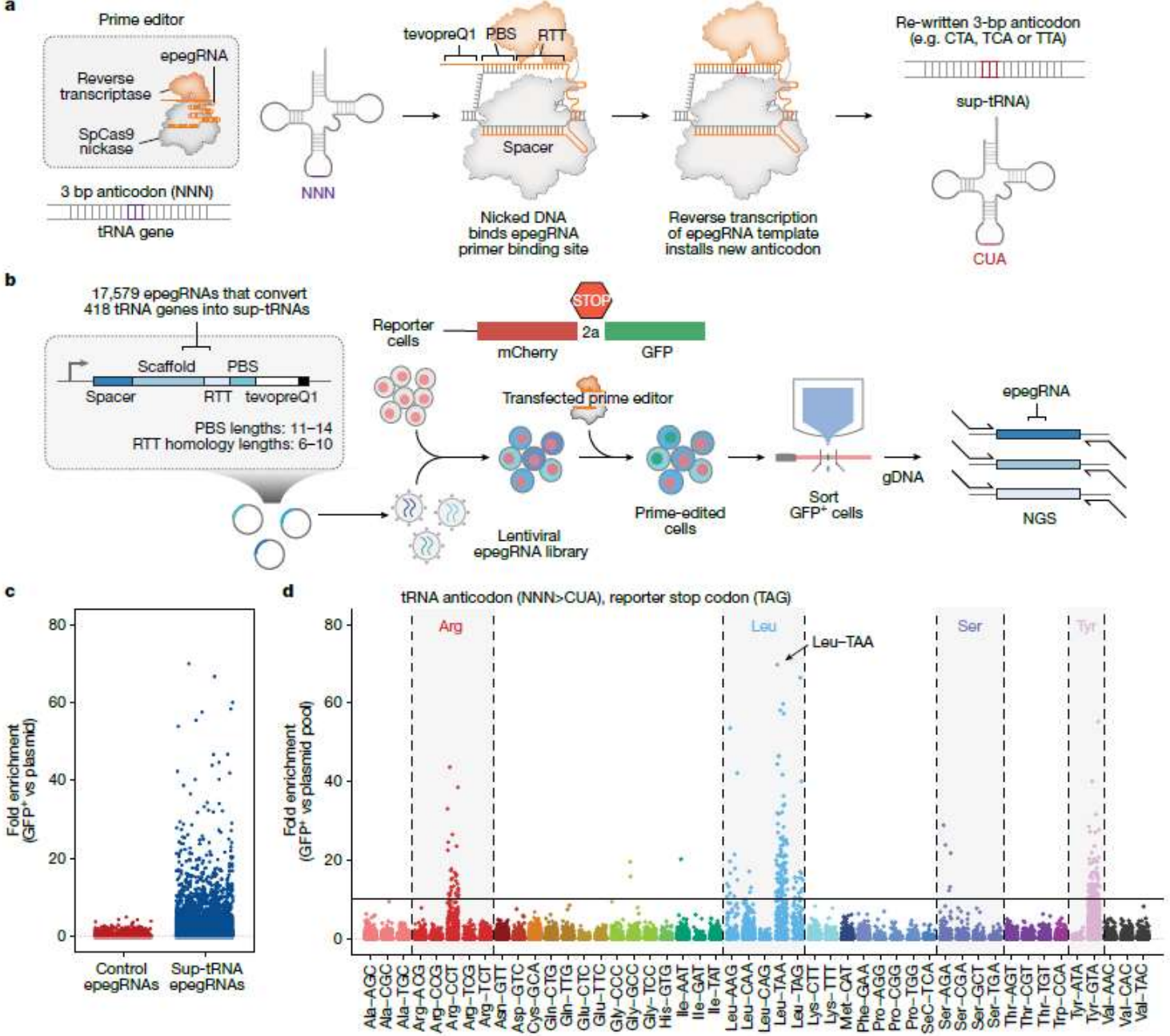
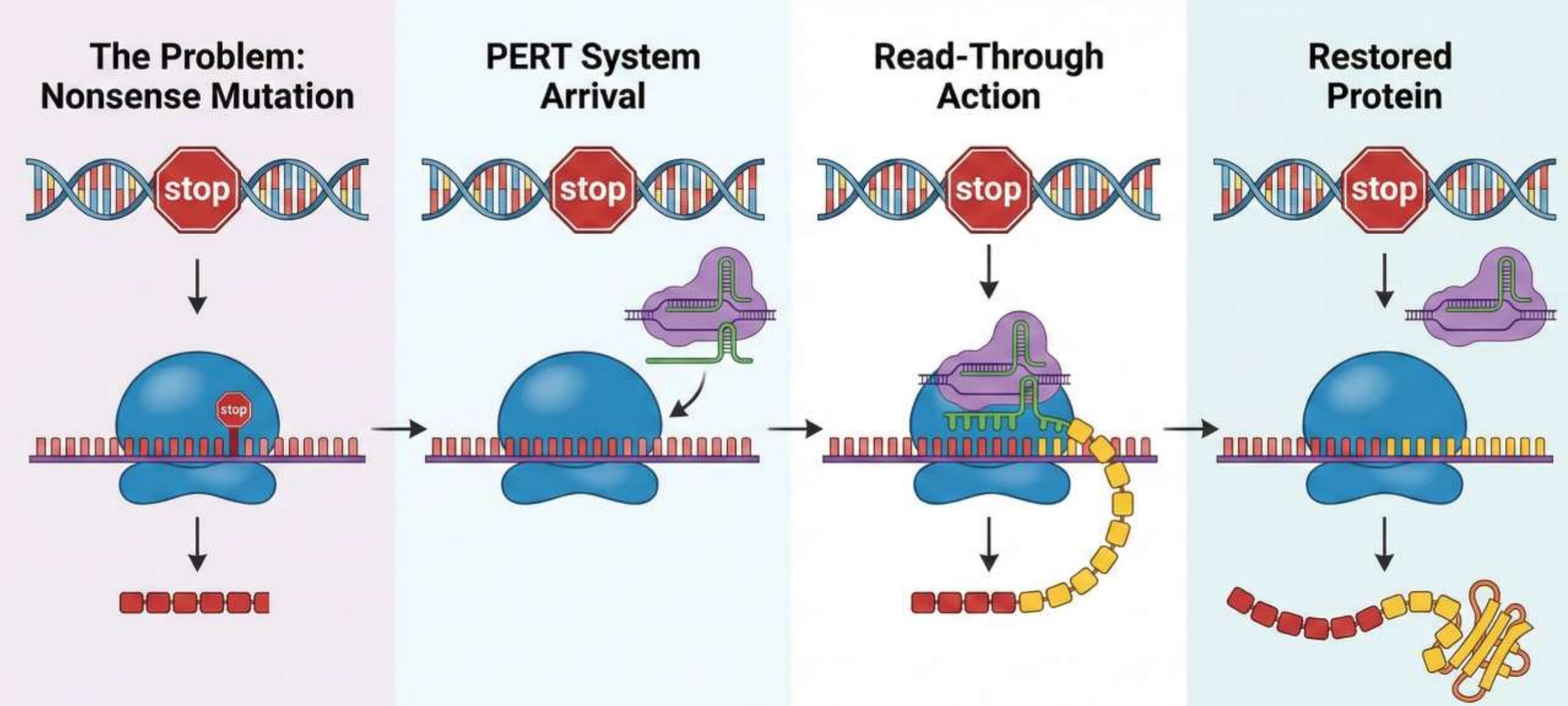


