Biopharma Market Update

October 6, 2025

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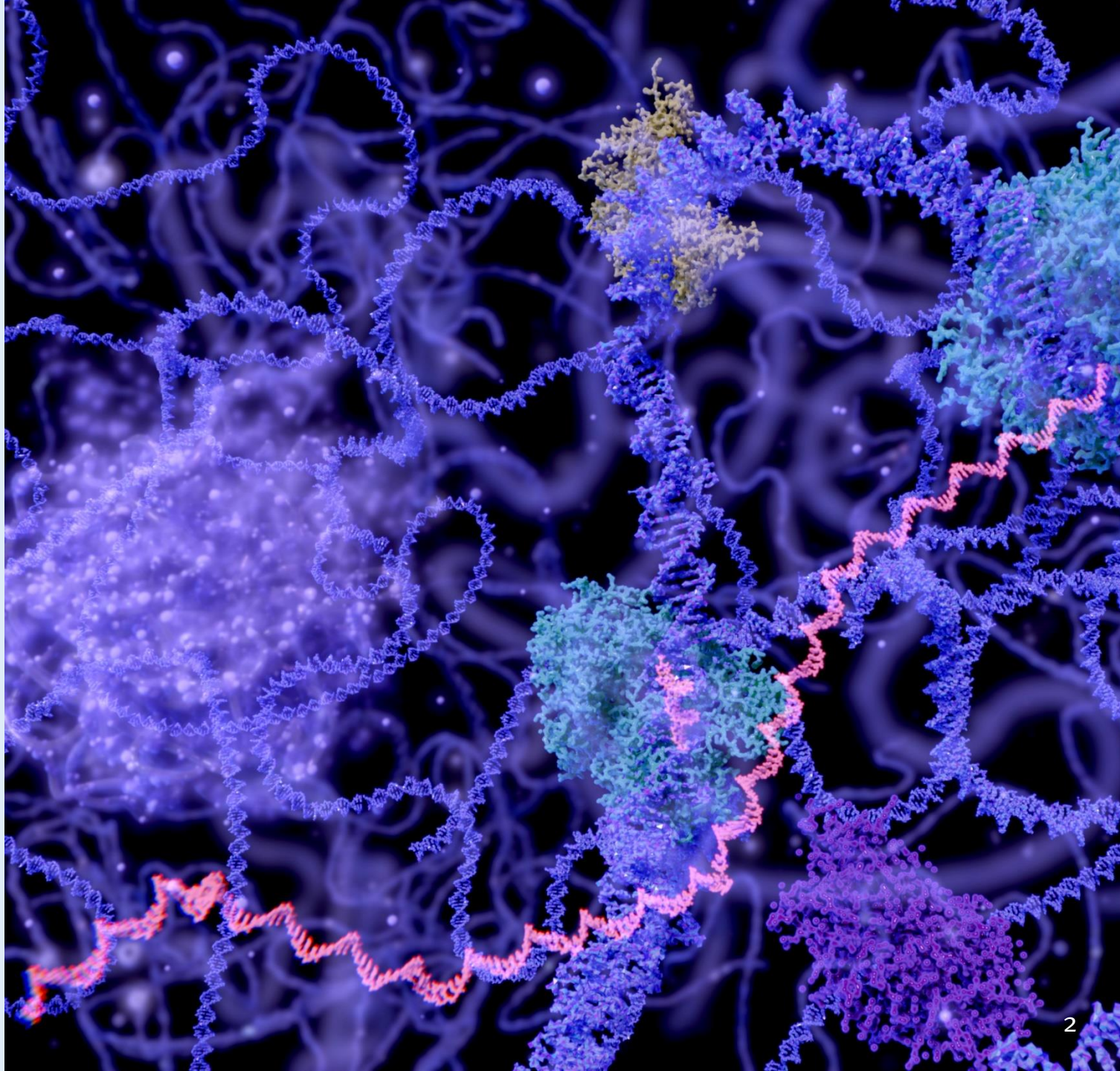

Stifel: A Powerhouse in Healthcare Financings and Advisory

Stifel has a broad team focused on Biopharma equity financings and strategic advisory work.

The team has deep scientific knowledge and strong relationships with KOLs.

Stifel has advised on 629 financing and strategic transactions in the healthcare sector over the last five years.(1)

Recent Financings

SEK 183,000,000 EGETIS THERAPEUTICS Follow-On Offering Sole Bookrunning Manager *October 2025*	$345,000,000 uniQure Follow-on Offering Joint Bookrunning Manager *September 2025*	$115,000,000 PepGen Confidentially Marketed Follow-on Offering Joint Bookrunning Manager *September 2025*	$327,750,000 pharmaceuticals Initial Public Offering Joint Bookrunning Manager *September 2025*	$287,500,000 rapport therapeutics Follow-on Offering Joint Bookrunning Manager *September 2025*
$288,420,000 DIANTHUS THERAPEUTICS Follow-on Offering Joint Bookrunning Manager *September 2025*	$287,500,000 MINERALYS Confidentially Marketed Follow-on Offering Joint Bookrunning Manager *September 2025*	$85,000,000 X4 PHARMACEUTICALS PIPE Sole Placement Agent *August 2025*	$460,000,000 LIGAND Convertible Senior Notes Joint Bookrunning Manager *August 2025*	$201,250,000 Rhythm PHARMACEUTICALS Confidentially Marketed Follow-on Offering Joint Bookrunning Manager *July 2025*
$230,000,000 Dyne THERAPEUTICS Follow-on Offering Joint Bookrunning Manager *June 2025*	$200,000,000 CRESCENT BIOPHARMA PIPE Joint Placement Agent *June 2025*	$862,500,000 insmed Confidentially Marketed Follow-on Offering Co-Lead Manager *June 2025*	$115,057,500 trevi THERAPEUTICS Follow-on Offering Joint Bookrunning Manager *June 2025*	$80,000,000 LEXEO therapeutics PIPE Joint Placement Agent *May 2025*
$502,908,800 Hinge Health Initial Public Offering Joint Bookrunning Manager *May 2025*	$300,000,000 Jade BIOSCIENCES PIPE Joint Placement Agent *April 2025*	$201,250,000 MINERALYS Follow-on Offering Joint Bookrunning Manager *March 2025*	$232,300,000 kestra MEDICAL TECHNOLOGIES Initial Public Offering Joint Bookrunning Manager *March 2025*	$219,200,000 sionna Initial Public Offering Joint Bookrunning Manager *February 2025*
EUR 12,000,000 FARON Follow-on Offering Joint Bookrunning Manager *February 2025*	CHF 80,000,000 BIOVERSYS Initial Public Offering Joint Global Coordinator *February 2025*	$150,000,000 GH RESEARCH Follow-on Offering Joint Bookrunning Manager *February 2025*	$251,600,000 Beta Bionics Initial Public Offering Joint Bookrunning Manager *January 2025*	$259,300,000 disc medicine Follow-on Offering Joint Bookrunning Manager *January 2025*

Recent Strategic Transactions

€ 190,000,000 VISUfarma Has Agreed to be Acquired by LUPIN Advisor to Seller *Pending*	SDSRx Has Agreed to be Acquired by DHL Supply Chain Advisor to Seller *Pending*	betterview Has Agreed to Sell all of its substantial operational assets to EuroEyes Sole Financial Advisor *Pending*	Bastide GROUPE Has Agreed to Sell its Subsidiary Baywater Healthcare to SAPIO Advisor to Seller *Pending*	Congenica Has Been Acquired by SeqOne Advisor to Seller *September 2025*
Dechra Has Sold its Poultry Vaccine Portfolio to vaxxinova Advisor to Seller *July 2025*	Up to $613,000,000 Otsuka Acquisition of the CAN10 IL1RAP Immunology Program from cantargia Advisor to Buyer *July 2025*	Up to $192,500,000 基石药业 CSTONE PHARMACEUTICALS Out-License of Sugemalimab in Western EU and UK GENTILI Advisor to Licensor *July 2025*	Up to $670,000,000 Otsuka In-Licensing of the Global Rights ex-Greater China to HBM7020 from HARBOUR BIOMED Advisor to Licensee *June 2025*	$155,000,000 Abeona THERAPEUTICS Sale of Rare Pediatric Disease Priority Review Voucher (PRV) to **Undisclosed Pharma Company** Advisor to Seller *June 2025*
$70,000,000 HANSA BIOPHARMA Restructured Product Finance Loan Sole Financial Advisor *June 2025*	Urology America GAUGE CAPITAL Strategic Alternatives Advisor *May 2025*	Up to €220,000,000 Cinclus Pharma Out-Licensing of Linaprazan Glurate in Europe ZENTIVA Sole Financial Advisor *May 2025*	$30,400,000 Glochem Industries Pvt. Ltd. Has Sold its API Business to **Audhataam Pharmaceuticals Pvt Ltd** Advisor to Seller *May 2025*	£25,000,000 HeliosX Financing by LIQUIDITY Sole Financial Advisor *May 2025*
$22,300,000 GRANULES Has Acquired SENN Solutions Synchronized Advisor to Buyer *April 2025*	€35,000,000 FARON Convertible Bond Sole Financial Advisor, Sole Placement Agent *April 2025*	SANOVA DERMATOLOGY Has Been Acquired by DOCS DERMATOLOGY GROUP Advisor to Seller *April 2025*	Has Been Acquired by CALLISTA PRIVATE EQUITY Advisor to Seller *March 2025*	radar healthcare Has Acquired EIDO HEALTHCARE Advisor to Buyer *February 2025*
SeQure Dx Has Been Acquired by MaxCyte Advisor to Seller *January 2025*	基石药业 CSTONE PHARMACEUTICALS Out-License of Sugemalimab in LATAM Region STEINCARES Advisor to Licensor *January 2025*	Up to $230,000,000 ImaginAb Sale of Radiopharmaceutical Therapy Business to Telix Advisor to Seller *January 2025*	teva Divestiture of Provigil and Nuvigil ex-U.S. NEURAXPHARM Advisor to Seller *December 2024*	teva Divestiture of Provigil and Nuvigil U.S. APOTEX Advisor to Seller *December 2024*

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Note: As of October 3, 2025. Deal values and dates represented are as of the announcement that the definitive agreement was signed. Stifel transactions include deals completed by Stifel, Nicolaus & Company, Incorporated and its affiliated entities, Torreya Capital LLC and its affiliated entities, and Bryan Garnier and its affiliated entities.

(1) Since 2020.

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To get on the mailing list for this publication feel free to contact Jenna Hill (hillje@stifel.com). Past issues of this publication can be read online at:

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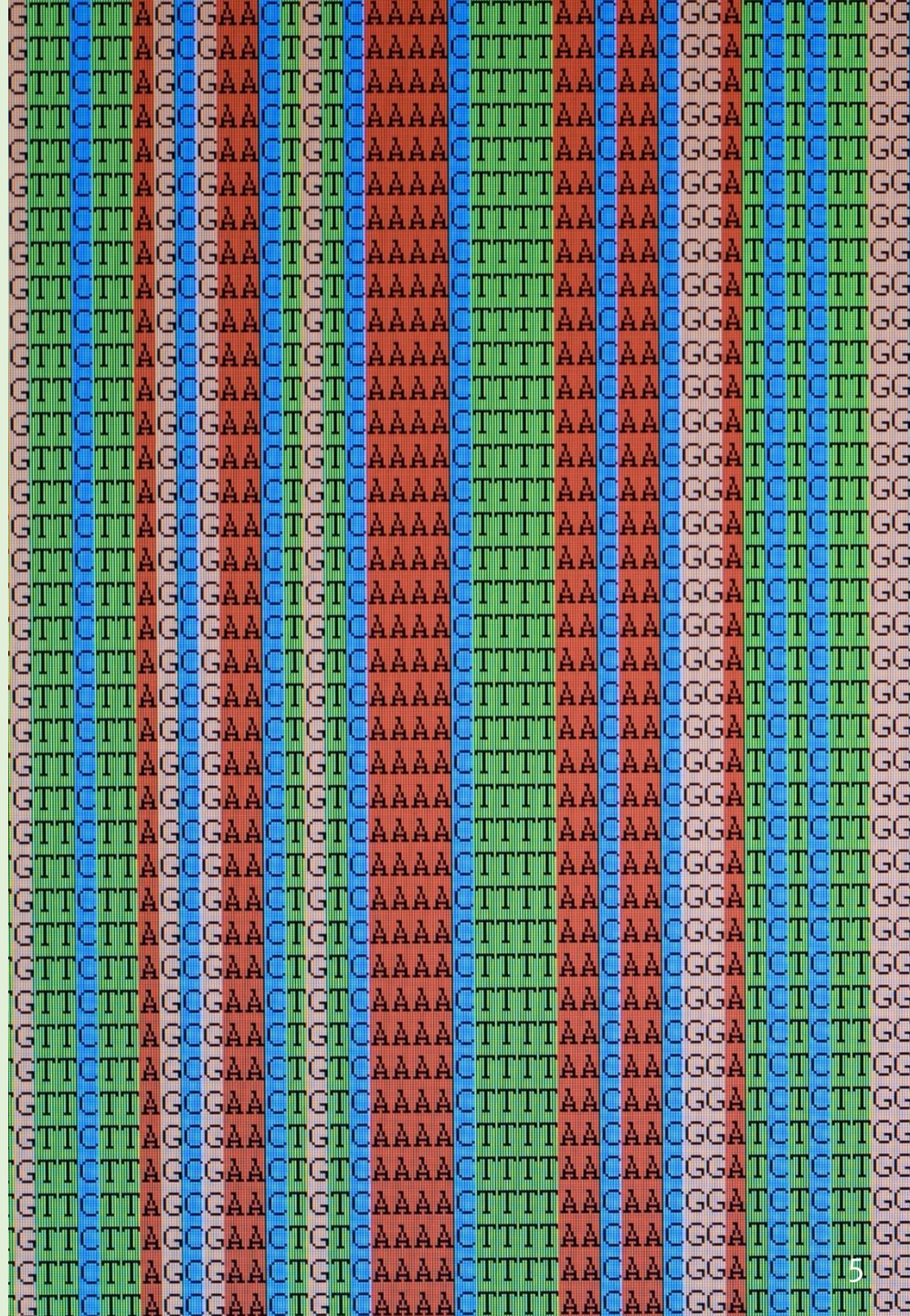
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Pharma Strategy)



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[Sep 11, 2025]

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[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]

AI in medicine

[Jan 22, 2024]

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[November 22, 2023]

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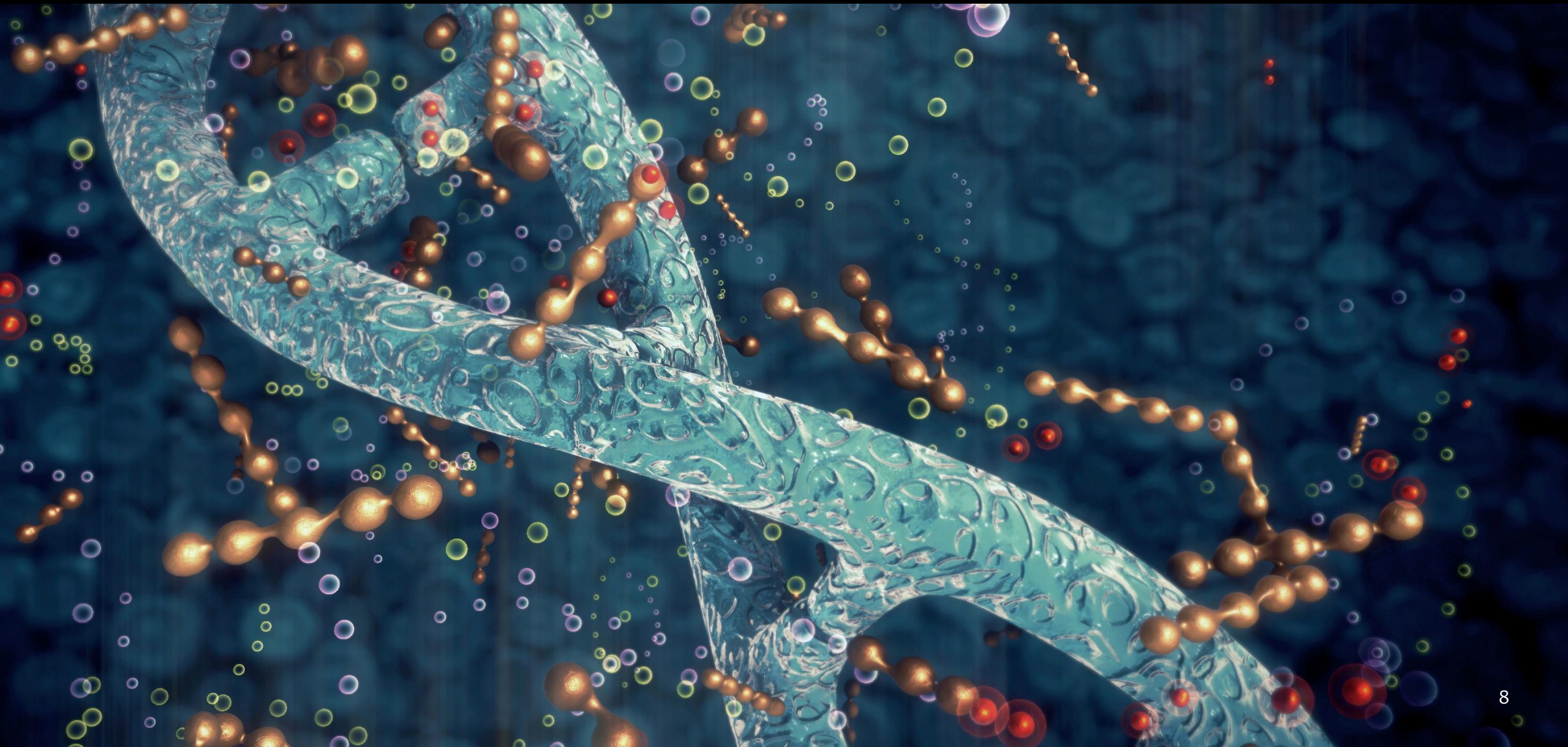
Macro and Political Update



Senate Stalemate Sends US Shutdown into Second Week

Bernd Debusmann Jr and Ana Faguy, *BBC*, October 4, 2025 (excerpt)

US Senators have for a fourth time failed to pass spending proposals to reopen the federal government, extending the ongoing shutdown into next week.

Two separate spending proposals - one from the Democrats and one from Republicans - failed to reach the required 60-vote threshold.

With both sides deadlocked, the White House on Friday said it would be left with the "unenviable task" of mass layoffs to keep essential government services operating if the shutdown continues, which Press Secretary Karoline Leavitt described as "fiscal sanity".

The scope of those potential lay-offs remains unclear, but the White House has been in discussions with the Office of Management and Budget, or OMB.

Both Republican and Democratic lawmakers have dug in their heels on the main point of disagreement: healthcare. Democrats have hoped to capitalise on the impasse to ensure health insurance subsidies for those with low-income do not expire and reverse the Trump administration's cuts to the Medicaid health programme.

Republicans, for their part, have repeatedly accused Democrats of shutting down the government in a bid to provide healthcare to undocumented immigrants - a charge that Democratic leaders have denied.

Source: https://www.bbc.com/news/articles/ce32eegrlpko

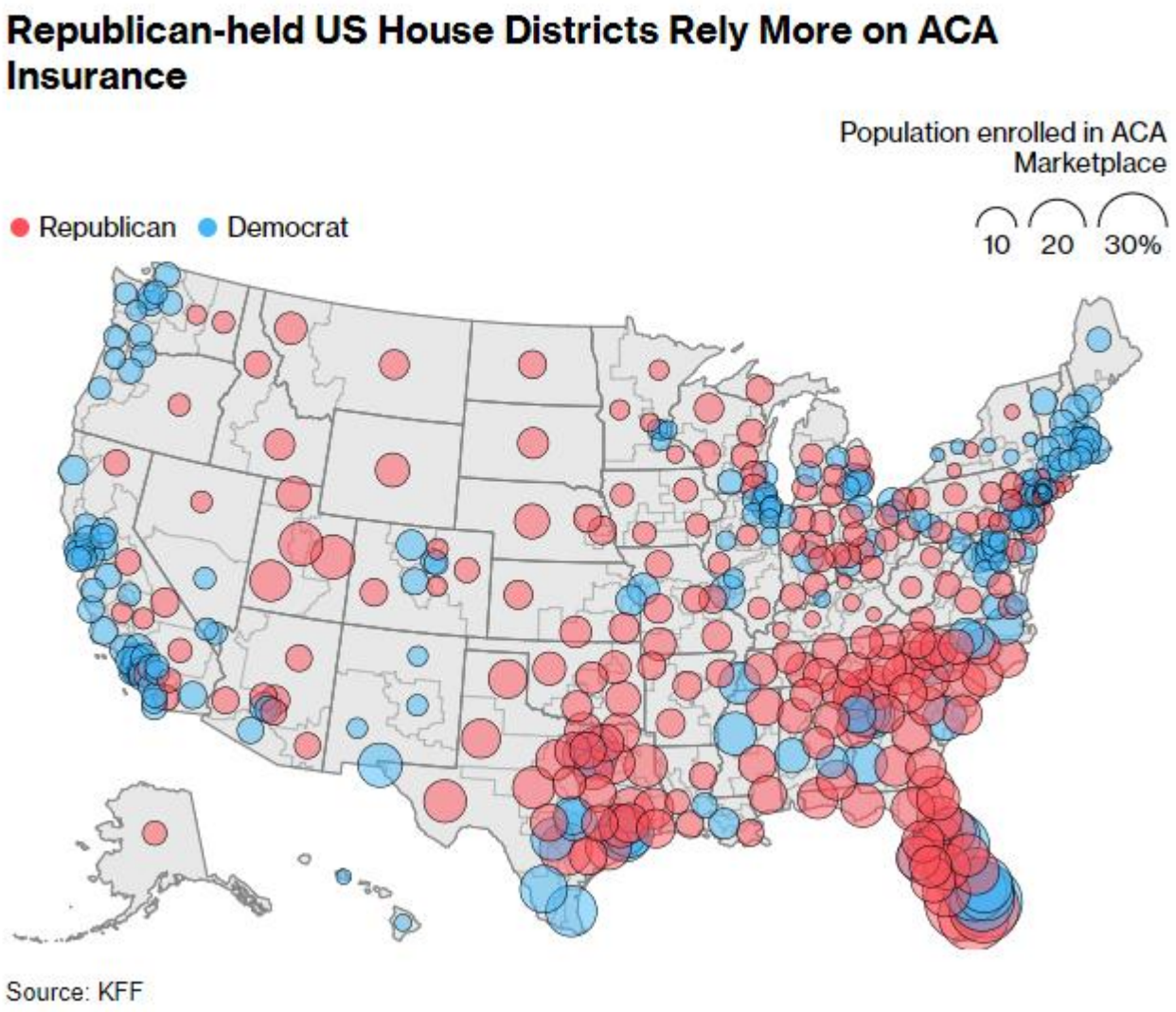
Why Obamacare Haunts Republicans in Shutdown Fight

David Rovella, *Bloomberg*, October 3, 2025 (excerpt)

The health insurance subsidies at the center of the US government shutdown fight disproportionately benefit areas of the country represented by Republican lawmakers, posing a potential vulnerability for President Donald Trump's party in next year's midterm congressional elections.

Twelve million Americans in GOP-held US House districts are covered by health plans purchased through Affordable Care Act exchanges established by the 2010 law pushed through by Democratic President Barack Obama. That compares to the nine million living in Democratic-held districts.

Of the 75 districts where at least 10% of the people are enrolled in ACA policies, 47 are represented by Republicans in the House. Ironically, the disparity is due in part to Republican politicians' hostility toward Obama's health insurance program. GOP-run states, particularly in the South, rejected the federally subsidized Medicaid expansion available under Obamacare, so more individual residents receive coverage through ACA policies.



Source: https://www.bloomberg.com/news/newsletters/2025-10-03/obamacare-bites-gop-in-shutdown-fight-evening-briefing-americas?srnd=homepage-americas

The Shutdown Meant No Jobs Report. Here's What it Would Have Said

Jeff Cox, *CNBC*, October 4, 2025 (excerpt)

If it just seems like the first Friday of the month wasn't the same without being able to pore through the Bureau of Labor Statistics' hotly watched monthly jobs report, don't worry. You probably didn't miss much.

While the BLS has gone dark with the shutdown in Washington, other reports outside the government data suggest the labor market just plodded along in September.

The Dow Jones consensus forecast was for growth of 51,000 in nonfarm payrolls with the unemployment rate holding steady at 4.3%.

High-frequency data that includes job postings, private payrolls and state-by-state figures for initial jobless claims indicate that while employment growth continues to be anemic, the labor market overall isn't capsizing, at least not anytime soon.

"We fight with the army we have at moments like this, where it's critically important that we're figuring out whether the economy is in a moment of transition," Chicago Federal Reserve President Austan Goolsbee said in a CNBC interview Friday. "This is what we have, and thus far it still continues to point to a pretty stable labor market."

Source: https://www.cnbc.com/2025/10/03/shutdown-jobs-report-economy.html

As Shutdown Begins, FDA to Stop Accepting New Drug Submissions

Kristen Jensen, *Biopharma Dive*, October 1, 2025 (excerpt)

A shutdown of a few days or a week likely won't have a major impact on Americans or on the health-care industry. But an extended standoff between Republicans and Democrats over the budget would affect research funding, health insurance negotiations and eventually the flow of new medical products onto the market, analysts said.

While the agency emphasized that most of its employees will stay on the job, the total number of workers is less than its previous contingency plan before President Trump took office. That plan called for 77% of the FDA's staff, or 15,223 employees, to be retained during a shutdown.

The numbers "reflect the impact of the significant job cuts at FDA early in the Trump Administration, with many non-user fee positions already eliminated," TD Cowen analyst Rick Weissenstein wrote in a note to clients. Still, he said, the earlier actions mean the agency probably won't be significantly impacted now if Trump follows through on his threat to fire more of the federal workforce because of the shutdown.

The budget impasse comes during a year that has already featured much uncertainty for the industries regulated by the FDA. In addition to layoffs throughout the Health and Human Services Department, many key officials have either resigned or been forced out of the FDA, thinning expertise and heightening scrutiny of the agency's ability to complete reviews on time.

Source: https://www.biopharmadive.com/news/fda-government-shutdown-new-drug-applications-reviews/761576/

Fed's Logan Signals Inflation Is Top Issue, Urges Rate Caution

Jonnelle Marte, *Bloomberg*, Oct 3, 2025 (excerpt)

Federal Reserve Bank of Dallas President Lorie Logan said the US central bank is further away from its inflation target than it is from the maximum employment goal, and reiterated that officials should move cautiously with interest-rate reductions.

"Right now, we're furthest away on the inflation side of those objectives, with a forecast that takes some time to get back to 2%," Logan said Friday during a conference in Mexico City. "But of course, there's a lot of uncertainty in the world."

The Dallas Fed chief said that when it comes to assessing the US labor market, she is primarily focused on the unemployment rate, rather than payrolls figures. She added that the jobless rate is near the level where many economists expect it should settle over the long run. In August, that rate was 4.3%; the federal government shutdown meant September data weren't released Friday.

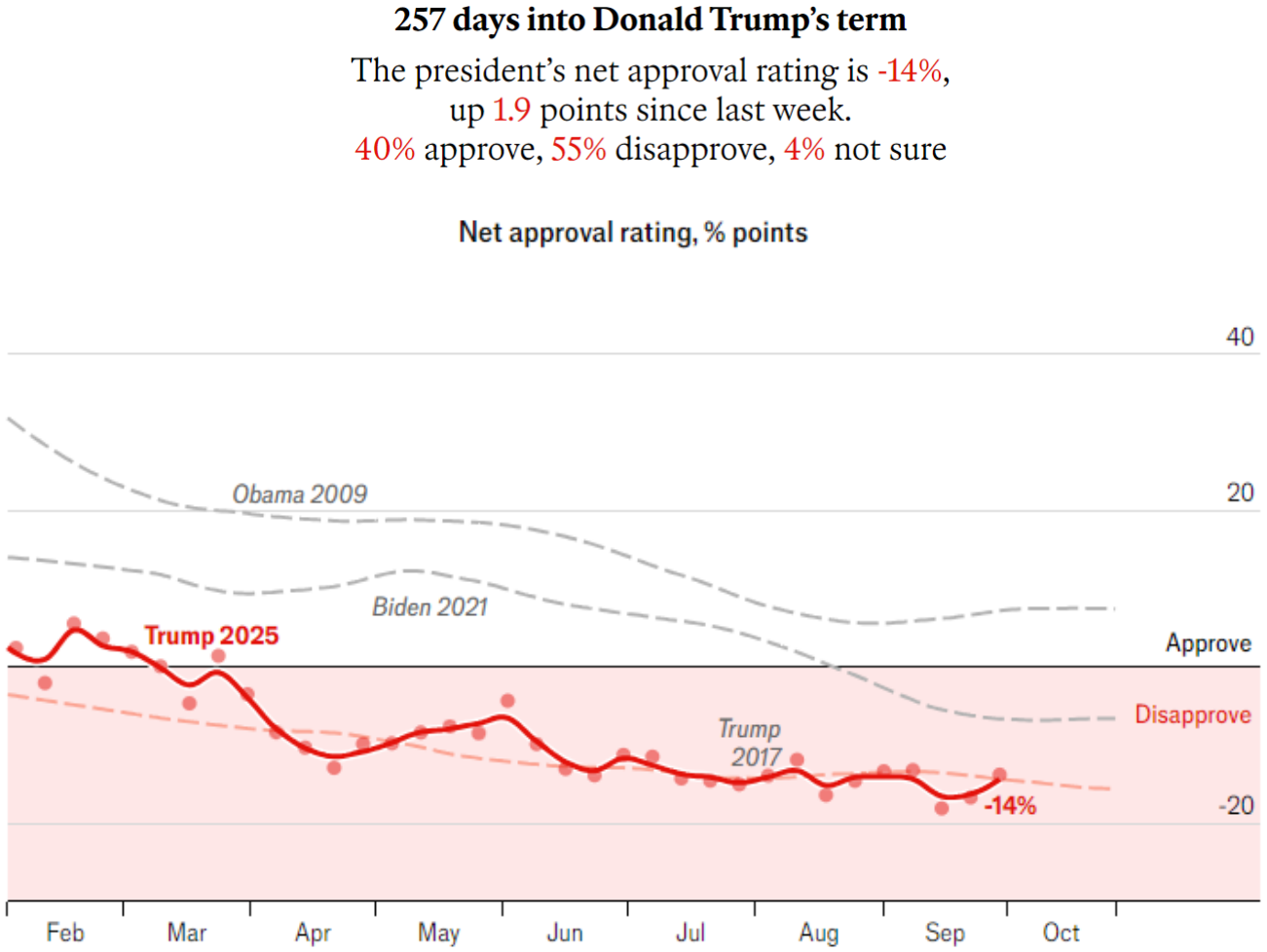
The Fed lowered rates last month after holding borrowing costs steady, citing concern about elevated inflation, since the end of last year. A sharp slowdown in employment growth raised worries about weakness in the labor market. But some officials remain primarily concerned about inflation, which has run above the Fed's 2% target for more than four years. "We really need to be cautious about further rate cuts from here," Logan said Friday. Speaking at a separate event a day before, she said she preferred a cautious approach with inflation still running above the Fed's target and policy not being more than moderately restrictive.

Source: https://www.bloomberg.com/news/articles/2025-10-03/fed-s-logan-signals-inflation-is-top-issue-urges-rate-caution

Lorie Logan

Head, Federal Reserve Bank of Dallas, Texas

Trump Approval Ratings Continue to be Wobbly



Source: https://www.economist.com/interactive/trump-approval-tracker

Supreme Court Declines to Take Action on Trump's Request to Fire Fed Governor For Now

Amy Howe, SCOTUSblog, October 1, 2025 (excerpt)

The Supreme Court on Wednesday announced that it will hear oral arguments in January on a request from the Trump administration to allow the president to fire Lisa Cook, a member of the Federal Reserve's Board of Governors. In a brief, unsigned order, the justices delayed their decision on the administration's plea to pause a ruling by a federal judge in Washington, D.C., that keeps Cook in office despite President Donald Trump's efforts to remove her from the board.

The dispute is the latest chapter in an ongoing battle over the president's power to remove the heads of independent federal agencies created by Congress. Under federal law, members of the Federal Reserve's Board of Governors are appointed by the president and confirmed by the Senate to serve staggered 14-year terms, a design intended to prevent any one president from "stacking the deck" with his own nominees. They can also only be removed "for cause" – a term that the Federal Reserve Act does not define.

Then-President Joe Biden nominated Cook to the Fed board in 2023. But in late August, Trump – who has also criticized the chair of the Fed, Jerome Powell, for the board's failure to lower interest rates – posted screenshots on the social media site Truth Social of a letter to Cook in which he fired her.

Source: https://www.scotusblog.com/2025/10/supreme-court-declines-to-take-action-on-trumps-request-to-fire-fed-governor-for-now/

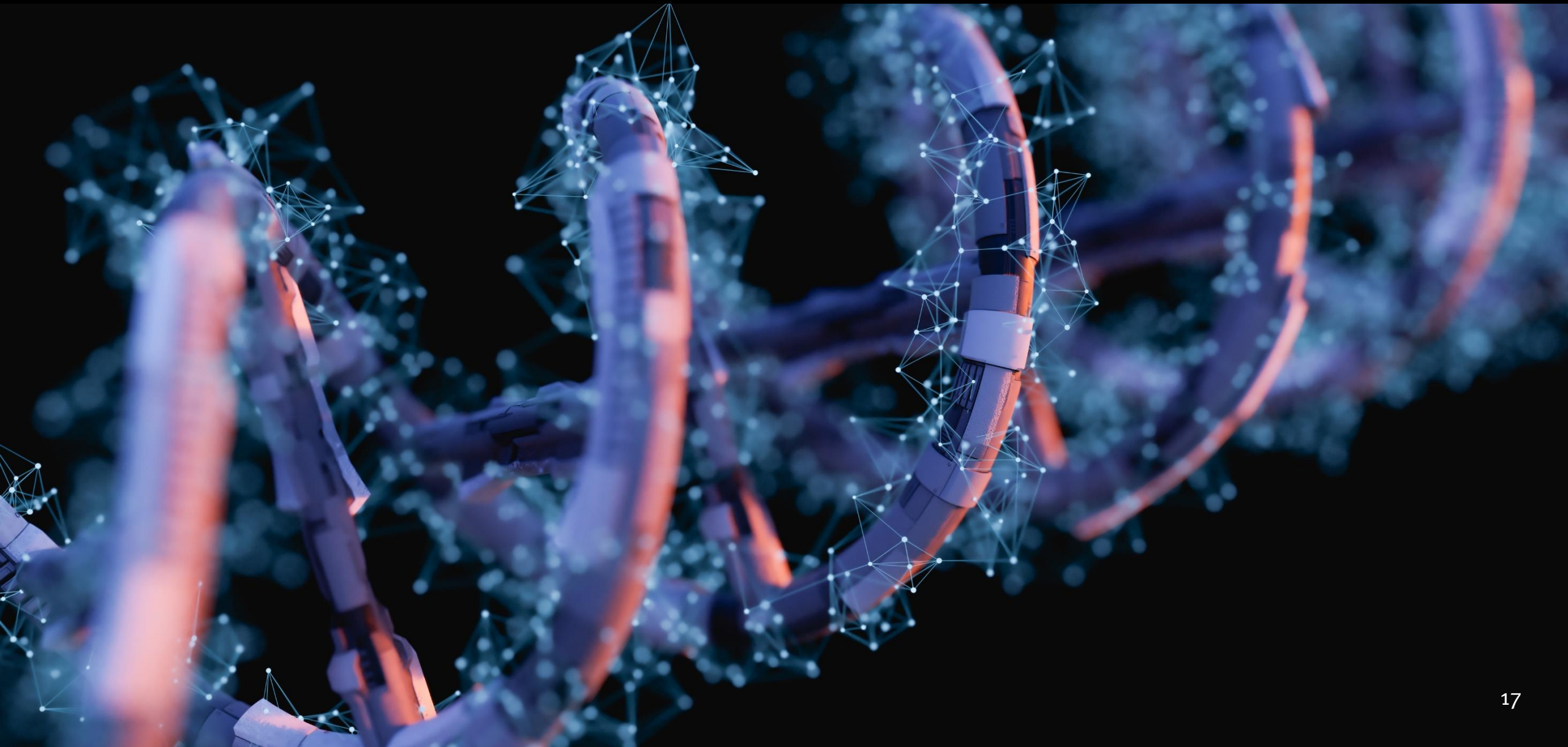
From NYT Story on the Lisa Cook Decision

“The wrecking ball that the Trump administration has been wielding through the administrative state just hit a brick wall that it could not crumble.”

Peter Conti-Brown, Professor of Administrative Regulation, University of Pennsylvania, October 2, 2025

Source: https://www.nytimes.com/2025/10/02/business/federal-reserve-independence-lisa-cook.html

Biopharma Market Update



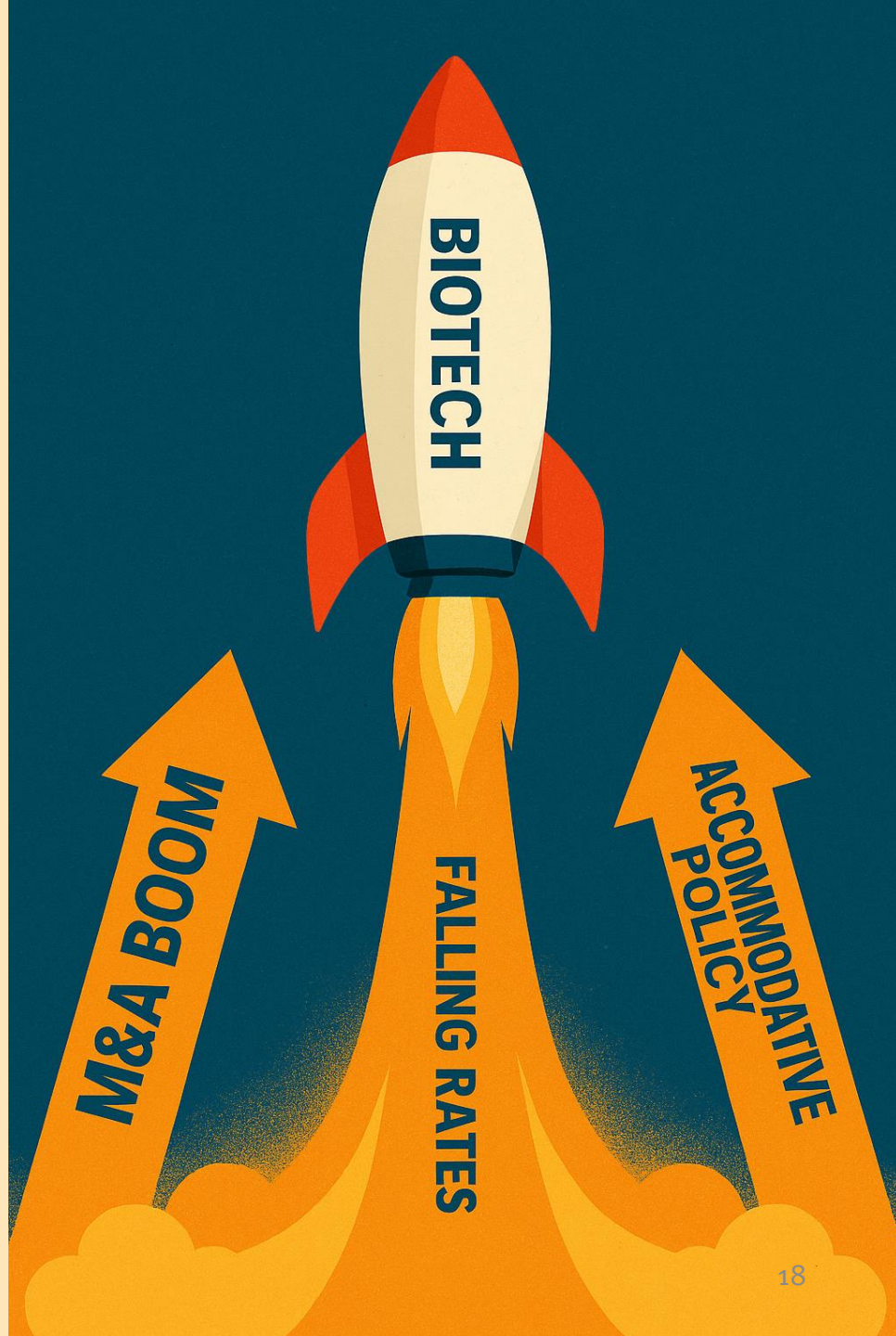
Biotech Sentiment Continuing to Rebound

It's sort of like a "pinch me" moment. The XBI is now at 103.6 and biotech stocks have been on a tear lately. Financing activity has been strong and investors are now hunting hard for bargains – *trying* to put money to work.

The market has radically changed in the last six months. It's as if we didn't go through three plus years of a market swoon.

We have gone from despondent days of darkness to talking about the many sources of upside for biotech. Some funds came out of the downturn wounded but, by and large, the buyside is intact and is now rapidly picking up assets. Numerous specialty funds are now up double digits (sometimes big double digits) for the year despite occasional potholes such as last week's Moonlake implosion on disappointing data. All of the topics investors should have been focusing on in recent years have now come into sharp relief: improving rates, substantial M&A pressure, the explosion in bioscience innovation, a cooperative FDA etc. etc.

Some investors remain mixed about the market but these group are now far fewer. At right, we highlight what is fueling today's rocketing biotech market. The big thing is the pickup in M&A, accompanied by a (relatively) accommodative policy environment. Rates are also headed in the right direction with the Fed's recent rate cut.



We Expect Biotech Momentum to Continue

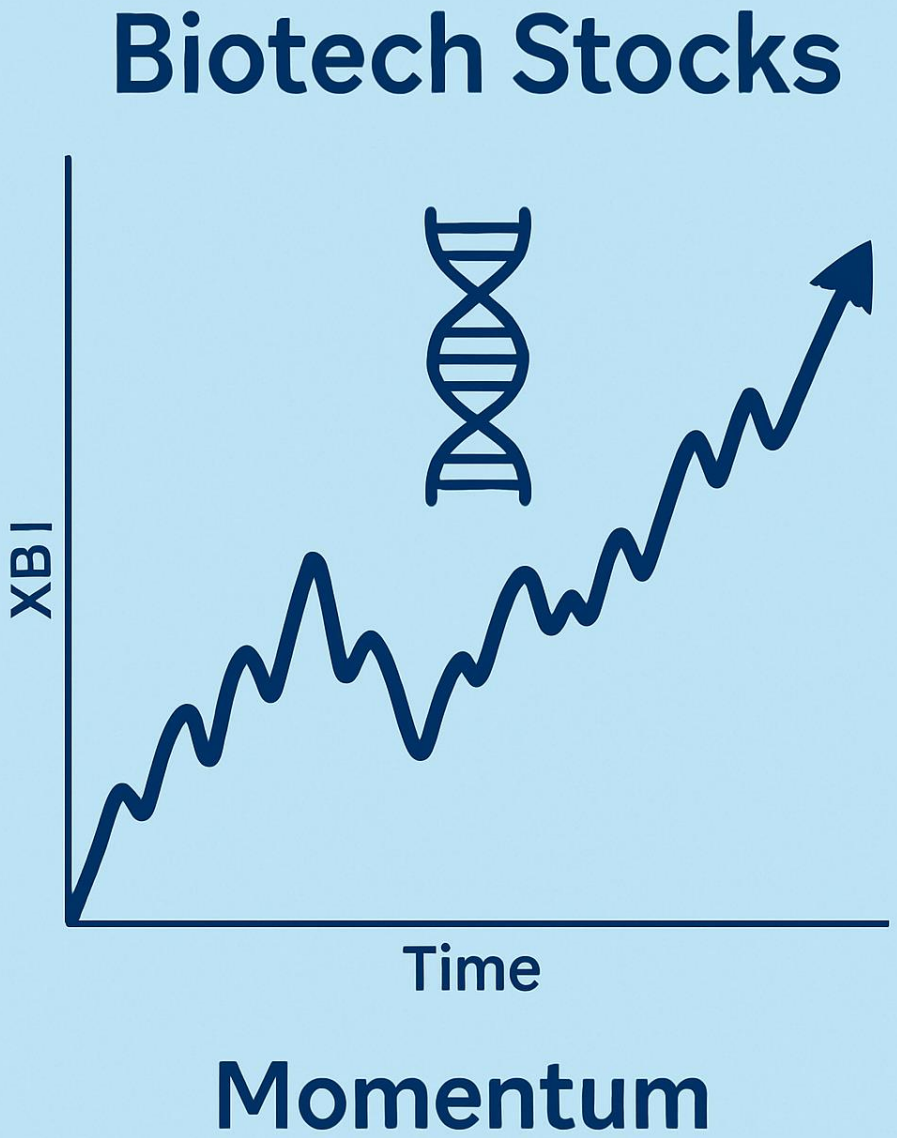
We addressed the underlying fundamentals of the biotech market in our Sep 16th issue where we took a "long and strong" stance on the market.

The two big fundamentals are a shifting market risk appetite amidst dropping rates and a strong M&A market. The S&P 500 hit an all-time high last week, fueled by investor enthusiasm for tech stocks and growth stories across the economy. While biotech is nowhere near its all-time high, momentum is clearly picking up.

Investors on the hunt for upside are finding many attractive stocks in the biotech market. As an example, Intellia a few months ago was trading near cash yet had a line of sight to three meaningful drug approvals. Today, that stock is up 80%. And likely to continue its rise.

So many other stories like this have been evident in the market. We still see many bargains in today's market although investors are quickly moving to fix the numerous obvious value mistakes.

We see more M&A, more policy accommodation from the Trump Administration and ever-improving innovation trajectories. Because these underlying fundamentals are so strong – it seems logical to us to see the XBI continue its rise to levels well above today's value point.



The XBI Closed at 103.6 On Friday (Oct 3), Up 11% in Two Weeks

The Stifel Global Biotech Value Tracker rose by 7% last week, more than the XBI. Treasury yields are in the low 4's. The XBI is up 15% for the year while the Stifel Global Biotech Value Tracker is up 62% for the year (reflective of the boom in China which is not included elsewhere).