Fig. 1 | Prime editing-mediated conversion of endogenous tRNAs to sup-tRNAs in mammalian cells. a, Schematic of prime editing strategy to generate sup-tRNAs. **b**, Lentiviral epegRNA design and screening strategy. gDNA, genomic DNA; NGS, next-generation sequencing. **c**, Fold enrichment of epegRNAs, designed as controls (red) or to generate sup-tRNA (blue), in GFP-sorted cells, compared to the plasmid pool in the TAG screen. **d**, Fold enrichment of epegRNAs, colour-coded by the amino acids of the isoacceptor tRNA family that they target.

Source: https://www.nature.com/articles/s41586-025-09732-2


The Problem: Nonsense Mutation
PERT System Arrival
Read-Through Action
Restored Protein
stop
stop
stop
stop
stop
Nonsense mutation prematurely stops protein synthesis, causing disease
PERT delivers engineered RNA patch
Engineered RNA allows ribosome to “read through” stop signal
Full-length, functional protein restored, correcting genetic condition

2025 Biosciences Case Study

BCMA T-Cell Engagers for Autoimmunity

BMCA T-Cell Engager Associated with Profound Responses in Autoimmunity

The October 15, 2025 *NEJM* publication on TCE's by Ricardo Grieshaber-Bouyer (and Georg Schett) is quite impressive.

In his ten-patient series, individuals with refractory diseases including systemic sclerosis, Sjögren's syndrome, rheumatoid arthritis, and IgG4-related disease received a single course of teclistamab, a BCMA T-Cell engager.

B-cell depletion lasted a median of five months, and autoantibody levels dropped sharply, with normalization of disease biomarkers such as IgG4 and C-reactive protein. This was with *refractory* patients who were not responsive to other therapy.