Biotech Stocks Up Big Last Week

Return: Sep 27 to Oct 3, 2025

Nasdaq Biotech Index: +5.1%
Arca XBI ETF: +5.8%
Virtus LifeSci Biotech ETF (BBC): +5.0%
Stifel Global Biotech EV (adjusted): +7.0%*
S&P 500: +1.1%

Return: Dec 31, 2024 to Oct 3, 2025 (YTD)

Nasdaq Biotech Index: +17.8%
Arca XBI ETF: +15%
Virtus LifeSci Biotech ETF (BBC): +17.6%
Stifel Global Biotech EV (adjusted): +62%*
S&P 500: +14.2%

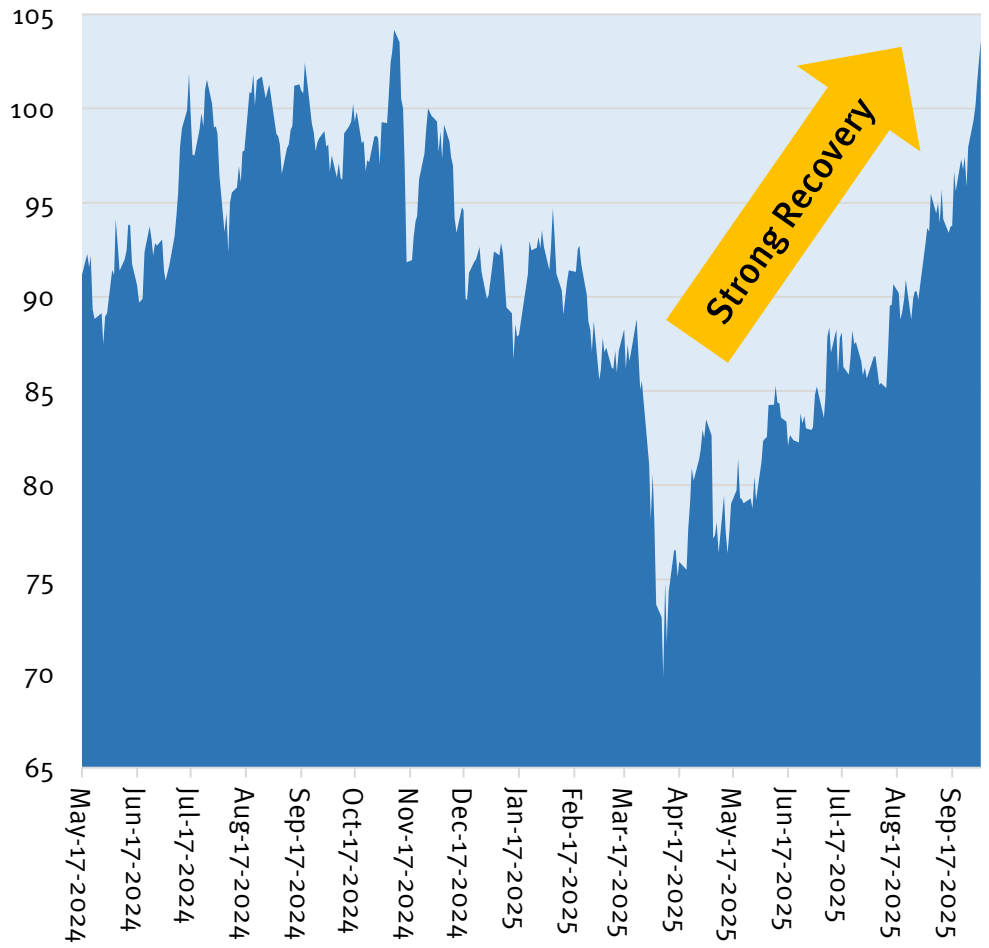
VIX Up a Bit

Mar 28, 2025: 21.7%
Apr 11, 2025: 37.6%
May 16, 2025: 18.4%
Jun 20, 2025: 20.4%
Jul 12, 2025: 16.4%
Aug 15, 2025: 15.1%
Sep 15, 2025: 15.7%
Oct 3, 2025: 16.6%

10-Year Treasury Yield Flat

Mar 28, 2025: 4.27%
Apr 11, 2025: 4.48%
May 16, 2025: 4.43%
Jun 20, 2025: 4.3%
Jul 12, 2025: 4.43%
Aug 15, 2025: 4.3%
Sep 15, 2025: 4.05%
Oct 3, 2025: 4.1%

XBI, May 16, 2024 to Oct 3, 2025



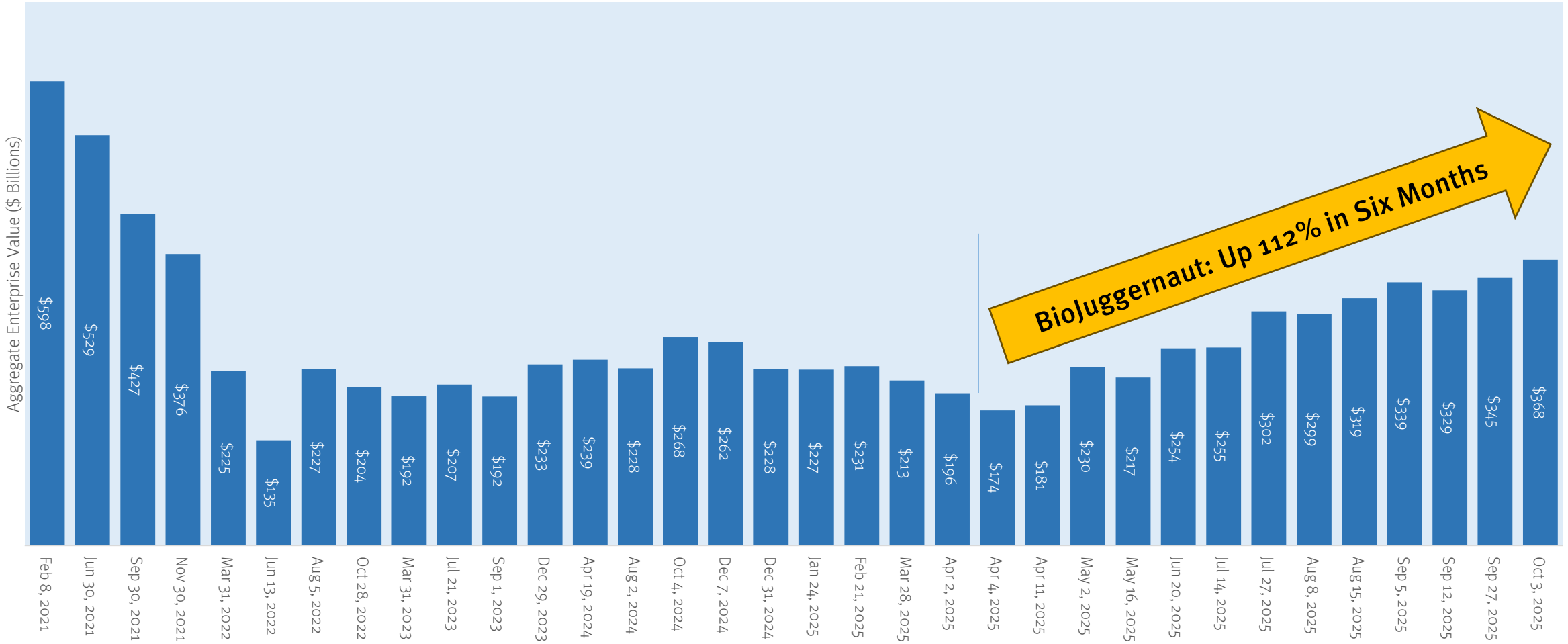
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Rose 7% Last Week

On April 4th, the enterprise value of the entire global biotech sector was $174 billion. Today, it's $368 billion (up 112%). Biotech stocks ended last week up 62% for the year. Biotech in 2025 is having its strongest year since 2020. It is important to note that the figures on this chart include the China sector – which has had particularly good performance in 2025. The charts on the pages that follow break out performance by country.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Oct 3, 2025 ($ Billions, Addition / Exit Adjusted)

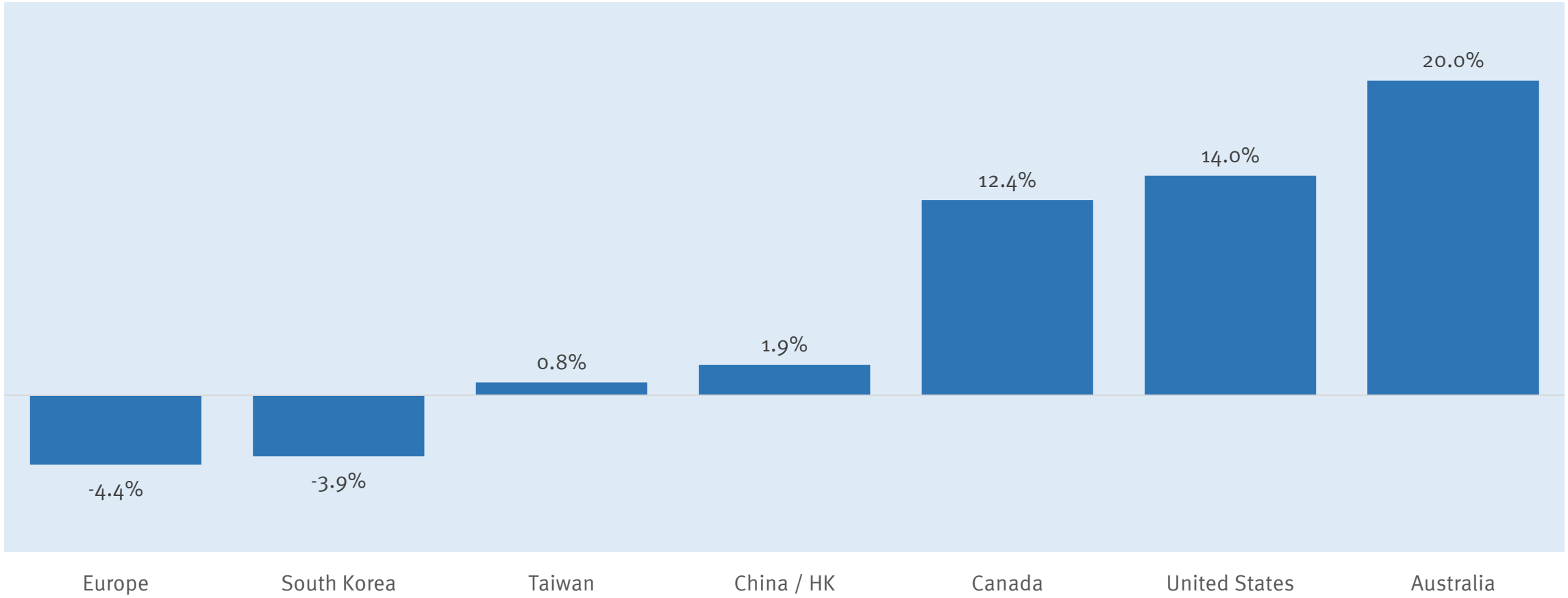


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Australia and U.S. Biotech Up the Most in Last 3 Weeks

U.S., Australia and Canada biotech has been on fire as the U.S. market has rallied in the last three weeks. In contrast, Europe, South Korea and China biotech – which were quite strong leading into September – have had tepid performance recently.

Percent Change in Total Market Cap of Public Biotech by Country/Region, Sep 12, 2025 to Oct 3, 2025

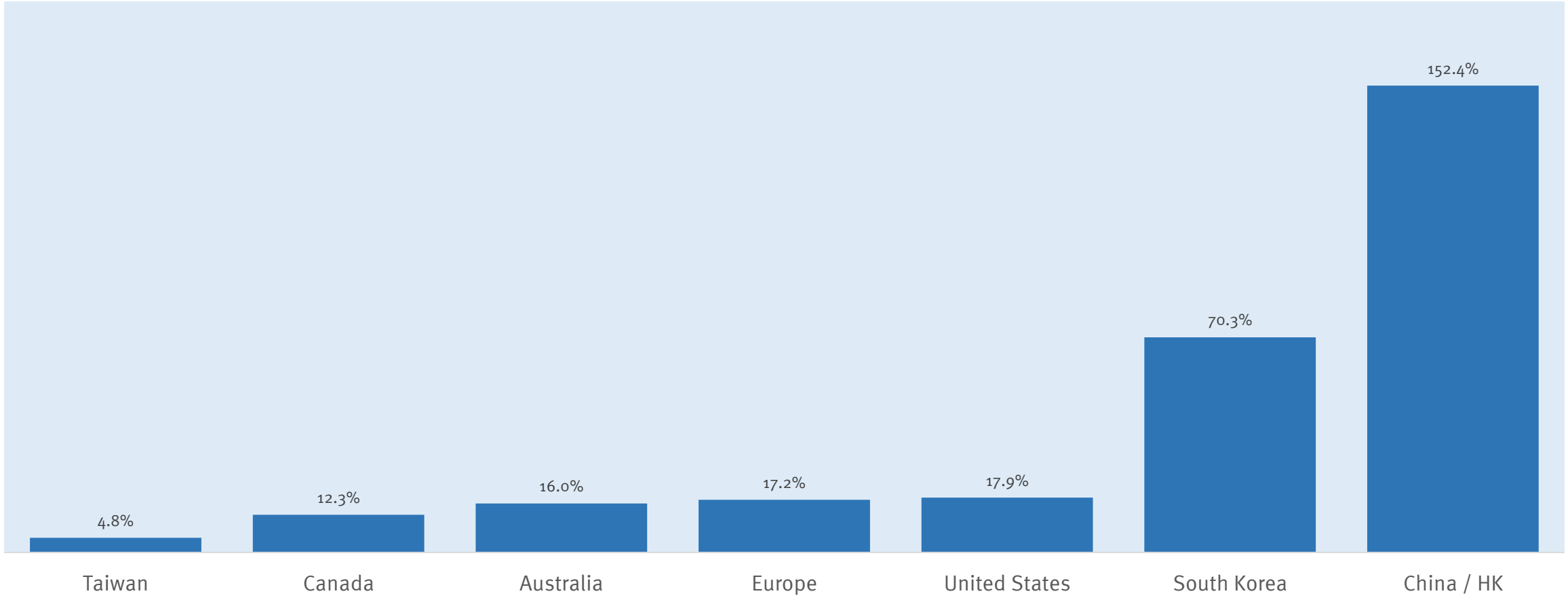


Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange. Europe biotech includes companies from all major EU countries.

China Biotech Has Done Extremely Well This Year

China biotech is up 152% this year. South Korea is up 70% while the U.S. is now up 18%. Amazingly, U.S. biotech sector was down more than 30% just six months ago. It's been a highly volatile year.

Percent Change in Total Market Cap of Public Biotech by Country/Region, Dec 31, 2024 to Oct 3, 2025

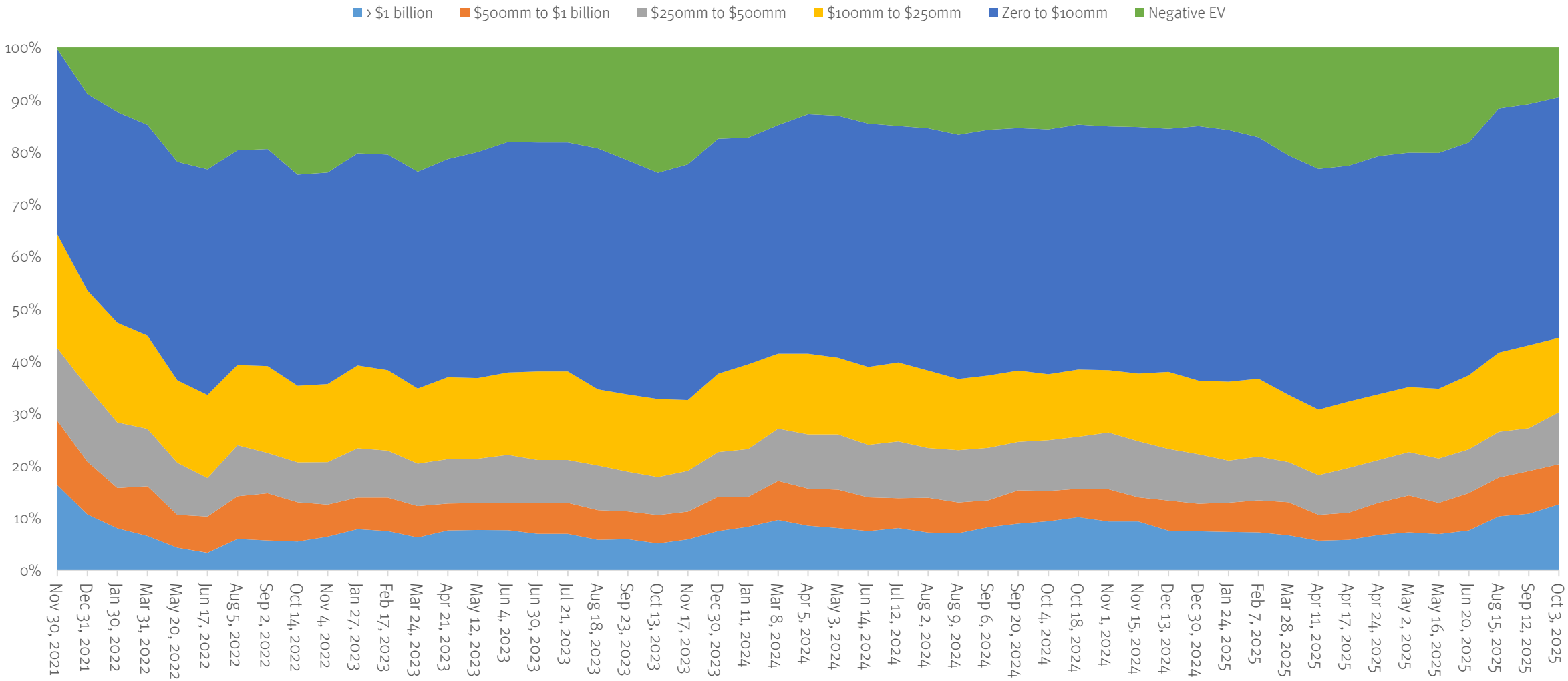


Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange. Europe biotech includes companies from all major EU countries.

The “Good Neighborhood” in Biotech Is Growing Fast

We have seen substantial reduction in the negative EV population in the last six months.

Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Oct 3, 2025

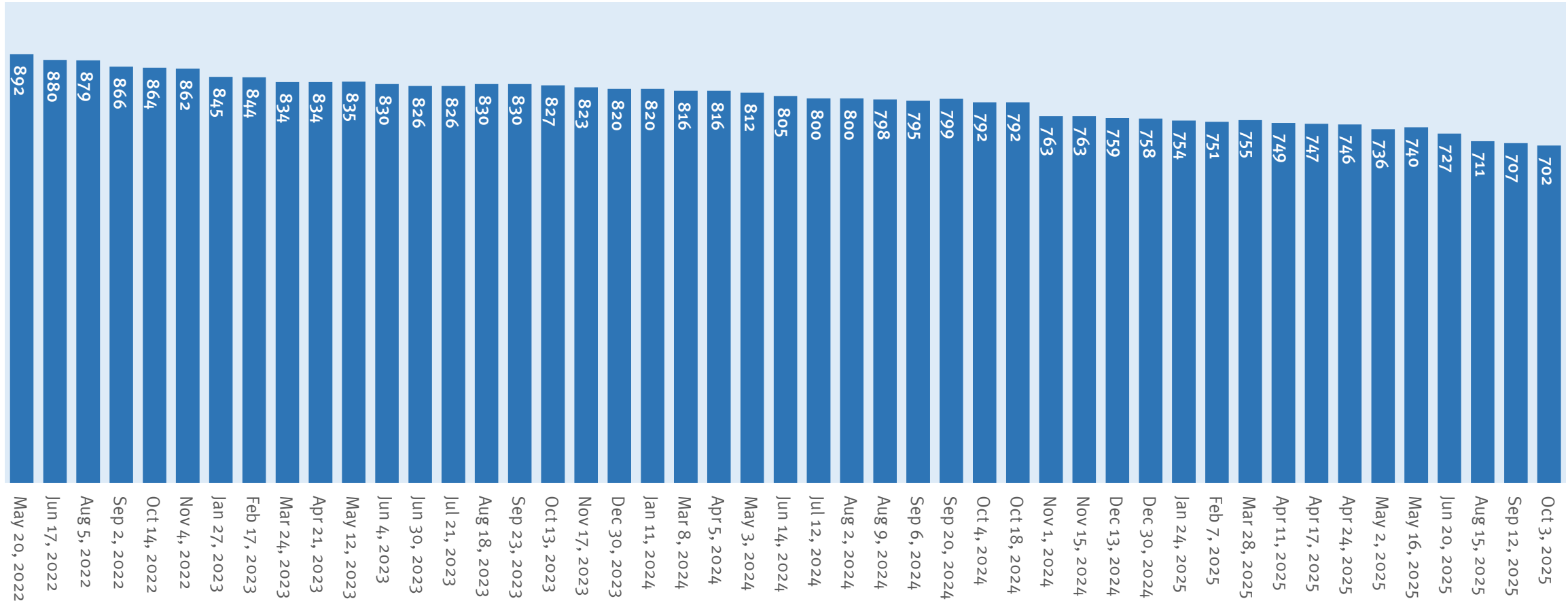


Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Public Biotech Population Has Dropped 21.4% In Last 41 Months

Five more companies have dropped out of the biotech ranks in the last three weeks. The cleansing of the industry continues.

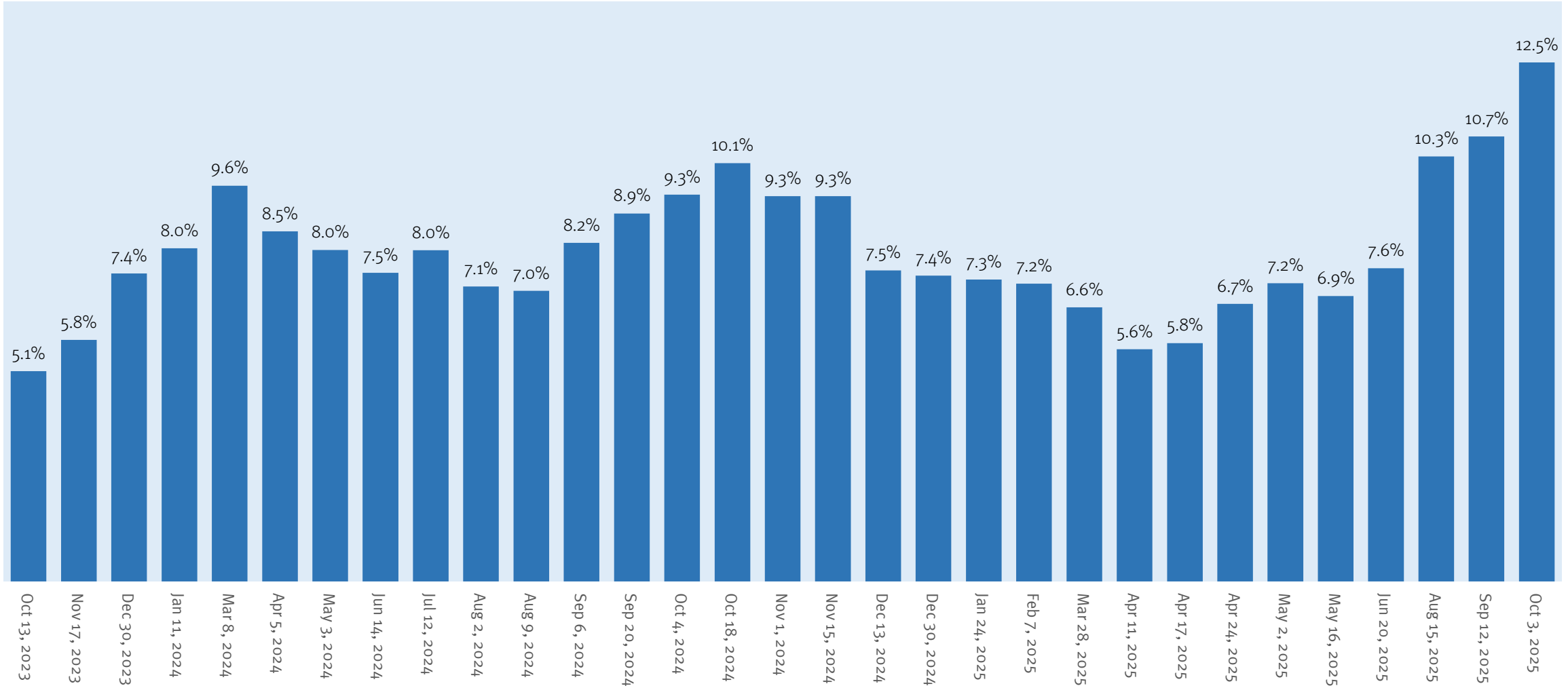
Number of Publicly Traded Biotech Companies Worldwide, May 2022 to Oct 2025



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

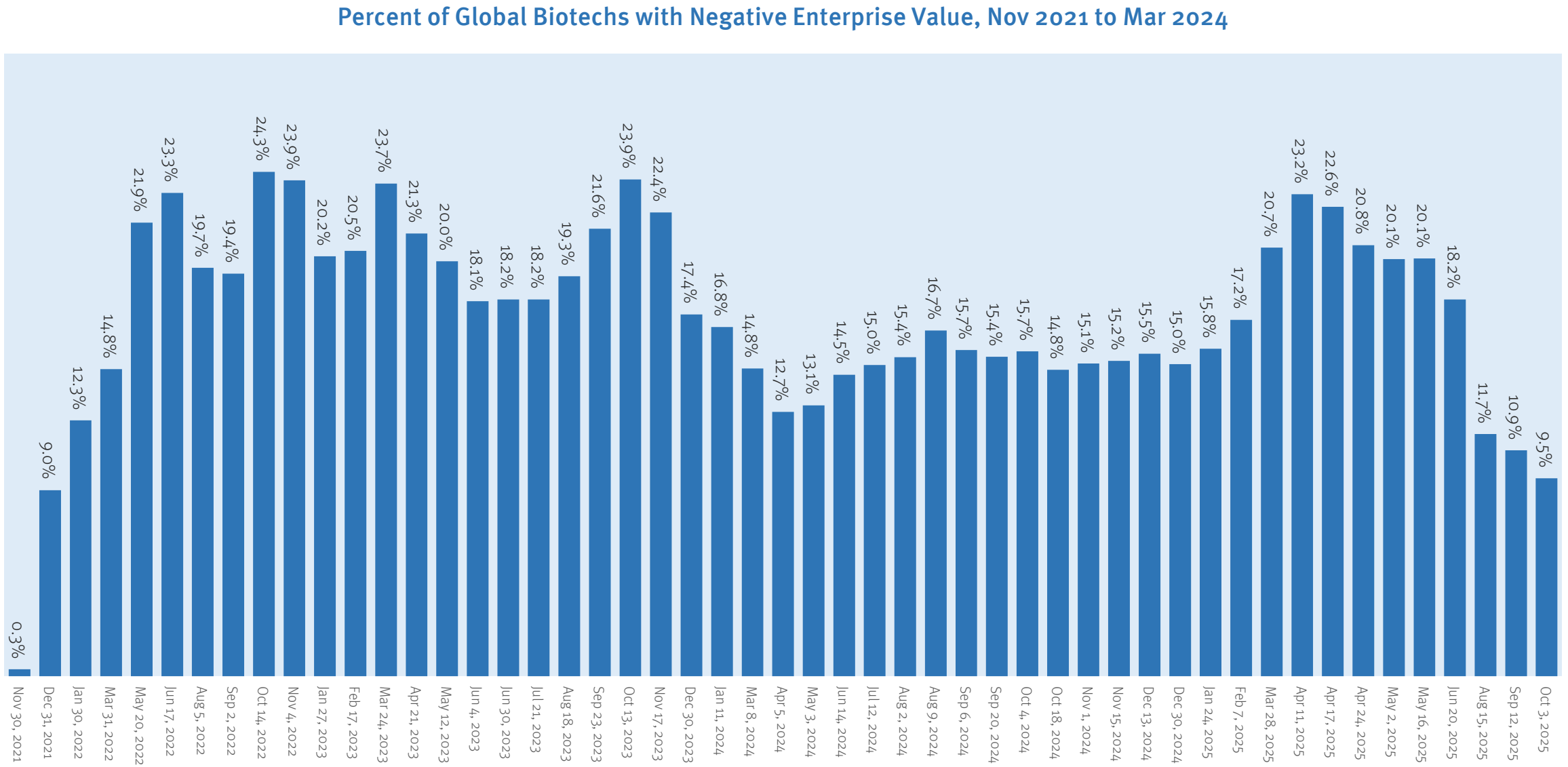
Billion Dollar Biotech Population Has Doubled Since April

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



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

Negative EV Biotech Population Down Under 10% Again



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

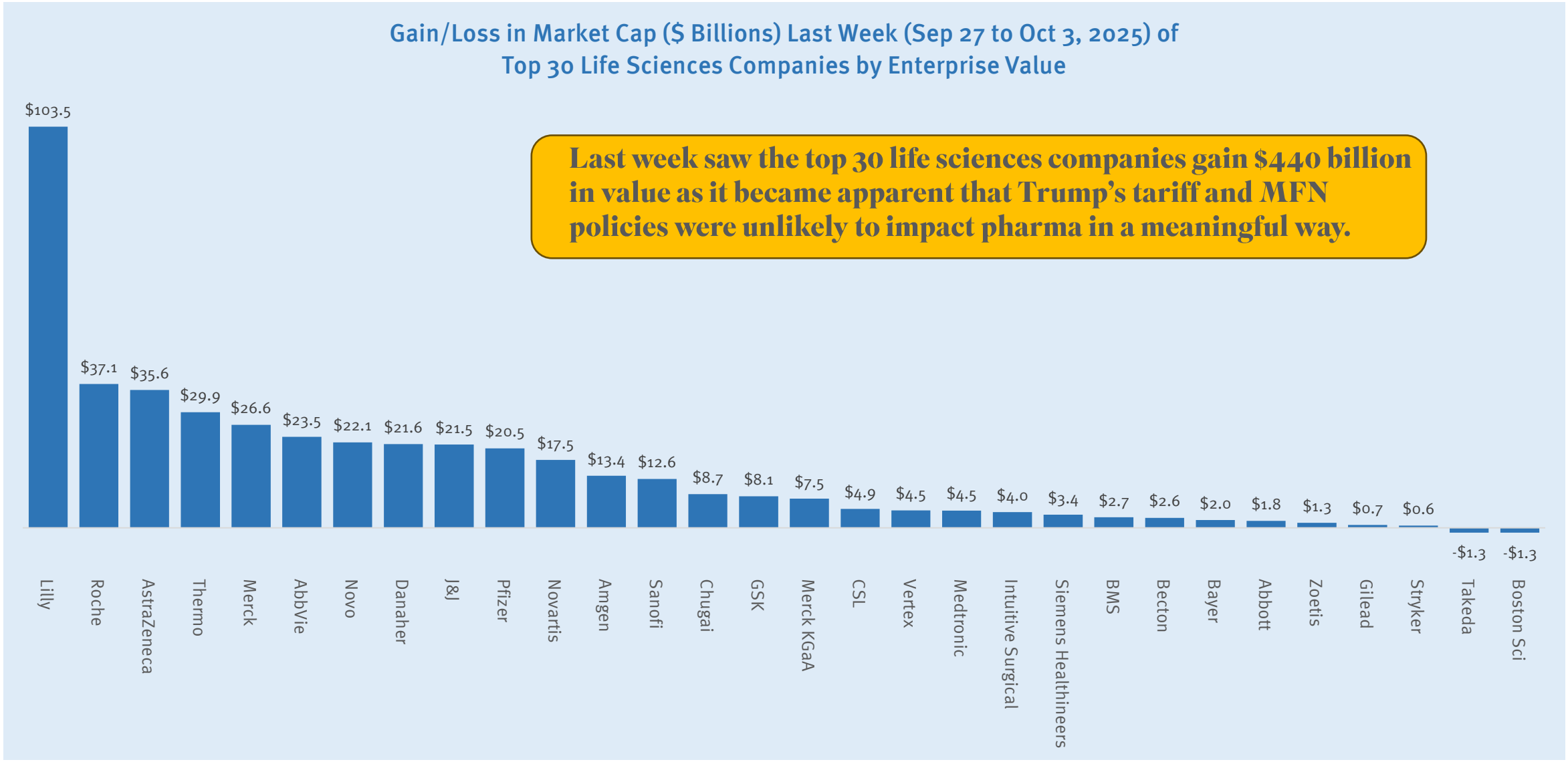
Life Sciences Sector Rose 6.4% Last Week

The sector skyrocketed in value last week – rising 6.4% in total. This is the first time in several years where the sector is worth more than $10 billion ($10.27bn last Friday). Life science tools, commercial pharma, pharma services and biotech performed best.

Sector	Firm Count	Enterprise Value (Oct 3, 2025, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	79	$98,053	1.6%	-1.6%	1.9%
Biotech	681	$353,455	7.0%	11.4%	-5.1%
CDMO	36	$167,689	3.5%	0.6%	8.4%
Diagnostics	74	$277,649	2.8%	-0.7%	7.0%
OTC	28	$23,146	0.5%	-1.6%	-12.1%
Commercial Pharma	683	$6,696,950	7.3%	4.7%	0.2%
Pharma Services	38	$206,023	7.6%	8.0%	9.8%
Life Science Tools	48	$632,039	13.8%	8.7%	-12.7%
Medical Devices	170	$1,792,471	2.0%	-1.0%	0.8%
HCIT	7	$31,564	3.4%	5.4%	19.9%
Total	**1844**	**$10,279,040**	**6.4%**	**3.9%**	**0.7%**

Source: CapitalIQ and Stifel analysis

Last Week Was Exceptional for the Life Sciences Sector



Why Pfizer's Trump Deal Is Good News for All of Big Pharma

David Wainer, *Wall Street Journal*, Oct 2, 2025 (excerpt)

Big Pharma has been out of favor with investors on fears of tariffs and price controls. This week might have marked a turning point.

On Tuesday, Pfizer Chief Executive Albert Bourla stood alongside President Trump at the White House to unveil "TrumpRx," a government website that will allow Americans to buy certain medicines at discounted cash prices.

According to Pfizer, the price cuts on its products will average around 50% and in some cases reach as high as 85%. The company also committed to price all new medicines at parity with other developed markets while extending "most-favored-nation" pricing to Medicaid patients. Bourla paired the announcement with a $70 billion pledge to expand U.S. drug manufacturing and research and development. In return, the company gains a three-year grace period to exempt it from national-security-related tariffs.

Plenty of questions remain. For one, it isn't obvious how useful TrumpRx will be for most Americans, who already receive coverage through private insurance, Medicare or Medicaid. And details are lacking on how Pfizer will price future drug releases, both overseas and in the U.S. But the big picture is that Trump's pressure campaign on the pharma industry might be winding down. Since most Big Pharma companies are already pledging large investments in U.S. manufacturing, they should now be able to steer clear of heavy tariffs. For products still being imported from European countries, a deal reached with the European Union in late July capping U.S. tariffs on pharma exports at 15% also helps. And now the standoff over pricing is nearing resolution. The optics of the Pfizer announcement signal that Trump is eager to strike deals with the industry.

The setup is reminiscent of the early 1990s, when drug stocks were pummeled by fears of "Hillarycare," the Clinton administration's proposed healthcare overhaul. When the plan collapsed in late 1994, the group snapped back sharply. **A more forgiving environment in Washington, D.C., combined with a slowing economy could be just what the doctor ordered for pharma stocks.**

Source: https://www.wsj.com/health/pharma/pfizer-trumprx-deal-pharma-stocks-7e2724f4

Trump's Pharmaceutical Tariff Threat Loses Bite After Pfizer Deal Reassures Drugmakers

Annika Kim Constantino, *CNBC*, Oct 1, 2025 (excerpt)

President Donald Trump's long-awaited threat to impose pharmaceutical tariffs may not pose as much of a challenge as drugmakers once feared, following his new drug pricing deal with Pfizer.

Trump's Tuesday agreement with the company to voluntarily lower U.S. drug prices included a three-year exemption from pharmaceutical-specific tariffs, as long as the firm further invests in domestic manufacturing. Pfizer on Tuesday pledged to put $70 billion into U.S. manufacturing and research, on top of previous investments.

That deal brought relief and clarity to Pfizer and the broader pharmaceutical industry, signaling that many drugmakers could strike similar agreements that would make them immune to the levies for most of Trump's term.

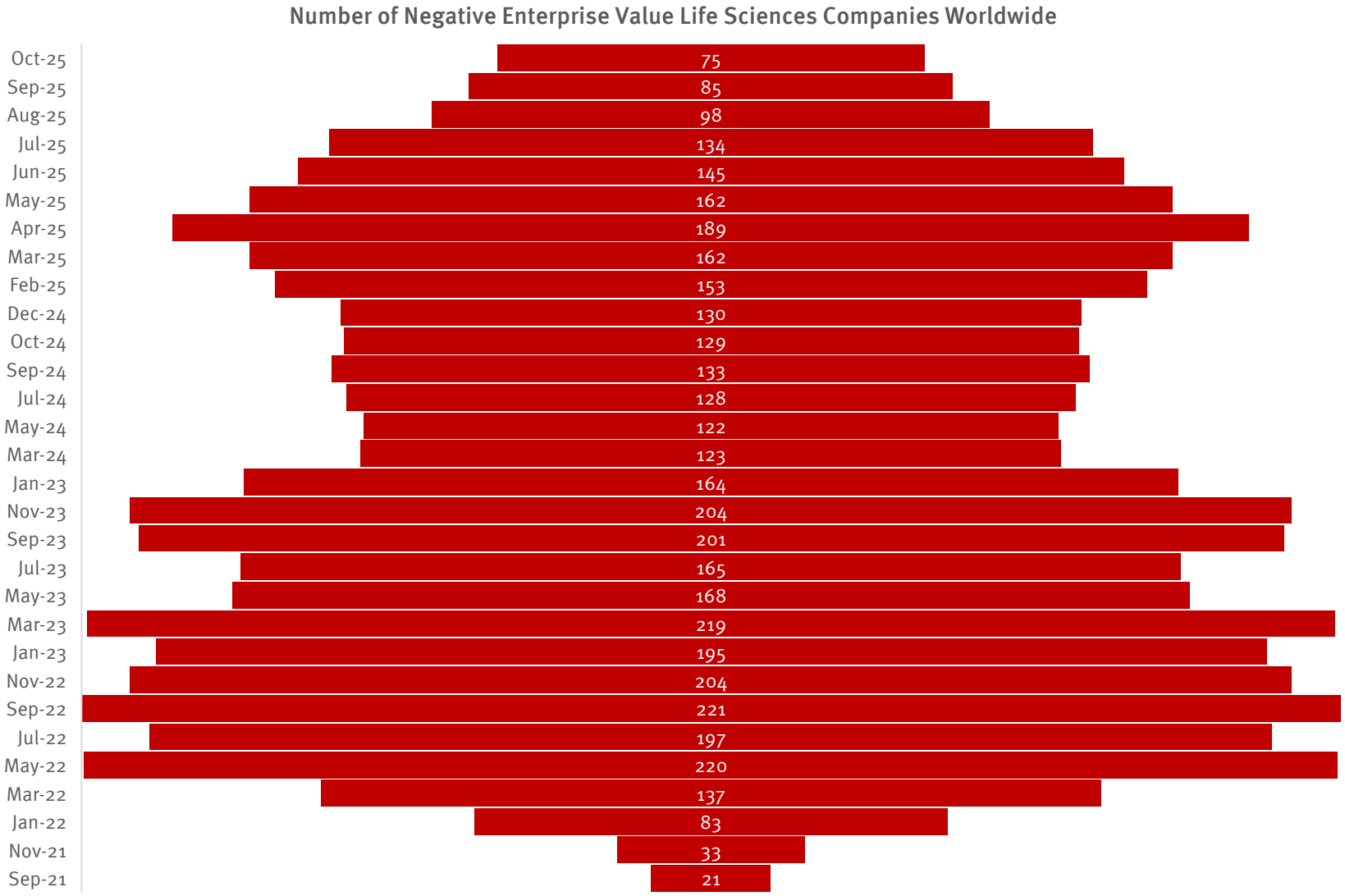
The Trump administration also made it clear that it will try to secure those drug pricing agreements before it imposes tariffs. Commerce Secretary Howard Lutnick on Tuesday said he will let companies finish their negotiations with the administration before setting pharmaceutical-specific levies under the legal authority known as Section 232.

Trump on Tuesday said he's working with other drugmakers to secure similar pacts over the next week, and the White House confirmed that Eli Lilly is expected to strike the next drug pricing deal. The vast majority of major pharmaceutical companies, including Eli Lilly, Johnson & Johnson, AstraZeneca, AbbVie, Roche, Novo Nordisk and Amgen have unveiled new U.S. investments in manufacturing or research facilities in recent months to build goodwill with the president.

Shares of Pfizer and several other drugmakers rose on Tuesday following the agreement. Pfizer's stock ended more than 6% higher, while Eli Lilly rose 5%. Shares of AbbVie and AstraZeneca climbed more than 3%, while J&J and Bristol Myers Squibb's stocks increased more than 2% each.

Source: https://www.cnbc.com/2025/10/01/trump-pharmaceutical-tariffs-pfizer-deal.html

Number of Negative Enterprise Value Life Sciences Companies Continues to Decline



The count of negative EV life sciences companies worldwide fell from 85 on Sep 12, 2025 to 75 as of last Friday.

We are now returning to levels of this dubious metric not seen since 2021.

While negative EV companies are not yet an endangered species, they are becoming far less common in the life sciences sector.

Source: CapitalIQ

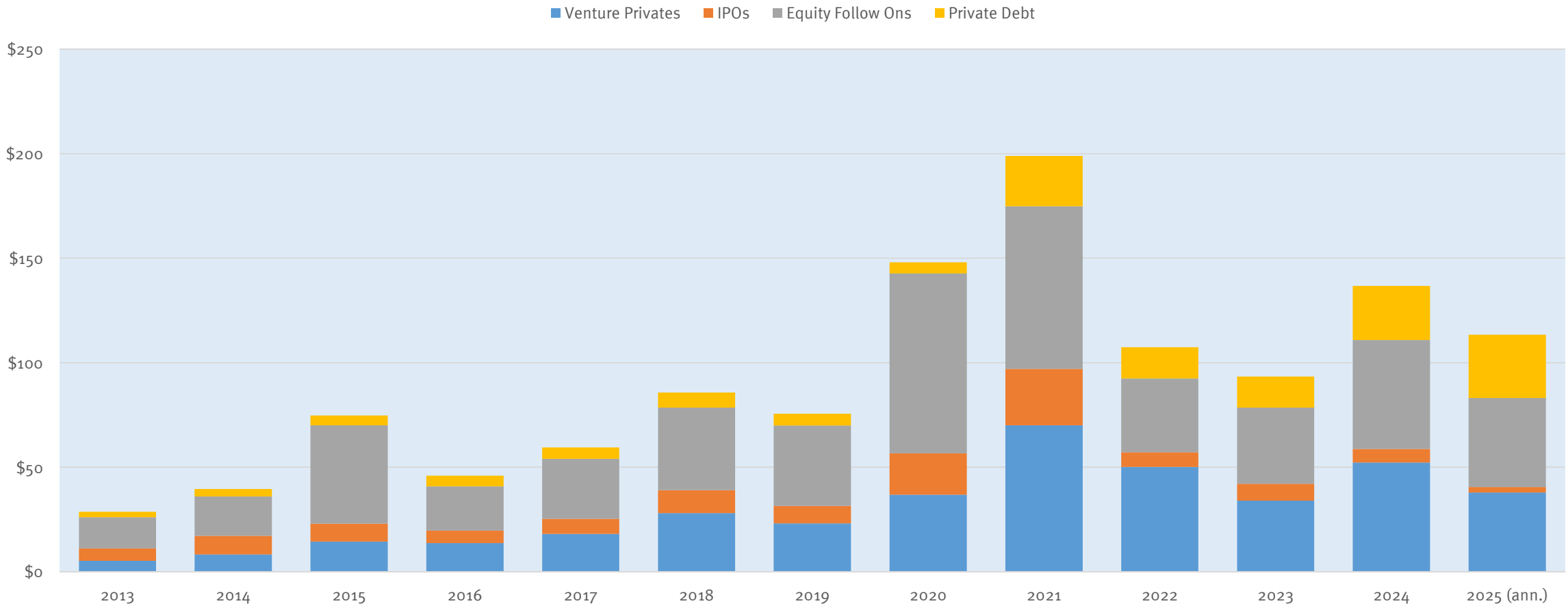
Capital Markets Update

Capital Raising Pace in 2025 Now Ahead of 2023 and 2022

The rapid pace of financings of the last three months has pushed up our estimates of total financing volume for 2025 to be above the levels of 2023 and 2022 (using data annualized as of Sep 30, 2025). There is a reasonable chance that this ends up being the fourth most active financing year on record despite a very slow first half.

Equity and Debt Raised in the Biopharma Sector, 2013 - 2025

(Annualized for 2025 based on Sep 30, 2025 data, $ Billions, Worldwide, Excludes Public Debt Market)



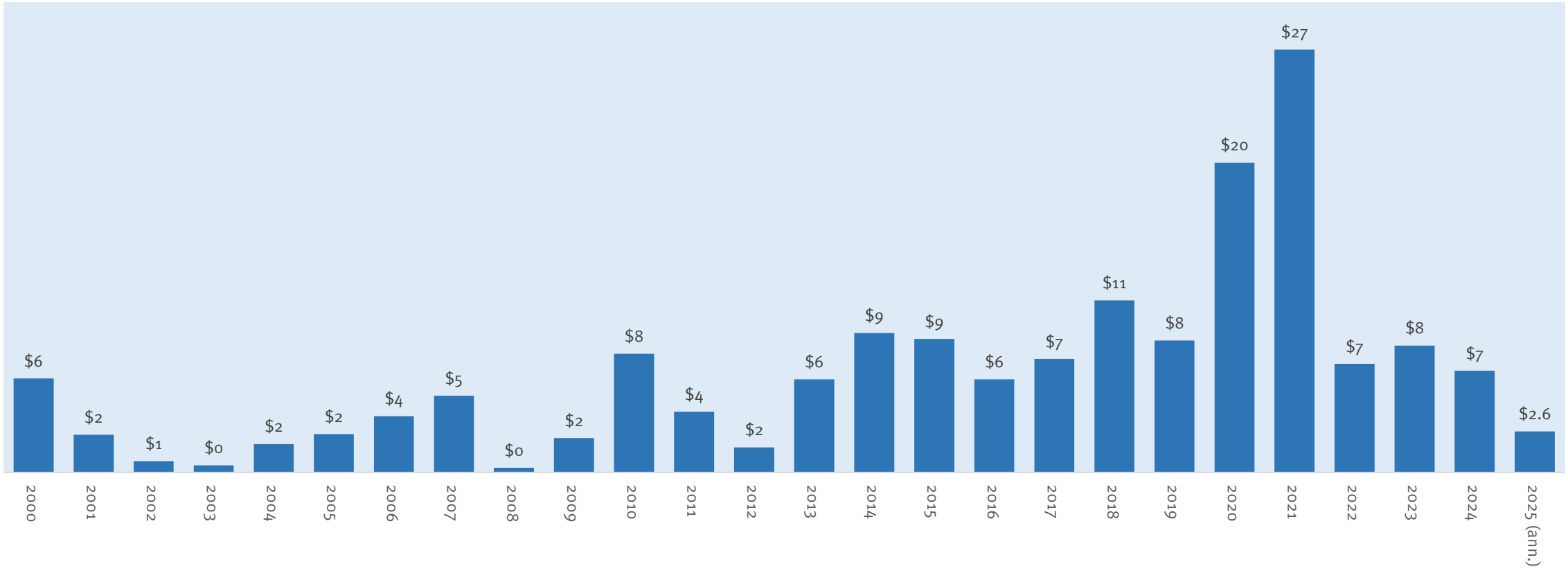
Source: Data from CapitalIQ. Note: Data for 2025 is annualized based on results as of Sep 30, 2025.

IPO Market Continues to Be Slow

We have not seen additional IPO's hit the market since LB deal. At present, the calendar is starting to fill but the recent government shutdown has put the brakes on a resumption of meaningful IPO activity in biotech. We hope that this is temporary.

IPO Volume in the Biopharma Sector, 2000 - 2025 (annualized)

($ Billions, Worldwide)



Source: Data from CapitalIQ. Note: Data for 2025 is annualized based on results as of Sep 30, 2025.