Six patients achieved drug-free remission lasting up to fifteen months, while others showed marked improvement in pulmonary and systemic manifestations.

Cytokine-release syndrome occurred frequently but was mild, and no neurotoxicity was observed.

The publication bodes well for Candid in the U.S. which has licensed Epimab's Chinese BCMA TCE.

While these data are not as good as seen with some of the BCMA and CD19 CAR-T therapies, they are quite strong and suggested the potential for curative or infrequent chronic treatments for giant markets in autoimmunity.

BCMA T-Cell Engager Therapy in Patients with Refractory Autoimmune Disease

TO THE EDITOR: T-cell engagers redirect T-cell cytotoxicity for precision cell depletion and are emerging as a promising therapeutic method in autoimmune diseases.[1-4] Teclistamab, a bispecific antibody approved for multiple myeloma,[5] binds to CD3 on T cells and to B-cell maturation antigen (BCMA) on B cells and plasma cells. Here, we report on the safety and efficacy of teclistamab in 10 patients with six different refractory autoimmune diseases, with up to 15 months of follow-up.

The patients — all of whom had active, multidrug-resistant autoimmune diseases with characteristic serologic profiles — received teclistamab therapy under compassionate use (Table 1). The median age of the patients was 55 years (range, 24 to 66); 60% of the patients were women. Five-month follow-up has been reported previously[3] for Patients 1 through 4; these patients are included in this report with 10 to 15 months of follow-up.[3] All the patients had a history of treatment failure with more than three immunomodulatory drugs (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Notably, nine patients had received previous B-cell depletion with rituximab.

Teclistamab was administered as standard step-up dosing during a 5-day period in an inpatient setting (at a dose of 0.06 mg per kilogram of body weight on day 1, 0.3 mg per kilogram on day 3, and 1.5 mg per kilogram on day 5). The initial administration of teclistamab was followed by a one-time maintenance dose of 1.5 mg per kilogram after 4 weeks, as described previously[3] (see the Supplementary Appendix). Two weeks before the initiation of teclistamab, glucocorticoids were tapered to less than 5 mg per day, and all other immunosuppressive medication was stopped.

Teclistamab induced rapid B-cell depletion, with a median B-cell aplasia of 157 days (Fig. S1A in the Supplementary Appendix). Free kappa and lambda light chains dropped below detection limits in all the patients (Fig. S1E and S1C), which indicated successful depletion of the plasma-cell compartment, and serum immunoglobulin levels substantially decreased (Fig. S1D, S1E, and S1F).

Cytokine release syndrome occurred in 8 patients (grade 1 in 4 patients and grade 2 in 4 patients) within 2 days after induction therapy and resolved with a single dose of tocilizumab. No grade 3 or 4 cytokine release syndrome and no neurotoxicity occurred. Mild upper respiratory tract infections were common (in 8 of 10 patients) (Table 1). Patient 1 received inpatient hydration to treat viral gastroenteritis. Two bacterial infections warranted antibiotic therapy (*Clostridium difficile* infection in Patient 7 and urinary tract infection in Patient 3). Hypogammaglobulinemia developed in all 10 patients, with a median onset of 4 weeks after induction therapy; all cases were treated with a median of two immune globulin infusions.

Levels of disease-specific autoantibodies decreased, and seroconversion was observed for multiple antibodies, including Scl-75, Scl-100, RF, SS-A, PM75, Mi2a, and Mi2 (Fig. S2). In Patients 9 and 10 who had IgG4-related disease, levels of IgG4 and C-reactive protein (markers of humoral inflammation) normalized (Fig. S2), a change that was accompanied by a substantial improvement in constitutional symptoms.