A Buzzy IPO Market Just Got Stuck in a Government Shutdown

Shannon Carroll, *Quartz*, Oct 3, 2025 (excerpt)

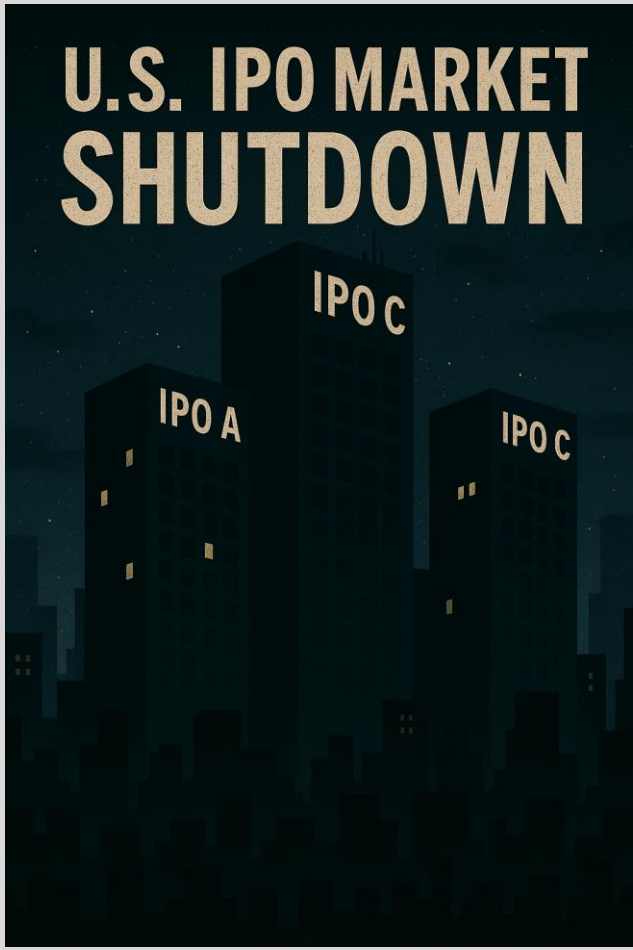
Wall Street had its popcorn ready: After three years of sputters, the IPO screen was lighting up again, with Klarna, CoreWeave, and a handful of buzzy consumer names. Then Washington tripped over the power cord, plunging the whole IPO theater into darkness.

With a federal government shutdown having started this week, the Securities and Exchange Commission is running on a skeleton crew. That means no new registration statements get reviewed, no comment letters get cleared, and no "effective" notices get stamped. The EDGAR paperwork portal is technically open, but without staff to process deals, it's like hitting "submit" into a black hole.

That leaves high-profile would-be stock issuers — electric-aircraft maker Beta Technologies, Jennifer Garner's baby-food brand Once Upon a Farm, and insurer Ethos Technologies — stuck at the gate. Alliance Laundry Systems and the University of Phoenix, both already on roadshows, are hoping that their timing bet (that the shutdown would be short) pays off. But if history is any guide, the logjam fattens by the day.

Initial public offering calendars run on an unforgiving clock: Financial statements go stale if the balance sheet is more than 135 days old, meaning companies that miss their October or November windows have to update to third-quarter numbers. That means revised filings, fresh audit reviews, new comfort letters — all costly, all delaying the sprint until January at the earliest.

Vineet Jain, the CEO of cloud-based software company Egnyte, said that if the shutdown is "short-lived," he doesn't see much of an impact on IPOs. "But if it goes longer, like what happened in 2018... then there could be a potential impact."



Source: https://qz.com/ipo-sec-markts-government-shutdown

Biotech IPOs in Hong Kong Far Outpace the US, Driven by China's Buzzy Biotech Sector

Kyle LaHucik, *Endpoints News*, Oct 2, 2025 (excerpt)

As biotech IPOs hit a record low in the US, more than 40 Chinese biopharma companies have filed to go public so far this year. That's more than four times the number that have sought a Nasdaq or New York Stock Exchange listing. It's the latest signal of China's booming biotech scene, which is increasingly viewed as a go-to place for Western startups and large drugmakers to license or buy new medicines at a time when the biotech sector has stalled in the US.

In the first three quarters of 2025, at least 42 biopharma companies in China have filed for an IPO on the Hong Kong Stock Exchange, according to an Endpoints News tally. In that same nine-month stretch, only about a dozen biotechs have attempted to go public in the US.

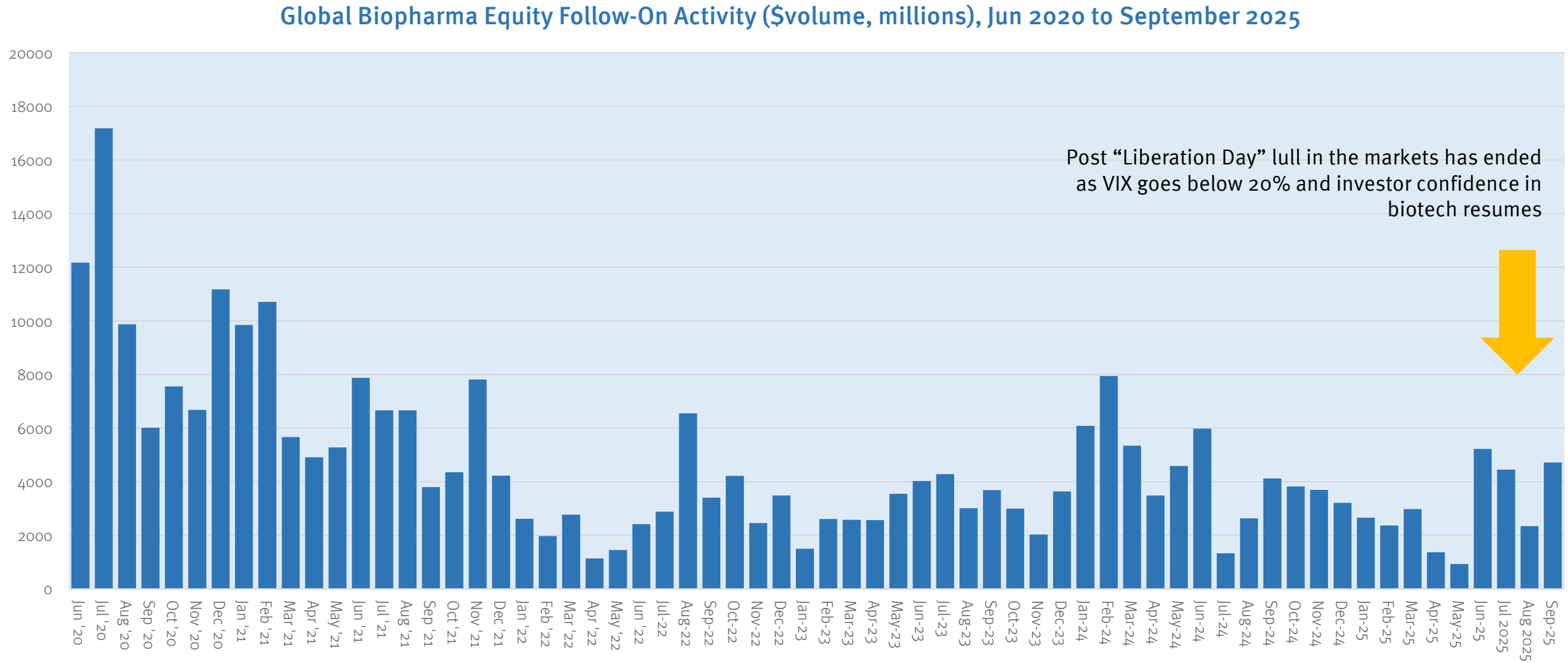
At least 10 biotech companies have listed on the Hong Kong Stock Exchange so far this year, including DualityBio and some companies, like Visen Pharmaceuticals, that filed for their IPOs last year. Nine companies have listed on the US exchanges.

That said, the Nasdaq has seen a massive drop in biotech IPOs this year compared to the pandemic peak of 2020 and 2021, when more than 100 biotechs went public. There were no sizable biotech IPOs in the US from mid-February until last month, when schizophrenia biotech LB Pharmaceuticals broke the dry spell with a $285 million IPO. In one telling example, Odyssey Therapeutics reneged on its plans in the spring and instead raised a $213 million Series D.

Source: https://endpoints.news/biotech-ipos-in-hong-kong-far-outpace-the-us-driven-by-chinas-buzzy-biotech-sector/

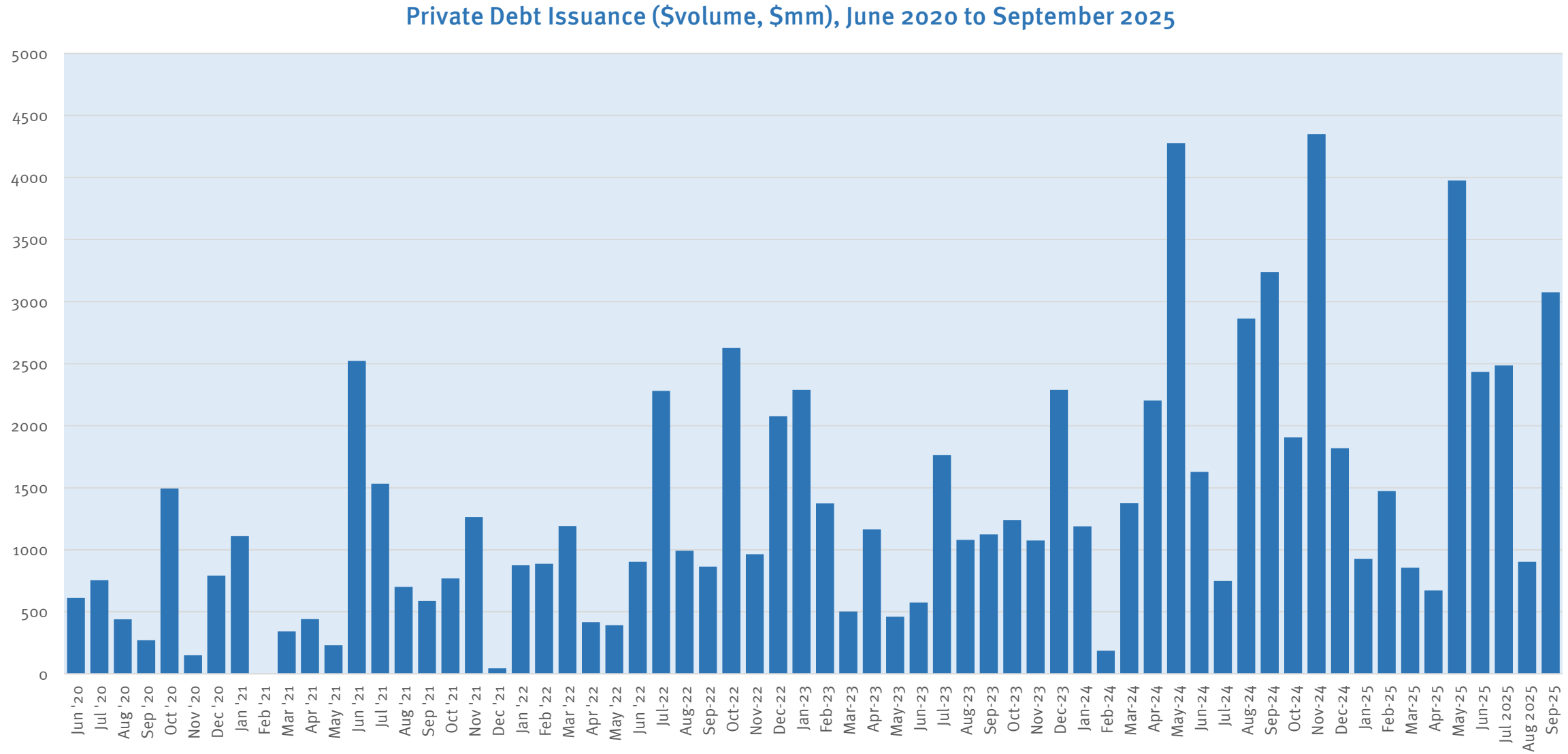
Global Follow-On Market Continues Renaissance in September

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. It's been quite a strong couple of weeks, and we anticipate continued activity after last week's stellar performance of the XBI.



Source: Data from CapitalIQ, Crunchbase.

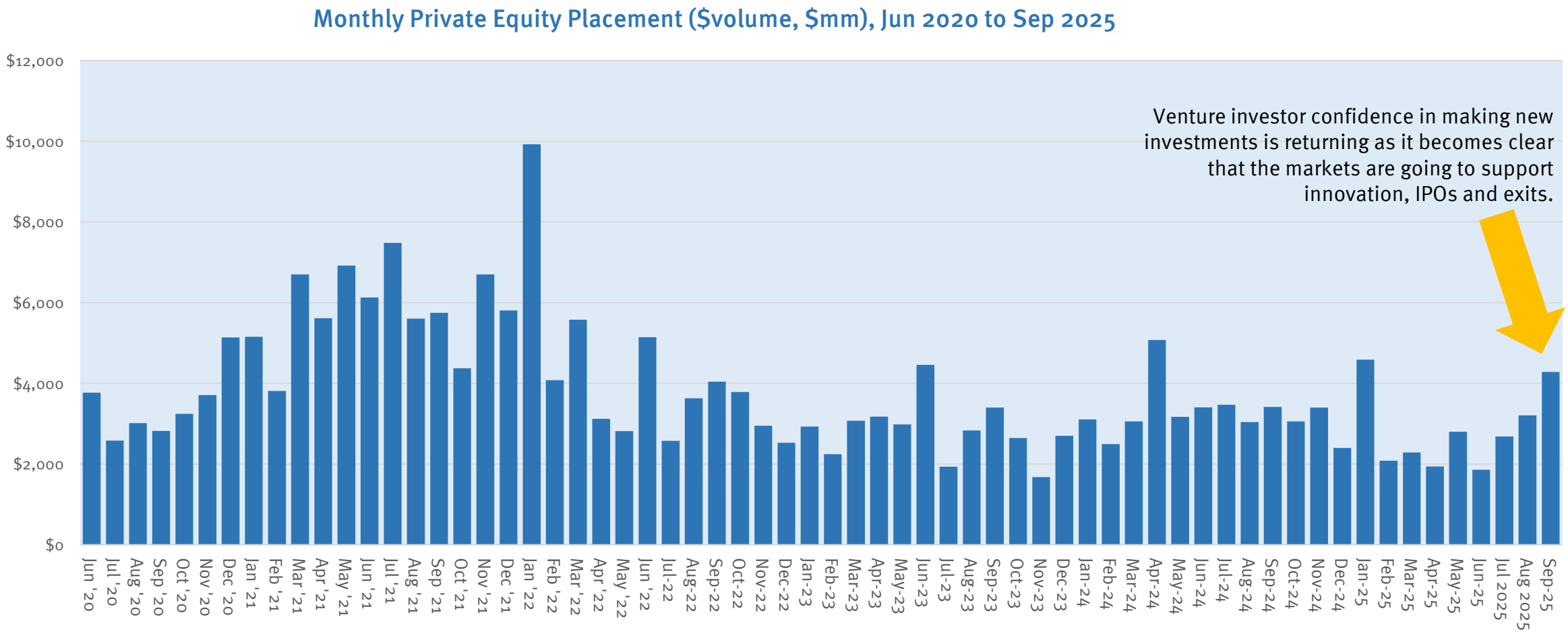
Biopharma Private Debt Placement Volume Strong in September



Source: Data from CapitalIQ, Crunchbase.

Venture Equity Private Deal Pace Showing Strength

Volume in the venture privates market crossed $4 billion in September – for the first time since January. The private market is starting to come out of the lull that it hit following the tariff "Liberation Day" in April.



Source: Data from CapitalIQ, Crunchbase.

Cartography Raises $67 Million

CARTOGRAPHY BIOSCIENCES

SAN FRANCISCO October 2, 2025 Cartography Biosciences, Inc., an oncology company advancing an innovative pipeline of T-cell engaging bispecific and multi-specific antibody therapeutics that target novel and highly specific tumor antigens, today announced the close of a $67 million Series B financing. The funding will help support the advancement of Cartography's lead program, CBI-1214, into the clinic and the continued acceleration of additional, highly differentiated oncology programs generated from its ATLAS and SUMMIT drug discovery platforms.

The Series B was led by new investor Pfizer Ventures and was joined by additional new investors LG Corp, Amgen Ventures, Finchley H.V., Global BioAccess Fund, and Lotte Holdings CVC, as well as existing investors Andreessen Horowitz (a16z) Bio + Health, 8VC, Wing Venture Capital, Catalio Capital Management, AME Cloud Ventures, ARTIS Ventures, and Gaingels. As part of the financing, Michael Baran, MBA, Ph.D., Partner at Pfizer Ventures, has joined Cartography's Board of Directors. Additionally, Troy E. Wilson, Ph.D., J.D., who had previously joined as an Independent Director, has been elected as Chairman of the Board.

Cartography's lead program CBI-1214 is a T-cell engager molecule that targets LY6G6D, an emerging and highly specific tumor antigen for treating colorectal cancer (CRC) patients. The target, which has minimal expression on healthy cells, is uniquely expressed within the microsatellite stable (MSS) and microsatellite instability-low (MSI-L) subtypes of CRC, which represent the vast majority of CRC patients and remains a major area of unmet medical need. CBI-1214 has protein engineering features that are specifically designed to optimize anti-tumor activity.

""Combining insights from thousands of patient tissue samples, our ATLAS and SUMMIT platforms have identified several novel targets and target pairs that we have engineered new T-cell engagers against. CBI-1214, our first announced program, has the potential to be a first- and best-in-class molecule targeting CRC and positions Cartography as an emerging leader in new targeted therapies."

Kevin Parker, Ph.D.
Chief Executive Officer
Cartography Biosciences

Source: https://www.businesswire.com/news/home/20251002482177/en/Cartography-Secures-%2467-Million-Series-B-Financing-to-Advance-Differentiated-Oncology-Pipeline-of-Antibody-Based-Therapies-into-the-Clinic

Healthcare Investors Vijay Pande, Zack Werner Team Up to Form VZVC

Brian Gormley, *Wall Street Journal*, October 2, 2025 (excerpt)

Former Andreessen Horowitz General Partner Vijay Pande and startup investor Zack Werner have formed VZVC, a new venture firm seeking to tap opportunities emerging as artificial intelligence plays an expanding role in healthcare.

Pande, the former Henry Dreyfus professor of chemistry, structural biology and computer science at Stanford University, joined Andreessen in 2014, initially as a professor in residence.

He became a general partner in 2015 and founded the Bio + Health fund that same year. With Andreessen he invested in startups such as Function Health, which provides consumers access to more than 100 lab tests through $499 annual memberships.

He also led Andreessen's investments in companies such as Insitro, which applies machine learning to drug discovery and development, and Freenome, a developer of blood tests for early cancer detection.

"Vijay was among the first to see how AI could revolutionize drug discovery and healthcare delivery," Andreessen co-founder and General Partner Ben Horowitz said in an email.

After more than a decade with the firm, Pande decided he was ready to branch out on his own, departing Andreessen in June. He and Horowitz indicated an interest in their firms collaborating on future deals. Andreessen General Partner Dr. Vineeta Agarwala now leads Andreessen's Bio + Health fund. Another theme for Pande and Werner is the consumer's role in healthcare. Their experience with Function Health illustrates consumers' willingness to pay for services they believe could improve their health and prevent illness. VZVC also will consider opportunities such as preventive diagnostics, Werner said.

Source: https://www.wsj.com/articles/healthcare-investors-vijay-pande-zack-werner-team-up-to-form-vzvc-eff3ed1f

A Growing Backlog Of Biotechs Haven't Raised Funding Since The Boom

Joanne Glasner, *Crunchbase*, October 2, 2025 (excerpt)

As biotech startup funding continues to decline, the backlog of funded, private companies that haven't raised capital in several years has grown quite large.

Per Crunchbase data, more than 200 private U.S. biotechs with $50 million or more in funding to date secured their last reported financing between three and five years ago. The list includes at least 15 biotech unicorns and emerging unicorns that haven't raised known funding for at least the past three years.

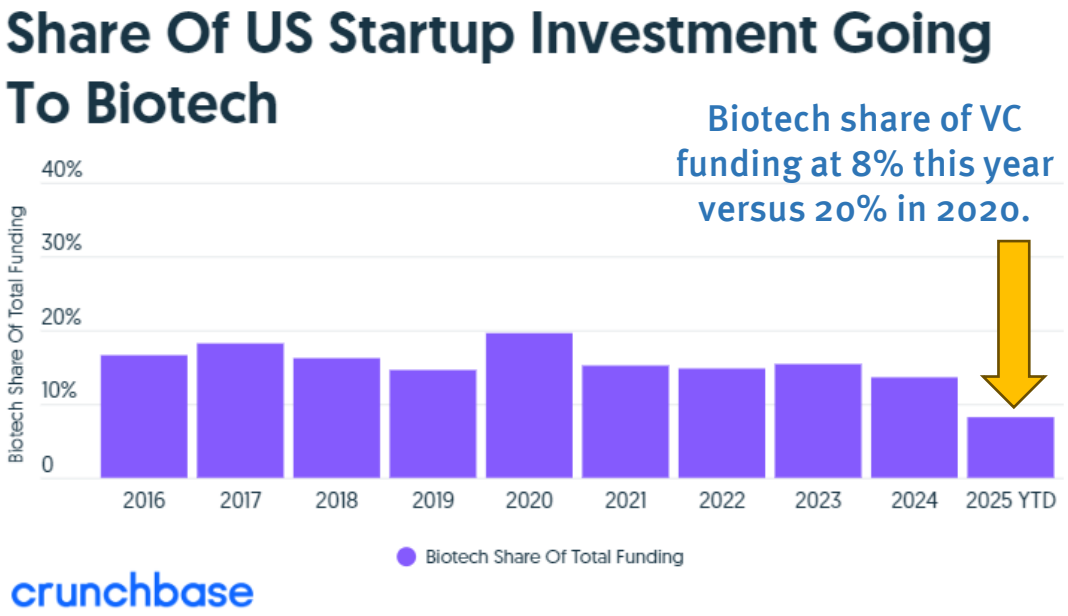
From boom to not

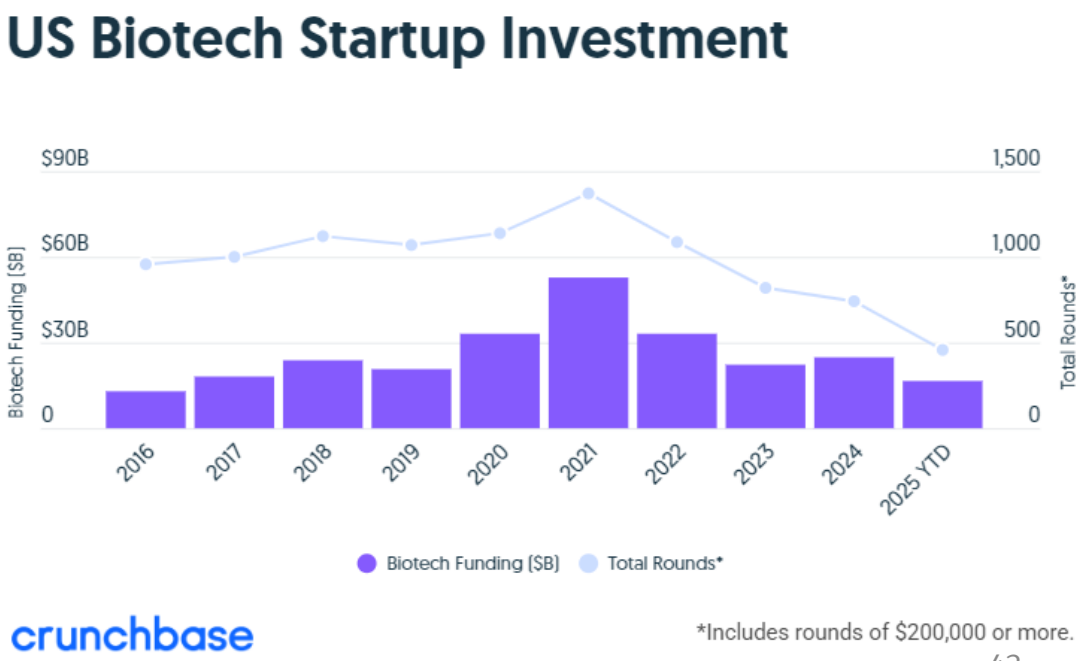
Part of the reason for the backlog of companies with long funding lags is the shift in investor appetite for biotech. During the boom years from 2020 through 2022, startup investors put an average of $40 billion per year into the space — well above current levels.

Some of those were truly huge financings as well. The largest, in early 2022, went to Altos Labs, a San Francisco startup focused on cellular rejuvenation that launched with $3 billion in committed capital.

The biotech IPO market was also quite happening then compared to now. This offered companies yet another avenue to raise capital to fund research and clinical trials.

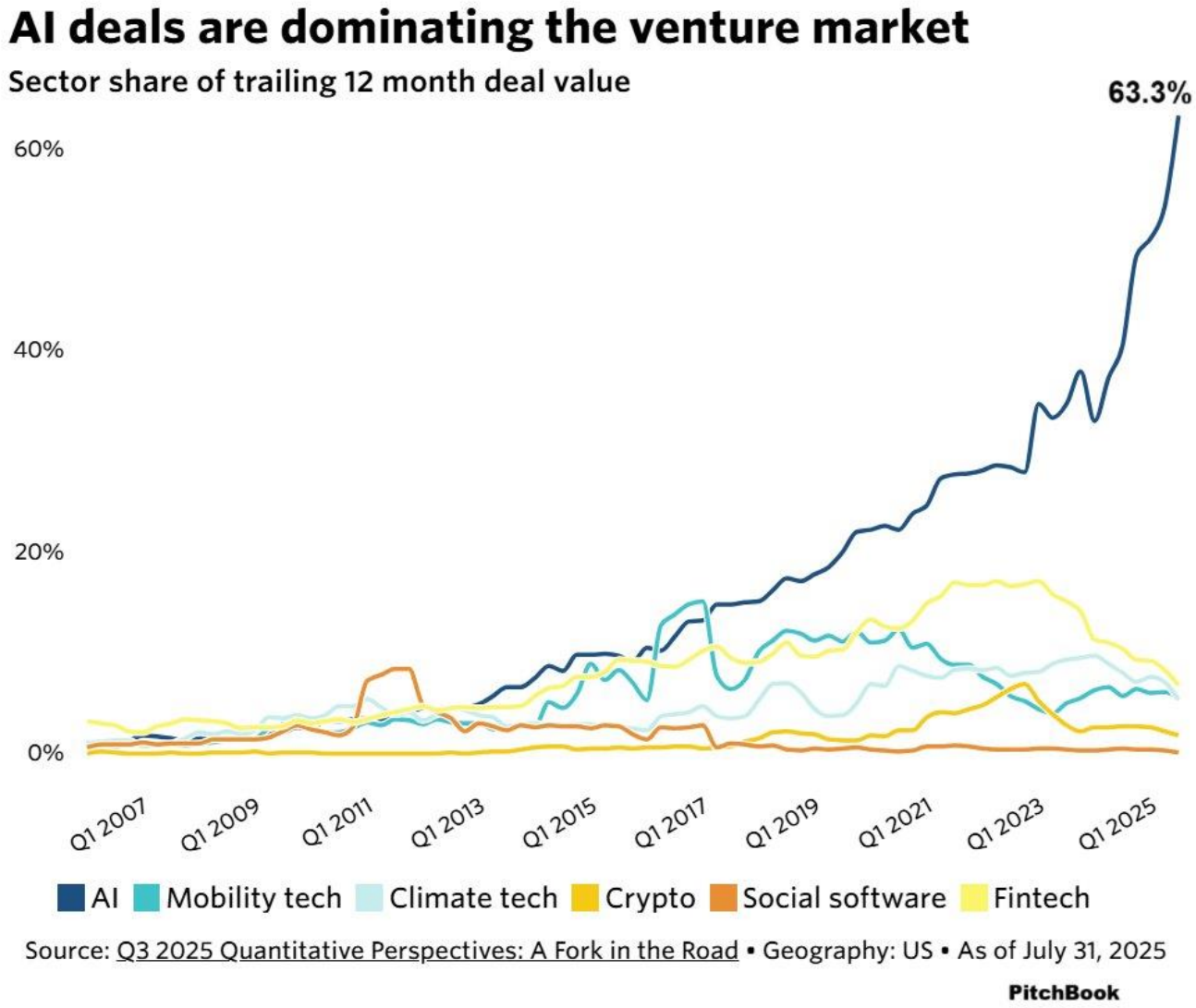
This year, by contrast, is on track to come in much lower. So far in 2025, only about $17 billion has gone to U.S. biotechs, per Crunchbase data. And of that, roughly half has gone to seed and early stage startups — leaving a smaller portion for late-stage financings for well-funded companies.





Source: https://news.crunchbase.com/health-wellness-biotech/biotech-unicorn-startups-funding-havent-raised-since-2022-data/

Tech Venture Market Seeing AI Take Over



Source: https://pitchbook.com/news/reports/q3-2025-quantitative-perspectives-us-market-insights

Private Markets Field Seeing Best Performance from Buyout Funds

Figure 19 ▸ **Pooled IRRs by strategy**

2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	15-year horizon IRR
Middle-market buyout 29.1%	Natural resources -0.4%	Private debt 19.1%	Secondaries 23.5%	Secondaries 19.4%	Buyout megafunds 17.8%	Buyout megafunds 26.1%	VC 21.0%	Buyout megafunds 19.0%	Middle-market buyout 19.7%	Buyout megafunds 19.5%	VC 20.3%	Middle-market buyout 18.2%	VC 43.2%	PE growth 55.6%	Natural resources 25.0%	Buyout megafunds 12.2%	Natural resources 12.6%	Buyout megafunds 16.5%
Secondaries 28.8%	Infrastructure -5.2%	Middle-market buyout 9.4%	Buyout megafunds 22.0%	Natural resources 16.3%	Opportunistic real estate 13.7%	VC 22.4%	Opportunistic real estate 16.8%	Value-add real estate 16.2%	Natural resources 16.5%	Middle-market buyout 17.6%	PE growth 19.4%	PE growth 18.1%	PE growth 34.9%	VC 55.1%	Infrastructure 14.1%	Private debt 10.5%	Infrastructure 11.5%	PE growth 15.8%
Infrastructure 27.7%	Secondaries -12.1%	Buyout megafunds 9.3%	PE growth 20.2%	Opportunistic real estate 12.8%	Private debt 13.4%	PE growth 17.6%	Buyout megafunds 16.8%	Middle-market buyout 11.9%	All private capital 10.8%	Secondaries 17.3%	Secondaries 16.6%	VC 17.0%	Buyout megafunds 28.0%	FoF 51.8%	Value-add real estate 10.0%	Middle-market buyout 9.4%	Buyout megafunds 10.1%	Middle-market buyout 15.7%
Opportunistic real estate 26.0%	VC -12.2%	PE growth 7.1%	Private debt 19.2%	Value-add real estate 11.9%	PE growth 13.0%	Value-add real estate 17.3%	Middle-market buyout 16.0%	Secondaries 11.9%	Opportunistic real estate 10.4%	PE growth 16.2%	Middle-market buyout 16.1%	Buyout megafunds 15.5%	FoF 27.9%	Secondaries 45.5%	Opportunistic real estate 9.9%	PE growth 6.9%	PE growth 9.9%	All private capital 13.1%
All private capital 19.7%	FoF -14.3%	Natural resources 3.6%	Opportunistic real estate 19.2%	PE growth 11.6%	Secondaries 12.2%	All private capital 17.0%	Value-add real estate 15.9%	VC 11.8%	Private debt 9.8%	All private capital 13.9%	FoF 15.6%	Secondaries 13.1%	Middle-market buyout 27.6%	Buyout megafunds 44.8%	Middle-market buyout 5.9%	All private capital 5.8%	Middle-market buyout 8.7%	Secondaries 13.0%
FoF 19.4%	Middle-market buyout -14.7%	FoF 3.5%	Natural resources 18.8%	VC 11.5%	All private capital 12.2%	Middle-market buyout 16.4%	PE growth 15.2%	Opportunistic real estate 11.8%	Value-add real estate 9.4%	Private debt 12.1%	Value-add real estate 11.8%	Opportunistic real estate 12.4%	All private capital 19.6%	Middle-market buyout 40.2%	Private debt 5.0%	Infrastructure 4.8%	All private capital 7.9%	VC 12.9%
Buyout megafunds 15.6%	PE growth -17.3%	All private capital 2.3%	All private capital 16.8%	Middle-market buyout 11.4%	Middle-market buyout 11.6%	Opportunistic real estate 14.8%	Infrastructure 15.2%	PE growth 11.7%	Buyout megafunds 8.7%	FoF 11.8%	All private capital 11.0%	All private capital 11.6%	Secondaries 14.3%	All private capital 39.0%	Secondaries 2.8%	Secondaries 3.0%	Private debt 7.8%	FoF 12.2%
Private debt 14.4%	All private capital -19.7%	VC -0.1%	Middle-market buyout 15.7%	FoF 10.6%	Value-add real estate 11.1%	Private debt 13.0%	All private capital 15.1%	FoF 11.4%	Infrastructure 8.7%	Value-add real estate 10.1%	Infrastructure 8.8%	FoF 11.4%	Private debt 6.3%	Natural resources 30.2%	All private capital 0.7%	FoF 2.6%	VC 4.6%	Opportunistic real estate 11.3%
VC 13.9%	Value-add real estate -25.6%	Infrastructure -5.0%	Infrastructure 13.2%	All private capital 9.8%	FoF 7.4%	FoF 12.6%	Private debt 14.2%	All private capital 10.3%	PE growth 8.3%	VC 9.2%	Buyout megafunds 6.9%	Value-add real estate 8.4%	Infrastructure 5.7%	Opportunistic real estate 29.7%	Buyout megafunds -5.0%	Natural resources -3.6%	Secondaries 3.3%	Private debt 10.0%
Natural resources 12.2%	Buyout megafunds -27.5%	Secondaries -7.1%	VC 12.3%	Buyout megafunds 9.0%	Infrastructure 7.4%	Secondaries 7.7%	FoF 14.1%	Infrastructure 8.9%	FoF 7.3%	Natural resources 9.0%	Private debt 5.7%	Private debt 8.1%	Value-add real estate 5.6%	Value-add real estate 28.7%	PE growth -6.2%	VC -5.2%	FoF 2.9%	Value-add real estate 9.5%
PE growth 10.0%	Private debt -27.7%	Opportunistic real estate -44.6%	FoF 11.4%	Infrastructure 5.0%	VC 7.1%	Natural resources 7.1%	Secondaries 13.4%	Private debt 3.3%	Secondaries 5.8%	Opportunistic real estate 8.9%	Opportunistic real estate 5.2%	Infrastructure 4.1%	Opportunistic real estate 3.6%	Infrastructure 18.3%	FoF -7.6%	Opportunistic real estate -5.4%	Opportunistic real estate -0.6%	Infrastructure 9.4%
Value-add real estate -3.9%	Opportunistic real estate -29.7%	Value-add real estate -45.0%	Value-add real estate -2.4%	Private debt 4.1%	Natural resources 5.9%	Infrastructure 6.1%	Natural resources -0.7%	Natural resources -17.6%	VC 0.2%	Infrastructure 8.7%	Natural resources 4.5%	Natural resources -9.7%	Natural resources -14.8%	Private debt 17.1%	VC -17.2%	Value-add real estate -10.3%	Value-add real estate -2.2%	Natural resources 5.3%

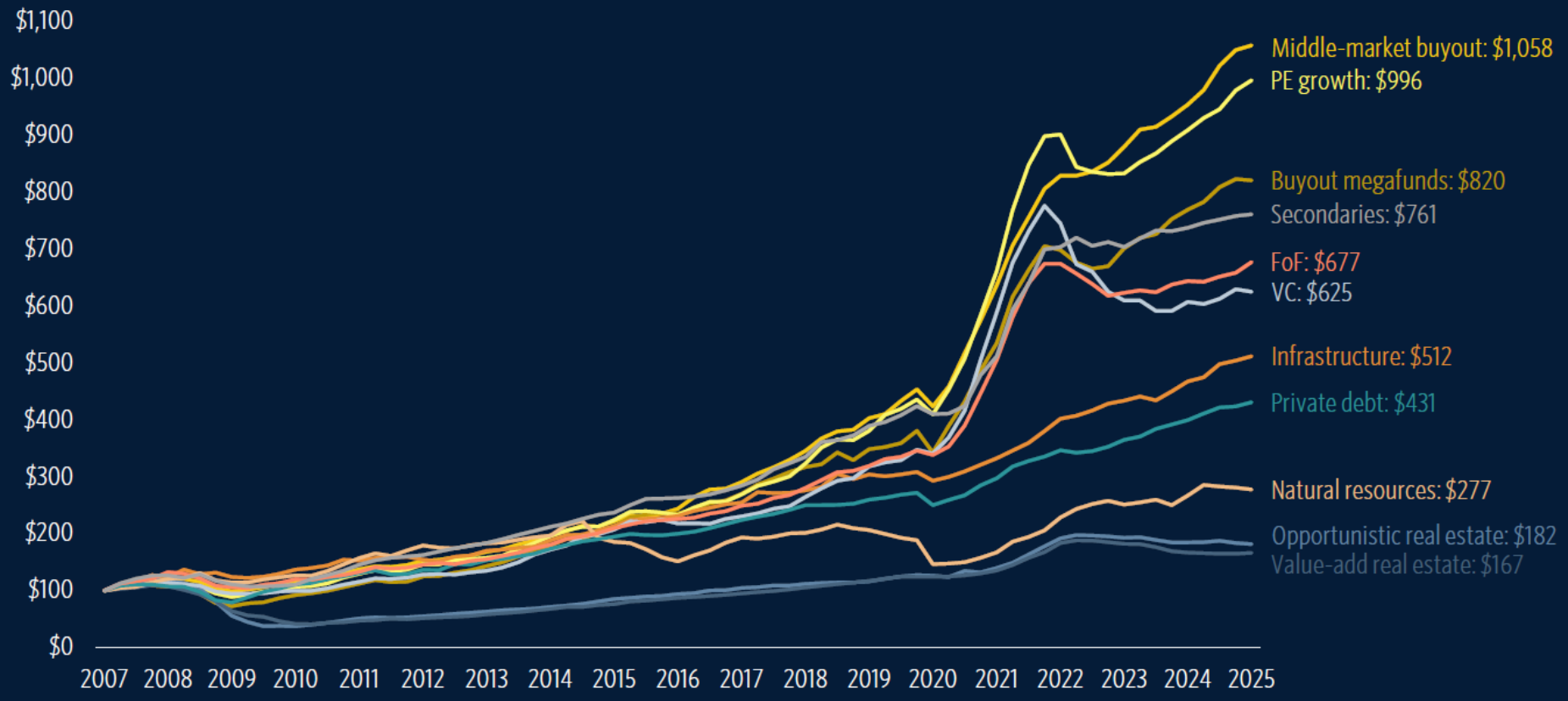
Source: PitchBook • Geography: US • As of December 31, 2024

Note: Middle-market buyout funds are those between $100 million and $5 billion. Buyout megafunds are $5 billion or larger.

Source: https://pitchbook.com/news/reports/q3-2025-quantitative-perspectives-us-market-insights

Overall, Venture Funds Have Increased Capital By Six Times Since 2007

Figure 22 ▸ **Hypothetical growth of $100 invested in Q1 2007 by PitchBook Private Capital Index**



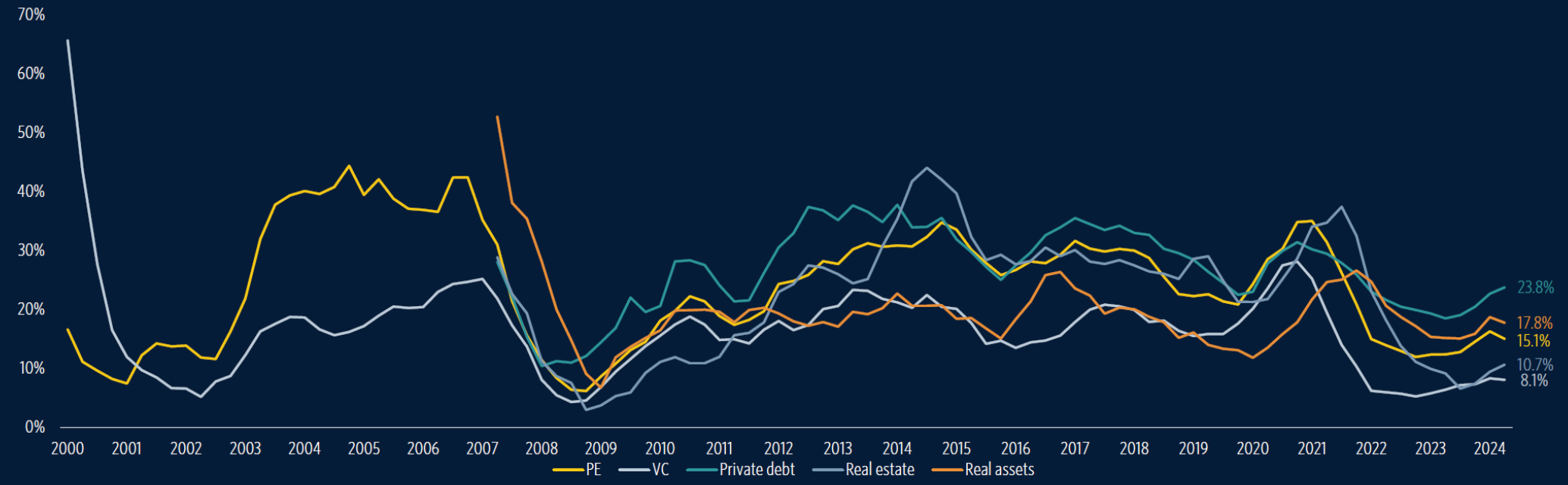
Source: https://pitchbook.com/news/reports/q3-2025-quantitative-perspectives-us-market-insights

Source: PitchBook • Geography: US • As of March 31, 2025
Note: Data for Q1 2025 is preliminary.

Tough Times for Raising a Fund Given the Paucity of Private Capital Distributions to LPs

With distributions at GFC-era lows, NAV is locked in private funds, straining LP liquidity. PE and VC lag, while private debt and real assets have delivered more reliable payouts lately.

Figure 41 ▸ **Rolling 12-month distribution yields as a share of beginning NAV by asset class**



Source: PitchBook • Geography: US • As of March 31, 2025
Note: Data for Q1 2025 is preliminary.

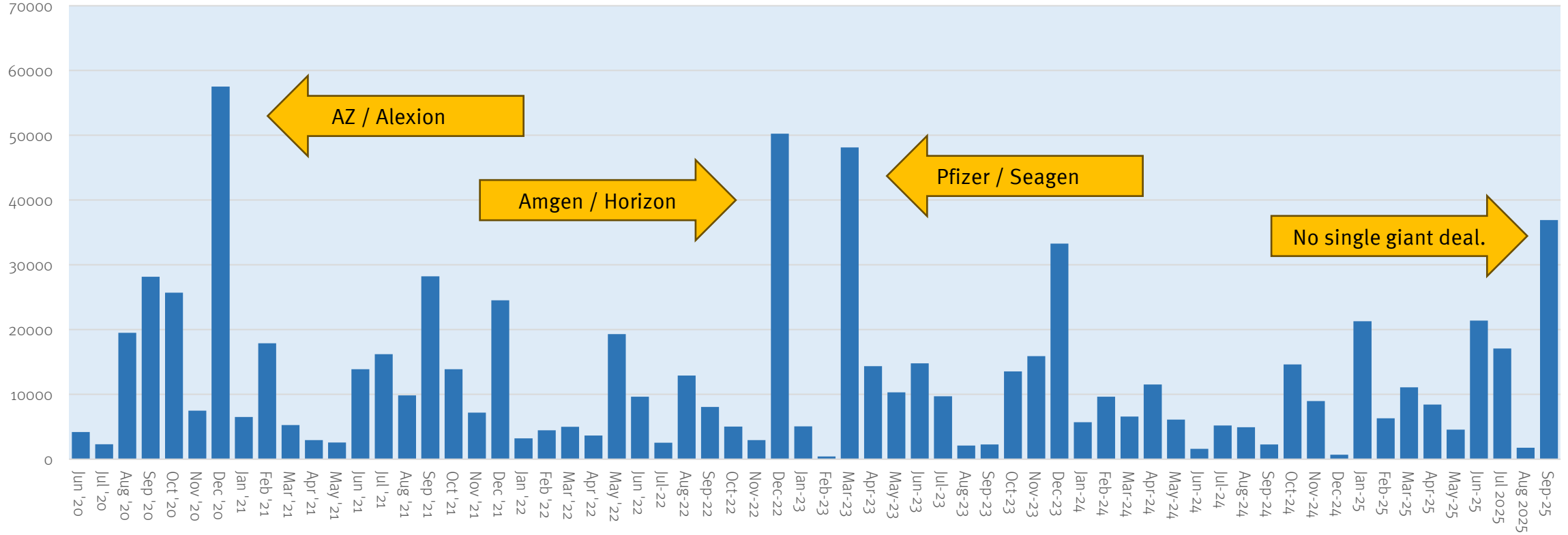
Source: https://pitchbook.com/news/reports/q3-2025-quantitative-perspectives-us-market-insights

M&A Update

September 2025 Was an Exceptional Month for M&A

September saw over $1 billion in M&A volume per day with a total of $36 billion in deal announcements. This was the strongest month for M&A since Pfizer announced the purchase of Seagen. What was so exceptional about the month is that there was no single large deal. The largest transaction announcements were Genmab/Merus and CapVest/Stada. Together, these don't add up to half of the month's volume. We continue to be highly bullish on M&A volume for the rest of the year. We believe that there is a good chance that the last four months of 2025 will see more M&A volume than the first eight months. The reason is that much of the industry's policy risk has been settled out. With less perceived risk from tariffs and MFN, pharma will continue to be far more active going forward given upcoming patent cliffs.