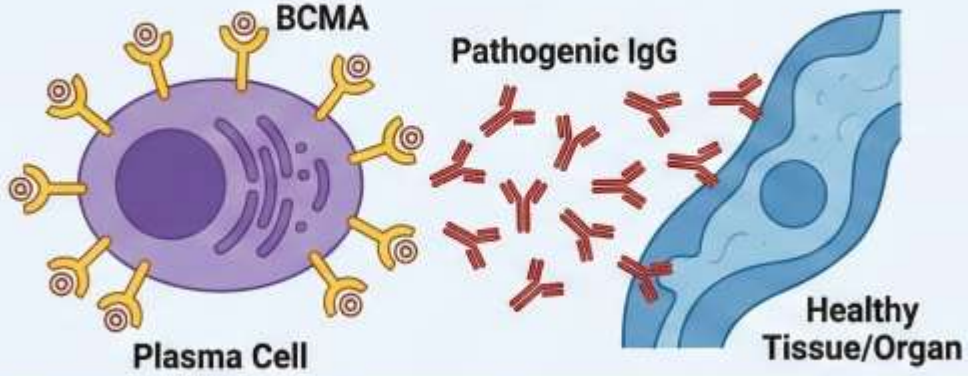
Clinical responses were observed in all but 1 patient (Patient 8) (Fig. S3A). Among the 5 patients with interstitial lung disease for whom longitudinal data on pulmonary diffusion capacity were available, symptoms abated and diffusion capacity improved in 4 patients, whereas both measures worsened in 1 patient, with an overall average change from a median carbon monoxide transfer coefficient of 45% to 53% (Fig. S3A). In the patient with Graves disease, magnetic resonance imaging showed reduced exophthalmos and muscle thickness (Fig. S3B). In Patient 9, who had IgG4-related disease, FAPI-PET-CT (fibroblast activation protein inhibitor–positron-emission tomography–computed tomography) showed reduced stromal-cell activation in the tissue (Fig. S3C). At the latest follow-up, 6 of 7 patients who were evaluated were not taking glucocorticoids, and 8 of 10 patients were not taking immunosuppressants (Table S1).

After a single treatment course, 6 patients were in drug-free remission, with a median recorded response of 11 months (range, 8 to 15); 3 patients had progression after a median of 5 months (Fig. S3D). In 2 patients, teclistamab was administered again, which was followed by a second response. The median duration of response across all patients was 10 months (range, 4 to 15), without concomitant glucocorticoid and immunomodulatory therapy.

Teclistamab appeared to show durable efficacy as rescue therapy across six different refractory autoimmune diseases. The incidence of cytokine release syndrome was common but mild and manageable with tocilizumab. Hypogamma-

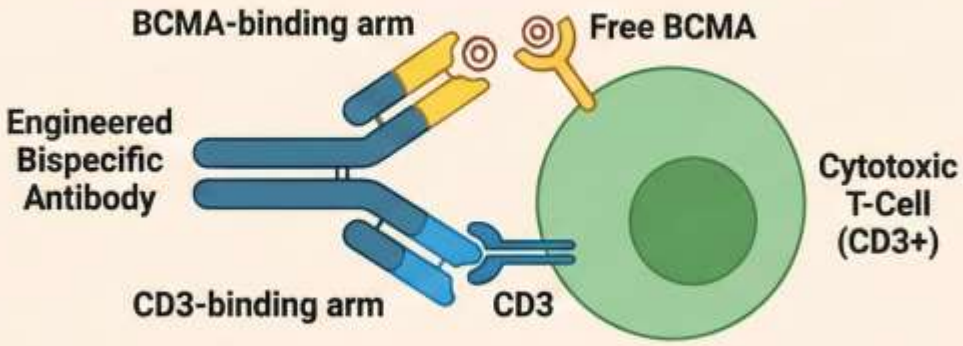
BCMA T-Cell Engagers: Mechanism for Curing IgG-Driven Autoimmunity (Corrected Pathways)

1. The Autoimmune Problem: Pathogenic IgG & Plasma Cells



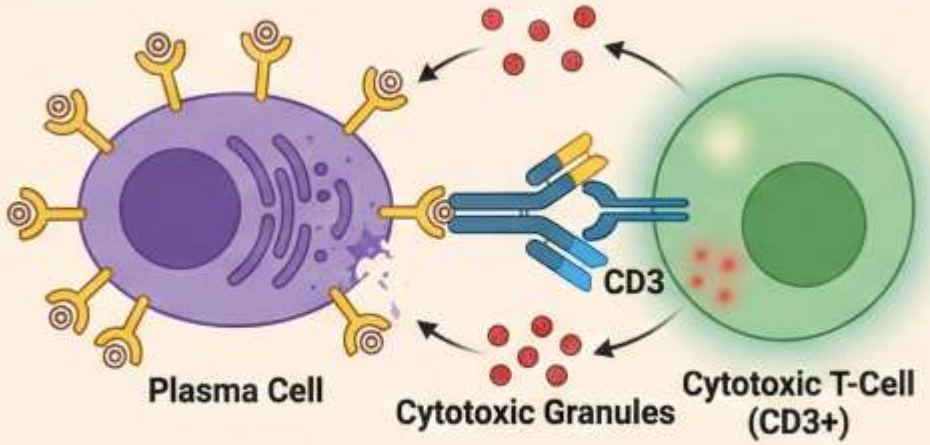
Plasma cells produce **pathogenic IgG** autoantibodies that attack **self-tissue**. These cells express BCMA on their surface.