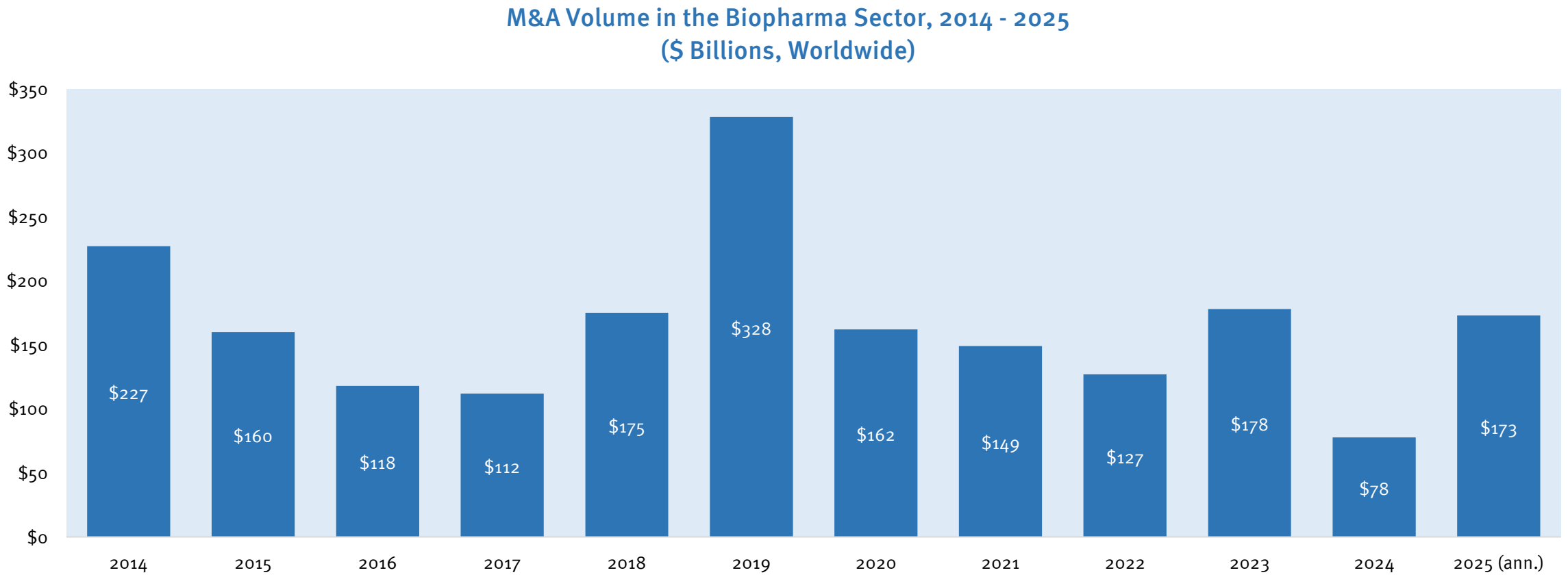
Monthly M&A Activity ($volume, $mm), Jun 1, 2020 to Sep 30, 2025



Source: S&P, CapitalIQ

M&A Market Is Picking Up Steam

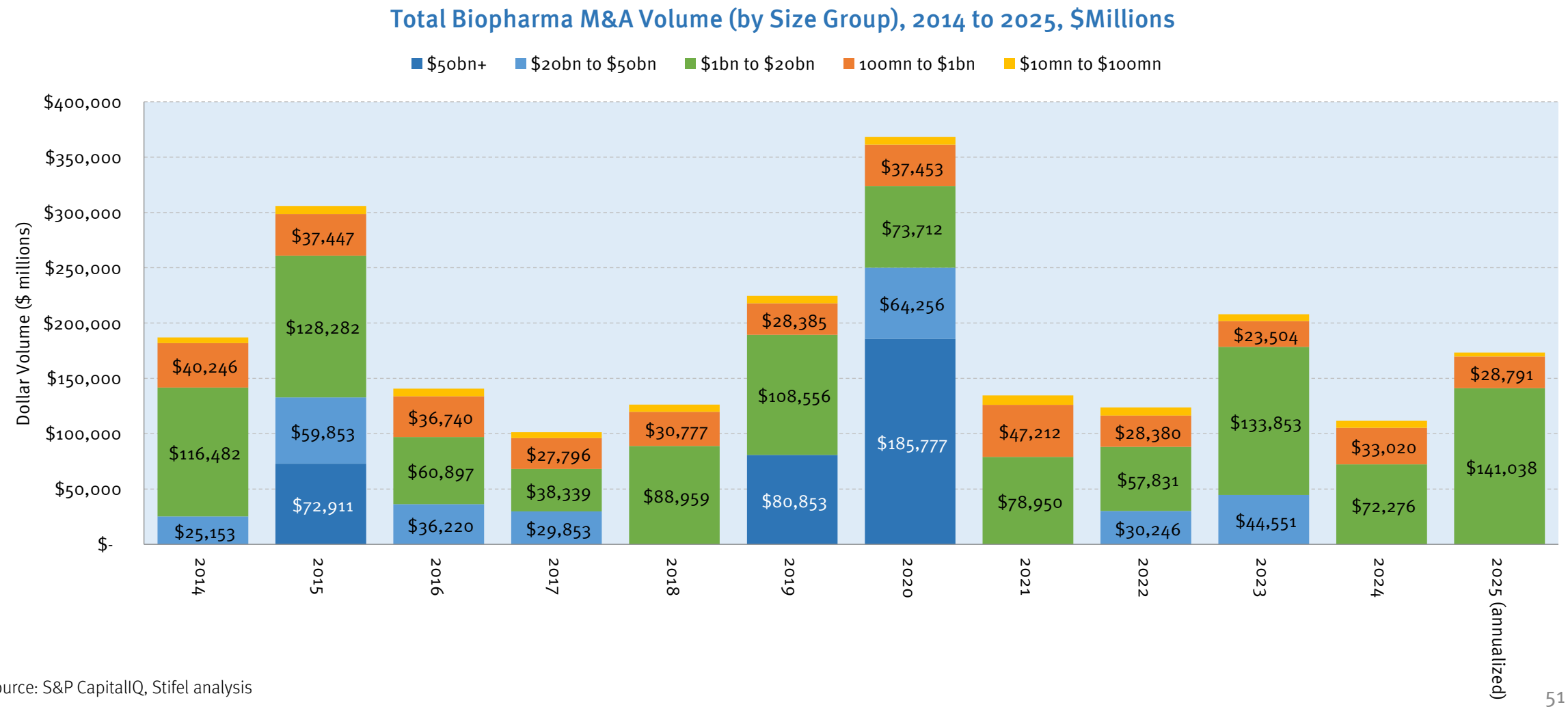
If one extrapolates M&A volume year-to-date, we are looking for 2025 to be the second strongest M&A year since 2019 and the fourth strongest year in history. What is remarkable is that there are no large ($15bn+) deals that have transpired so far in 2025. If our forecast of high M&A volume in Q4 2025 turns out to be correct, then we would expect to see this year turn out to be the second or third most active in history. A countervailing factor is the rise in prices of small cap and midcap biopharma. As prices come up there will be a natural brake on acquisition activity. But as of today, we are far from the point where valuations will be a major headwind on M&A.



Source: S&P CapitalIQ

Exceptional Dollar Volume in the $1bn to $20bn Category is Driving This Year's M&A Volume

We are tracking for a $141 billion year in the $1bn to $20bn M&A grouping. This is the most active year in this grouping in history.



Source: S&P CapitalIQ, Stifel analysis

Genmab to Acquire Closely Watched Cancer Drug in $8B Merus Buyout

Delilah Alvarado, *Biopharma Dive*, Sep 29, 2025 (excerpt)

Merus had already seen its share value jump by more than 50% since late May, when its ASCO presentation showed that petosemtamab kept nearly 80% of study participants with advanced head and neck squamous cell carcinoma alive for at least a year.

The results positioned Merus' drug, a type of bispecific antibody targeting the proteins EGFR and LGR5, to be a "market leader in the multi-blockbuster head-and-neck cancer treatment landscape," William Blair analyst Matt Phipps wrote in a research note on Monday.

Genmab is gambling on that outcome. While Merus' drug showed potential in Phase 2, those findings will need to be duplicated in a late-stage study comparing a petosemtamab-Keytruda combination to Keytruda alone. Results are expected in 2026. Genmab said Monday that the drug could eventually book $1 billion in yearly sales by 2029 and have multibillion-dollar annual sales potential afterwards. Phipps is projecting $3 billion to $4 billion in annual peak sales in head and neck cancer alone.

Petosemtamab "has the potential to be a transformational therapy for patients living with head and neck cancer," said Genmab CEO Jan van de Winkel, adding that the drug could provide "durable growth ... well into the next decade." The drug is also being evaluated for colorectal cancer. Phase 2 results had been expected shortly, leading some investors to question the timing of the deal, Phipps wrote Monday.

The asset adds to a large portfolio of antibody drugs for Genmab, which codeveloped the multiple myeloma therapy Darzalex with Johnson & Johnson, the cervical cancer medicine Tivdak with Seagen and the lymphoma drug Epkinly with AbbVie.

Source: https://www.biopharmadive.com/news/genmab-merus-deal-acquire-petosemtamab-head-neck-cancer/761340/

Halozyme's $900M Elektrofi Buyout Brings Two Big Pharma Partners Together

Tristan Manalac, *Biospace*, Oct 2, 2025 (excerpt)

Halozyme Therapeutics will acquire Elektrofi for up to $900 million in a deal that will combine two subcutaneous drug delivery specialists that have each lent their technologies to Big Pharma companies.

The deal, announced Wednesday, will involve a $750 million upfront payment from Halozyme, plus up to three $50-million milestone payments, each contingent on different product approvals. Halozyme and Elektrofi's respective boards of directors have unanimously signed off on the deal, and the companies expect the transaction to wrap up in the fourth quarter, pending customary closing conditions.

According to Halozyme's news release, the acquisition makes strong strategic sense, bringing together "complementary" subcutaneous technologies that boost the convenience and accessibility of innovative therapies. The Elektrofi buyout also promises to be a financial boon to Halozyme, with milestone payments potentially hitting $275 million, alongside royalty revenues from the microparticle platform that are set to begin in 2030.

Halozyme and Elektrofi are known for their drug delivery technologies, which many of pharma's biggest players have bought into. Halozyme, for instance, owns the Enhanze platform, which allows certain drugs to be administered via an under-the-skin injection. According to the company's website, there are currently 10 commercial products that use Enhanze, among which are Johnson & Johnson's multiple myeloma therapy Darzalex and lung cancer drug Rybrevant.

Takeda is also leveraging the Enhanze technology for its primary immunodeficiency drug Hyqvia, while Roche uses the platform for many of its products, including the PD-1 blocker Tecentriq and the multiple sclerosis medicine Ocrevus. Bristol Myers Squibb also partnered with Halozyme for the subcutaneous formulation of its cancer therapy Opdivo.

Elektrofi also has a high-profile roster of Big Pharma partners. The company's Hypercon technology uses microparticles to similarly allow a convenient, low-volume subcutaneous delivery of biologics as opposed to infusions.

Source: https://www.biospace.com/business/halozymes-900m-elektrofi-buyout-brings-two-big-pharma-partners-together

Roche: Exercised Price Discipline as the Sole Bidder for 89Bio

Nick Paul Taylor, *FierceBiotech*, Oct 2, 2025 (excerpt)

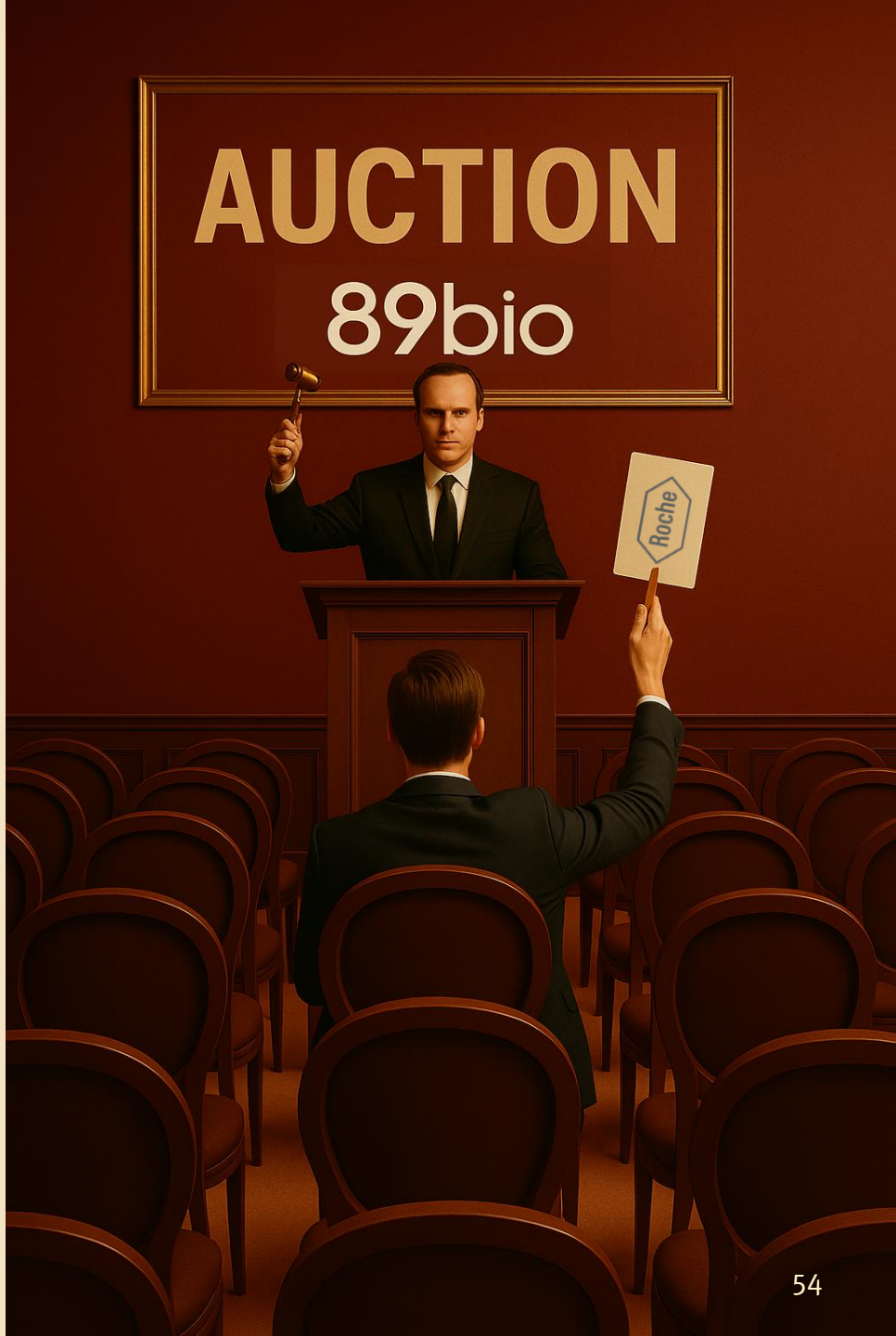
By July, 89bio had an offer from Roche—and confirmation that five other global biopharma companies had no plans to strike a deal. The five companies that turned 89bio down in July were among a total of seven, plus Roche, that the biotech spoke to in 2025.

89bio deemed Roche's initial offer—$13 a share at a time when the stock traded at $10.22—insufficient to merit further talks about an acquisition. The biotech pitched a $20-plus offer to Roche. After visiting 89bio's manufacturing facilities, Roche came back with an offer of $14 a share plus $2 a share tied to the first sale of pegozafermin for the treatment of stage 4 MASH.

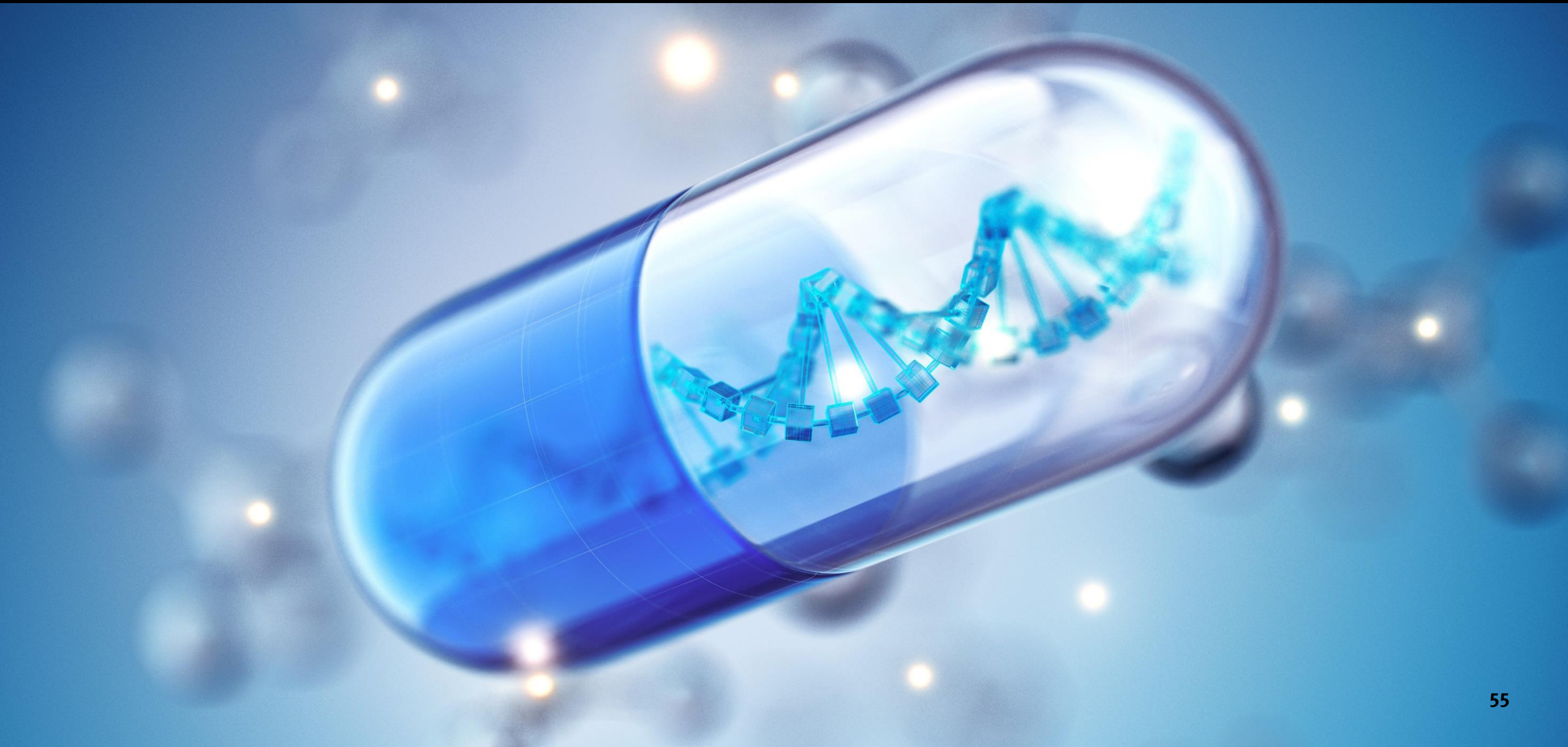
With the offer falling short of 89bio's $20 a share floor, further talks took place in August. Roche added more success-based payments and tagged 50 cents onto the upfront offer, bringing the potential deal value up to $19.50 a share. 89bio held out and days later received Roche's "best and final" offer, which failed to address the call for a bigger upfront but did tweak the success-based payments.

The two sides continued to negotiate over the timing of the success-based payments, but the core of the deal was in place by late August. Roche had avoided going much above the $13 a share it initially offered and, through the success-based payments, 89bio had secured a total package that crept above the $20 a share targeted by its board.

Source: https://www.fiercebiotech.com/biotech/after-courting-14-pharmas-89bio-was-left-between-roche-and-hard-place-buyout-talks



Industry Update



Donald Trump's Cure For Drug Prices is Worse Than the Disease

Economist, October 2, 2025 (excerpt)

Few things infuriate Americans as much as drug prices. Republicans and Democrats alike agree that poorly patients are being ripped off by greedy pharma firms. They point to the fact that America's list prices for branded drugs are, on average, more than four times those in other rich countries.

Donald Trump agrees with them and he has set out to do something about it. He has asked drugmakers to cut their prices to "most-favoured nation" levels, ie, to the cheapest price out there. If they don't, he says, he will use "every tool in our arsenal" against what he calls abusive drug pricing. But the president's battle to bring down prices is doomed to fail. Indeed, it could even make health care in America worse.

To answer the question, it helps to grasp why American patients pay more. They are not being ripped off on a grand scale by feckless foreigners. Many European governments buy drugs at the national level, because their health systems are publicly run. But they do so on the basis of a calculation of the value each drug provides, measured by the improvement it offers both to the length and the quality of a patient's life.

This value is often low enough for patients elsewhere to have worse access to new drugs than Americans do. Between 2014 and 2022 one in five medicines approved by Uncle Sam never won approval in Europe, and nearly half were not approved by Japan. Of those cleared in all three places, more than two-thirds were first approved in America—nearly six months before Europe, on average, and almost three years before Japan. When Mr Trump says he wants to match others' prices, he is therefore proposing to import the value that other countries place on treatments. But there is no reason why the world's wealthiest country should share that assessment of how to value good health. If it did, Americans would save money on drugs, but at the cost of worse care than they enjoy today.

Moreover, because pharma companies are, pace Mr Trump, not price-gouging monsters, imposing the most-favoured nation price on the world's biggest drug market would also curb innovation. Drugmakers take big risky bets on treatments, not all of which succeed; by some estimates, around 90% of clinical drug development ends in failure. If you cut the potential rewards, you cut the appetite for risk**. If its American revenues were threatened, the industry would either find ways to protect them, or innovate less, or both.** To lessen the pain, firms could further delay launching their products in other countries, to keep most-favoured nation prices high; or they could raise list prices everywhere, and offer opaque rebates to countries that are not willing to pay higher rates. To the extent that prices in America were forced down, firms would take fewer risks on innovation.

That is why Mr Trump's plan to "rebalance" the system, by making Europeans pay more and Americans less, cannot work. He cannot force the rest of the world to pay more for drugs; nor can he force drugmakers to keep spending as much on research even as their profits take a knock. The harmful consequences would affect patients everywhere—especially Americans, who are the keenest drug buyers of all.

Source: https://www.economist.com/leaders/2025/10/02/donald-trumps-cure-for-drug-prices-is-worse-than-the-disease

How Trump's Online Drugstore May Affect Your Drug Costs

***Rebecca Robbins, New York Times*, October 1, 2025 (excerpt)**

President Trump and top health officials heralded their drug pricing deal with Pfizer on Tuesday as a breakthrough that would save money for American patients struggling with prescription drug costs.

The reality is more complicated.

Under the deal, Pfizer agreed to charge Medicaid prices that are about the same as those it charges European countries. Trump officials also said they would push manufacturers to set prices for newly introduced drugs at similar levels in the United States and other rich countries. And they said they were planning to create a website, TrumpRx.gov, that would help people buy prescription drugs directly from manufacturers like Pfizer.

Much is still unknown about the administration's Pfizer deal and the planned drug-buying website. Trump officials hinted that similar deals with other pharmaceutical manufacturers would follow. But with the price equalization idea, Mr. Trump is tapping into widespread frustration that drug prices are too high in the United States. The Biden administration also took steps to try to lower drug costs for patients and the government, though it did not zero in as Mr. Trump has on the idea that drug prices are unfairly low in Europe.

The Trump administration's changes, however, may have little if any impact for the vast majority of Americans, who fill their prescriptions for medications through health insurance. Stacie Dusetzina, a health policy professor at Vanderbilt University who studies drug pricing, said **the administration's announcement was "a really good way to say you're doing something about drug prices, and not actually do anything to change the underlying profits of the industry."**

Mr. Trump's deal with Pfizer applied to only a tiny sliver of the drugs Americans take. But it could establish a precedent for more medicines and other types of health insurance.

If the plan was expanded, the most significant savings would accrue to American employers, private insurers and government health insurance programs like Medicare, which shoulder most of Americans' prescription costs.

In some cases, the price equalization idea could also generate direct savings for American patients. Using insurance, some patients must pay a percentage of their drug's sticker price, say 25 percent, in the form of coinsurance. Or they have to pay the drug's full cost until they hit up a certain annual limit — for example, $2,000.

Source: https://www.nytimes.com/2025/10/01/health/trump-pfizer-prescription-drug-prices.html

Trump Delays Pharma Tariffs Yet Again

Tristan Manalac, *Biospace*, October 2, 2025 (excerpt)

President Donald Trump last week announced that 100% pharma tariffs would come Oct. 1, but a White House official has clarified that that's when the government will "begin preparing" the levies.

President Donald Trump's pharma tariffs have been pushed off again, after Oct. 1 was set last week as the start date. A White House official told Endpoints News on Wednesday that the 100% levies will not take effect immediately. Trump last week said in a Truth Social post that he would slap a 100% tariff on "any branded or patented pharmaceutical product" starting Oct. 1. His post carved out an exemption for companies that have broken ground or started construction on their manufacturing facilities in the U.S.

But speaking to Endpoints News, an unnamed White House official said that Oct. 1 was not the start date for the tariffs. Instead, that's when the government will "begin preparing tariffs." Trump's exemptions will still apply to companies that are actively building out their domestic footprints, the official added, noting that those who fail to follow the Most Favored Nation pricing policy will also be subject to tariffs.

Trump has been threatening the industry with tariffs for months now. He first floated the idea in February, speaking to several industry leaders in a closed-door meeting. More recently, Trump in July said that the tariffs could reach as high as 200%—before raising the potential levies even further to 250% in August.

Trump has also said that he would give companies a grace period of "about a year, a year and a half" to build out their domestic supply chains.