2. The BCMA T-Cell Engager (Bispecific Antibody)



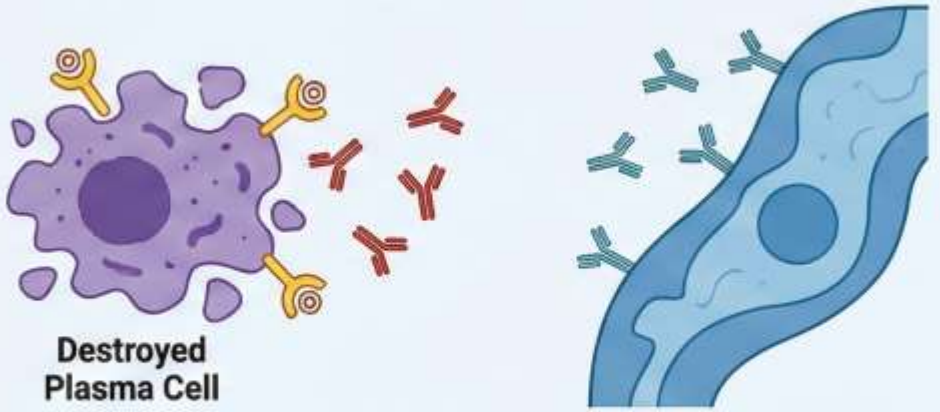
The engager is a **bispecific** molecule, bridging **T-cells** (via CD3) to BCMA-expressing plasma cells.

3. Engager Action: Bridging & T-Cell Activation



The engager brings the T-cell and plasma cell into close proximity. This activates the T-cell to release cytotoxic molecules.

4. Outcome: Plasma Cell Destruction & Disease Resolution



The destruction of BCMA-positive plasma cells leads to a sharp drop in pathogenic IgG, stopping the autoimmune attack and allowing tissue healing.

TCE's Can Achieve CAR-T Like Results

Patients with Autoimmune Disease Achieving Full B Cell Depletion in Blood

Therapeutic Agent	Mechanism	Key Trial/Source	Patients Achieving Full Depletion
Rituximab	CD20 mAb	LUNAR trial	Up to 24%
Obinutuzumab	CD20 mAb	MOBILITY trial	Up to 74%
Teclistamab (J&J) or Cizutambig (Candid)	BCMA TCE	>20 patients across studies	100%

CAR-T like result with long persistence time as documented in recent NEJM paper.

Source: Seminar by Ricardo Greishaber-Bouyer, October 2025

Strong Case for T-Cell Engagers in Autoimmunity

Criteria	Canonical mAb	TCE (T-Cell Engager)	Autologous CAR-T	Allogeneic CAR-T/NK	In vivo CAR-T
Therapy Class	Biologic	Biologic	Cell Therapy	Cell Therapy	Cell Therapy
Potency	Moderate (+)	Very High (+++)	Very High (+++)	Unknown (?)	Unknown (?)
Clinical Validation	Highest	High	Highest	Low	Low
COGS (Cost of Goods)	Lowest	Lowest	Highest	Medium	Low
Dosing Flexibility	High	High	Low	Medium	Medium
Delivery Method	Subcutaneous (s.c.)	Subcutaneous (s.c.)	Intravenous (i.v.)	Intravenous (i.v.)	Intravenous (i.v.)
Outpatient Use	Yes (✓)	Yes (✓)	Uncertain (?)	Uncertain (?)	Uncertain (?)
Scalability	Yes (✓)	Yes (✓)	No (X)	Yes (✓)	Yes (✓)
Therapeutic Delay	Short (Low)	Short (Low)	Long (High)	Short (Low)	Short (Low)
Patients Treated (Estimated)	Millions	100	200	50	20
Unique Challenges	Potency in tissue	Dosing	Logistics, Cost, Safety	PK, Dosing, Potency (?)	PK, Dosing, Potency (?)

Source: Seminar by Ricardo Greishaber-Bouyer, October 2025

Huge Opportunity in Upcoming Autoimmune Therapies

Conclusions – Deep cell depletion is the next blockbuster opportunity in I&I

1. CAR T cells and T cell engagers can achieve deep target cell dep letion in tissue and produce durable drug free remission in autoimmune patients with a 'one and done' approacch
2. BCMA targeting depletes B cells *and* plasma cells
3. Different patient populations might differentially bene't from CD19 or BCMA targeting target for autoimmune disease
4. New molecules will be designed specifically for autoimmunedısease with refined target selection, improved safety and efficacy and optimized dosing

Ricardo Grieshaber-Bouyer

Disclosure

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