Meanwhile, the government has also reached trade deals with certain markets that put tariffs at a much lower rate. In July, an agreement with the European Union set a 15% levy on generics, while an arrangement with Japan last month put a 15% tariff on pharma products, but with generics exempted.

In an effort to sidestep import levies, many of the industry's biggest players have pumped billions of dollars into their domestic operations. Earlier this week Pfizer agreed to offer many of its drugs direct-to-consumer and added a $70 billion investment in the U.S., motivated by the threat of tariffs. Also making big commitments is AbbVie, which in April announced a $10 billion investment over the next decade into its U.S. manufacturing capacity. On Tuesday, the pharma announced that construction has commenced on a $70 million expansion of a facility in Massachusetts.

Source: https://www.biospace.com/policy/trump-delays-pharma-tariffs-yet-again

US FDA Launches Program to Fast-track Review of Domestic Generic Drugs

Reuters, October 3, 2025 (excerpt)

Oct 3 (Reuters) - The U.S. Food and Drug Administration said on Friday it has launched a new pilot program to speed up the review process for generic drugs that are tested and manufactured entirely in the United States.

The program is designed to encourage companies to invest in domestic drug production and research by offering faster approvals for products made with U.S.-sourced ingredients and tested within the country.

Earlier this week, the FDA held a public meeting to discuss its broader efforts to support U.S. pharmaceutical manufacturing, including the PreCheck program, which aims to help set up high-priority drug facilities more quickly.

The FDA said these steps will help strengthen the U.S. drug supply chain and bring high-quality, U.S.-made generic drugs to market more quickly.
More than half of the pharmaceuticals distributed in the United States are made overseas, according to the health regulator.

As of 2025, only 9% of companies that produce the key ingredients in drugs - known as active pharmaceutical ingredients - are based in the U.S., compared to 22% in China and 44% in India, the FDA said.

The FDA also noted many important studies used to approve drugs - including tests to show that generic drugs work the same as brand-name ones - are now often done outside the U.S., which is weakening the country's ability to lead in drug research and development.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-launches-pilot-program-fast-track-review-domestically-made-generic-drugs-2025-10-03/

F.D.A. Approves Generic Abortion Pill as Opponents Push Trump for New Restrictions

Pam Belluck, *New York Times*, October 2, 2025 (excerpt)

The Food and Drug Administration has approved a generic version of the abortion pill mifepristone, expanding its supply at a time when the Trump administration is under pressure from abortion opponents to sharply restrict access to abortion medication.

The approval, issued on Tuesday without a public announcement, means that three American companies can now produce mifepristone for abortion. The F.D.A. approved the original pill 25 years ago and in 2019 approved the first generic version.

The decision comes as anti-abortion activists have been urging the F.D.A. and the Department of Health and Human Services to curtail access to abortion pills, which have been prescribed in increasing numbers in the years since the Supreme Court overturned the national right to abortion in 2022.

Currently, nearly two-thirds of abortions in the country are carried out with medication. Access to abortion pills, especially through telemedicine, is a major reason that the number of abortions in the United States has not decreased since the Supreme Court decision.

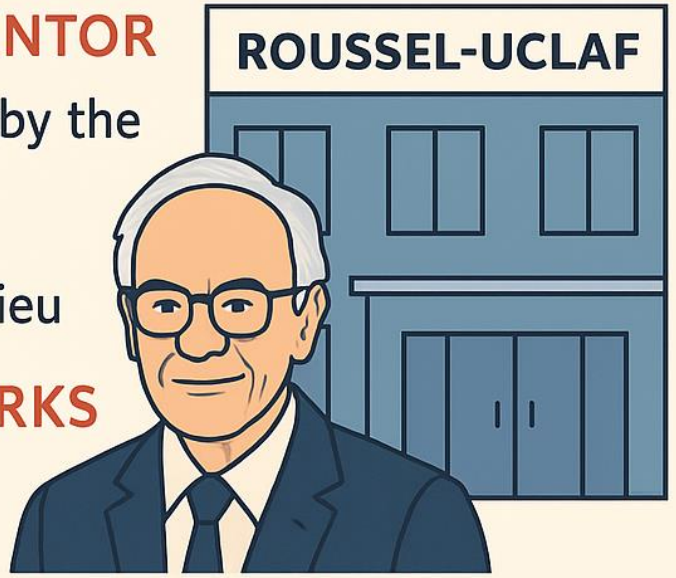
A spokesman for H.H.S., Andrew Nixon, said in a statement that "the F.D.A. has very limited discretion in deciding whether to approve a generic drug. By law, the Secretary of Health and Human Services must approve an application if it demonstrates that the generic drug is identical to the brand-name drug."

Source: https://www.nytimes.com/2025/10/02/health/abortion-pill-generic-fda.html

RU-486 (Mifepristone)

ORIGIN AND INVENTOR

- Developed in 1980 by the French company Roussel-Uclaf
- Étienne-Émile Baulieu



HOW RU-486 WORKS

- Progesterone receptor antagoist
  - Blocks hormone needed to maintain pregnancy
  - Causes breakdown of uterine lining, uterine contractions

USE IN ABORTION

- Early pregnancy termination (up to ~ 10 weeks)
  - Given orally with a prostaglandin (e.g., misoprostol)
  - Combined regimen has a >95% success rate

Luke Miels to Replace Emma Walmsley

***Elena Vardon and Adria Calatayud, Wall Street Journal*, Sep 29, 2025 (excerpt)**

GSK said Chief Executive Emma Walmsley would step down and be succeeded by commercial chief Luke Miels, as the drugmaker works to replenish its product lineup.

The leadership change comes as GSK seeks to bring to market more of the drugs in its late-stage pipeline to offset a coming loss of patent protection for its top-selling drug, HIV medicine dolutegravir.

“2026 is a pivotal year for GSK to define its path for the decade ahead, and I believe the right moment for new leadership,” Walmsley said.

Currently GSK’s chief commercial officer, Miels will take on the top job on Jan. 1. Miels joined GSK from AstraZeneca in 2017 and has since played a key role in building a portfolio of specialty medicines, particularly in the oncology and respiratory therapeutic areas, the company said.

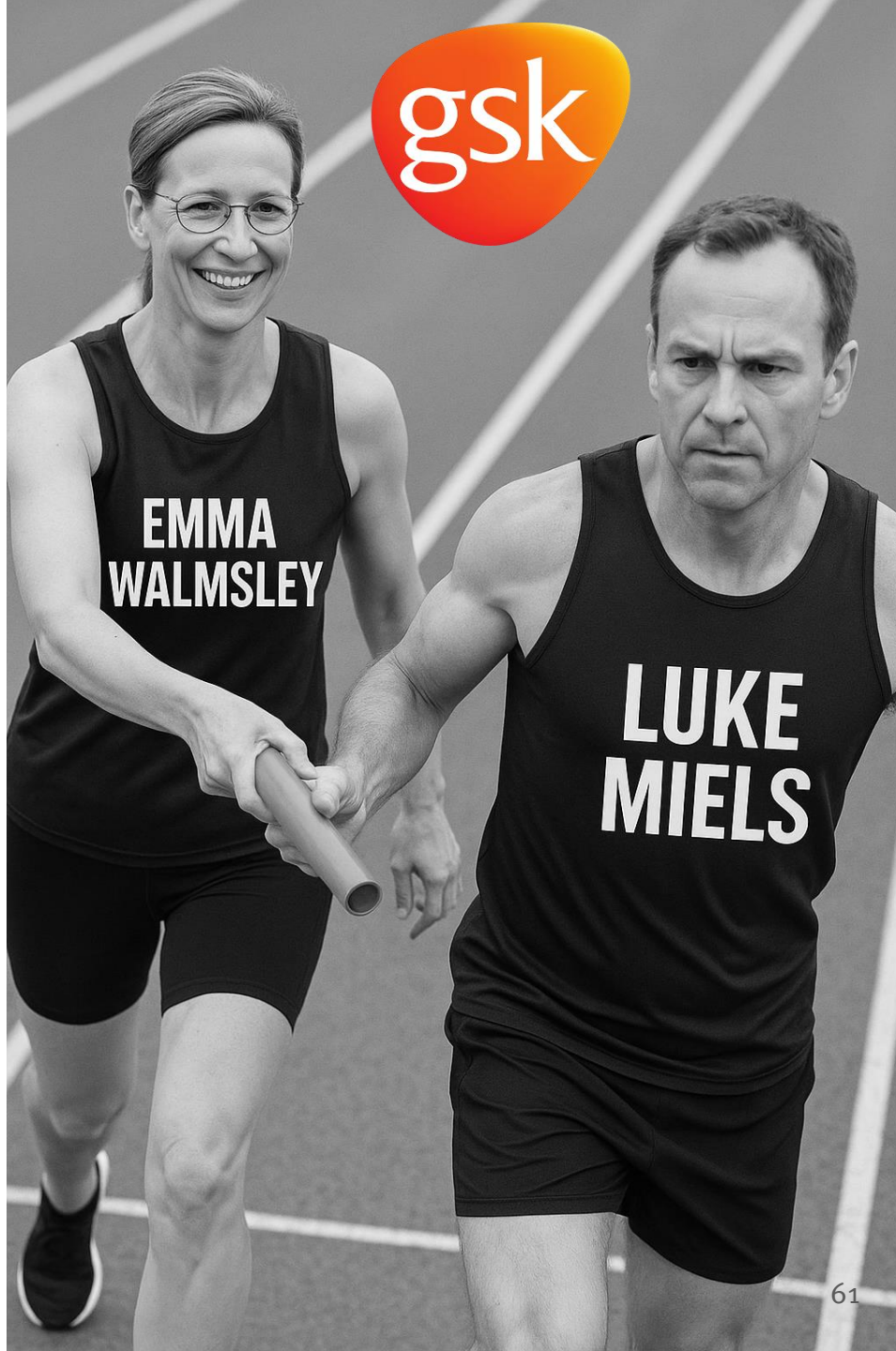
Longtime CEO Walmsley took the helm of the company in April 2017, becoming the first woman to run a top-tier pharmaceutical company.

Under her leadership, GSK boosted spending on research and bet big on cancer drugs with a number of acquisitions. The company also spun off its consumer division, which makes everything from toothpaste to painkillers, into a stand-alone business now called Haleon.

However, the moves failed to win over some investors. Those included Elliott, the activist hedge fund, which questioned at one point whether Walmsley was the best person to lead GSK. At the time, the company’s board backed its CEO.

GSK’s stock fell roughly 11% during Walmsley’s tenure. The London-listed stock was up about 1% in Monday afternoon trading.

Source: https://www.wsj.com/business/c-suite/gsk-names-luke-miels-to-succeed-ceo-emma-walmsley-17264317



Pharma's Hot Zone: A New Generation of Radiotherapies Promises a More Targeted Attack on Cancer

***Robert Service, Science*, Oct 2, 2025 (excerpt)**

Hundreds of clinical trials with targeted radioisotopes are now getting underway, marking a major acceleration in this once staid field.

The concept is decades old, but improvements to the three basic components of the drugs are helping fuel a boom. For years, oncologists exploited just a handful of radioisotopes, but researchers are exploring novel ones—including Ac-225-that emit different kinds of radiation over different time courses. Other work focuses on a second component, developing new antibodies, peptides, and small molecules to steer the radioisotopes more precisely to specific types of tumors. The third element of the drugs, the chemical linkers joining the isotopes to the targeting molecules, were once seen as utilitarian. But they, too, are now being redesigned to control how the radioisotopes pass through the body, with the goal of minimizing side effects.

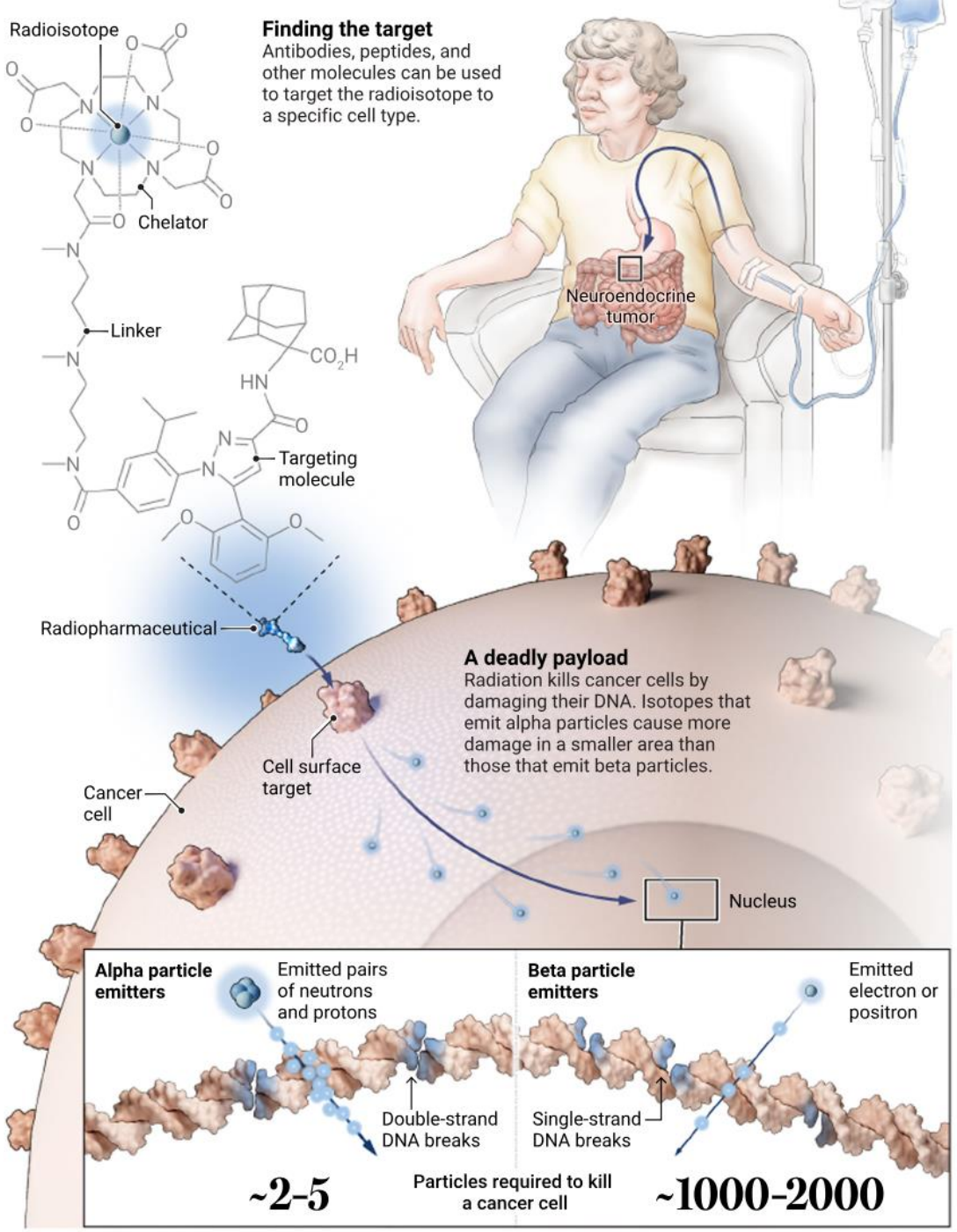
By mixing and matching these components, researchers are creating an armamentarium of new radiopharmaceuticals, tailored to hit malignancies from diffuse blood cancers like leukemia to large solid tumors such as cancers of the breast and colon. "It's a very exciting time for nuclear medicine," says Heather Jacene, the clinical director of nuclear medicine at Harvard University's Dana-Farber Cancer Institute.

The race to find precise targeting agents is heating up as well, and Telix is one of the leaders. Its monoclonal antibody targets prostate membrane specific antigen (PMSA), a protein that is upregulated in cancerous cells and is the same target Pluvicto uses to deliver Lu-177. But the name is a misnomer: PMSA is also found in healthy cells in the prostate and elsewhere in the body, exposing them to collateral damage from the isotope. Telix scientists have now modified the antibody so it still targets PMSA on prostate cancer cells but avoids binding to white blood cells and cells in the kidneys, which are especially vulnerable to radiopharmaceuticals because they filter the blood. The company's clinical tests indicate the modified antibody not only avoids unintended targets but is cleared from the body 50% faster, via the liver and GI tract, a route less susceptible to radiation damage. A phase 3 trial for prostate cancer should be completed in 2027.

Other companies are also looking for better ways to home in on prostate cancer cells. Researchers at Philochem AG recently used DNA-based barcodes to screen a library of 5.8 million potential small molecule drugs to identify the best ones to ferry Lu-177 to prostatic acid phosphatase (ACP3), an enzyme that's abundant in prostate cancer cells but virtually absent in healthy organs. Three of these compounds, linked to Lu-177, were highly effective at shrinking tumors in mice, the company reported last year in the Journal of Nuclear Medicine.

Source: https://www.science.org/content/article/new-radioactive-isotope-therapies-promise-more-targeted-attacks-cancer

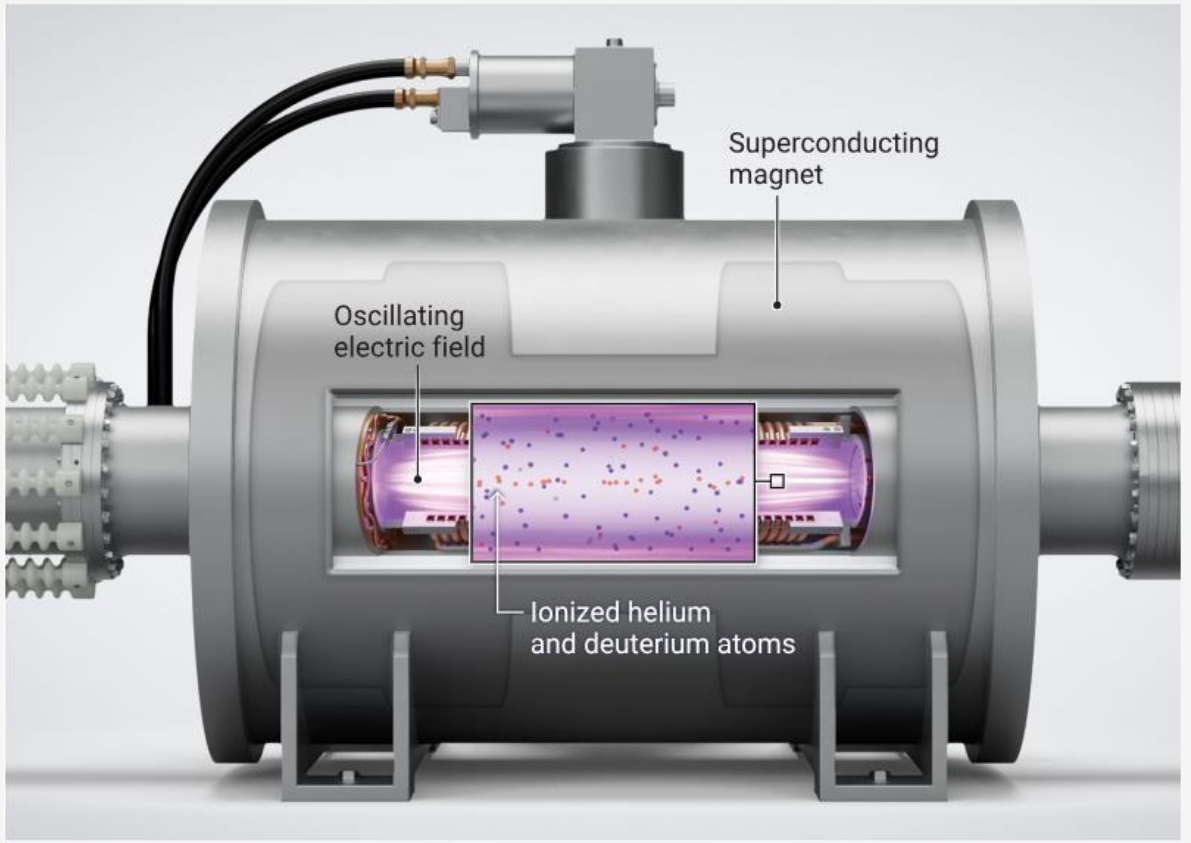
Furthe Material from Radiotherapy Article



N. BURGESS/*SCIENCE*

Widening the isotope pipeline

BY ROBERT F. SERVICE



Ion innovation Nusano's ion source magnetically confines ions and strips away their remaining electrons, making it possible for electric fields to accelerate them to high energies. NUSANO, ADAPTED BY C. BICKEL/*SCIENCE*

The radioactive isotopes powering a new generation of cancer drugs often begin their short lives in aging nuclear reactors. But a small company called Nusano is building a nimble new source. This fall, engineers will flip on 60,000 volts of electricity to ionize a swirling cloud of helium and deuterium atoms and then fire the ions into metal foils no bigger than a postage stamp, transmuting the metal atoms into as many as 40 different radioactive isotopes.

Nusano is one of several companies deploying new technologies to fill the skyrocketing demand for medical radioisotopes. Recent scientific advances have led to a new generation of targeted drugs that deliver a payload of radioactive isotopes to specific types of cancer cells (see main story, above), and early clinical successes have fueled an explosion of interest among doctors and patients.

Radiotherapy Pipeline Expanding

To J, Magid R, Cleland J, Panier V, Wu J. The landscape for radioligand therapies in oncology. *Nat Rev Drug Discov*. Aug 2025;24(8):584-585.

RLTs combine the potency of external radiotherapy with the precision of targeted therapy, presenting an opportunity to address unmet need across multiple cancer types. With ›60 assets in clinical trials across ›20 cancer types and continued innovation in radioisotopes and targeting moieties, RLTs are poised to affect the standard of care beyond NETs and prostate cancer. However, delivering this potential will require coordinated efforts from the ecosystem of biopharma/biotech companies, suppliers, providers and payers to harness advances and overcome complexities in supply, manufacturing and logistics that could otherwise impede scalability.

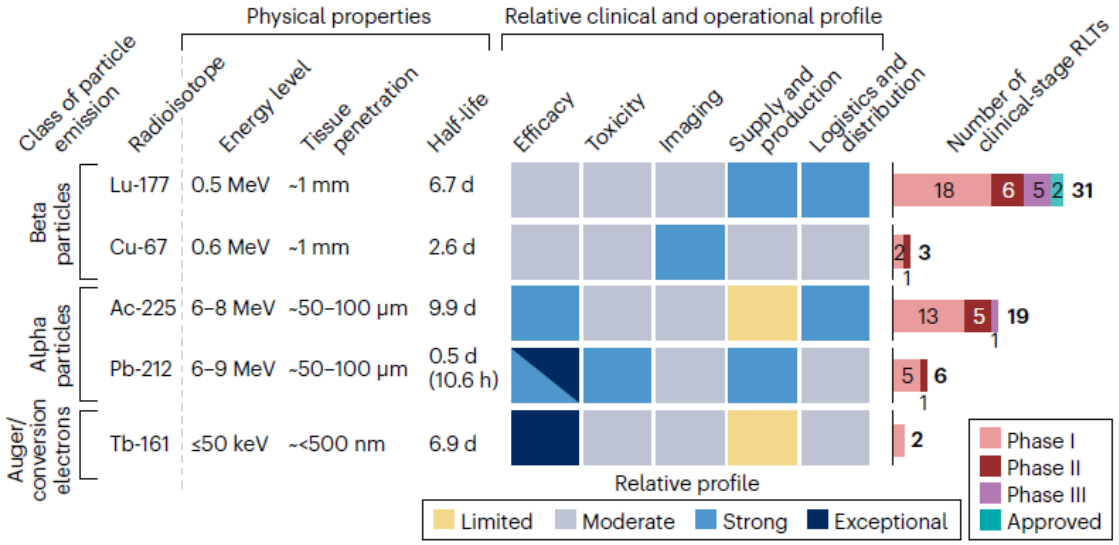


Fig. 1 | Radioisotopes used in clinical-stage radioligand therapies. Radioisotopes categorized by particle emission type, along with associated physical properties, an evaluation of their relative clinical and operational profiles, and prevalence in clinical-stage radioligand therapies.

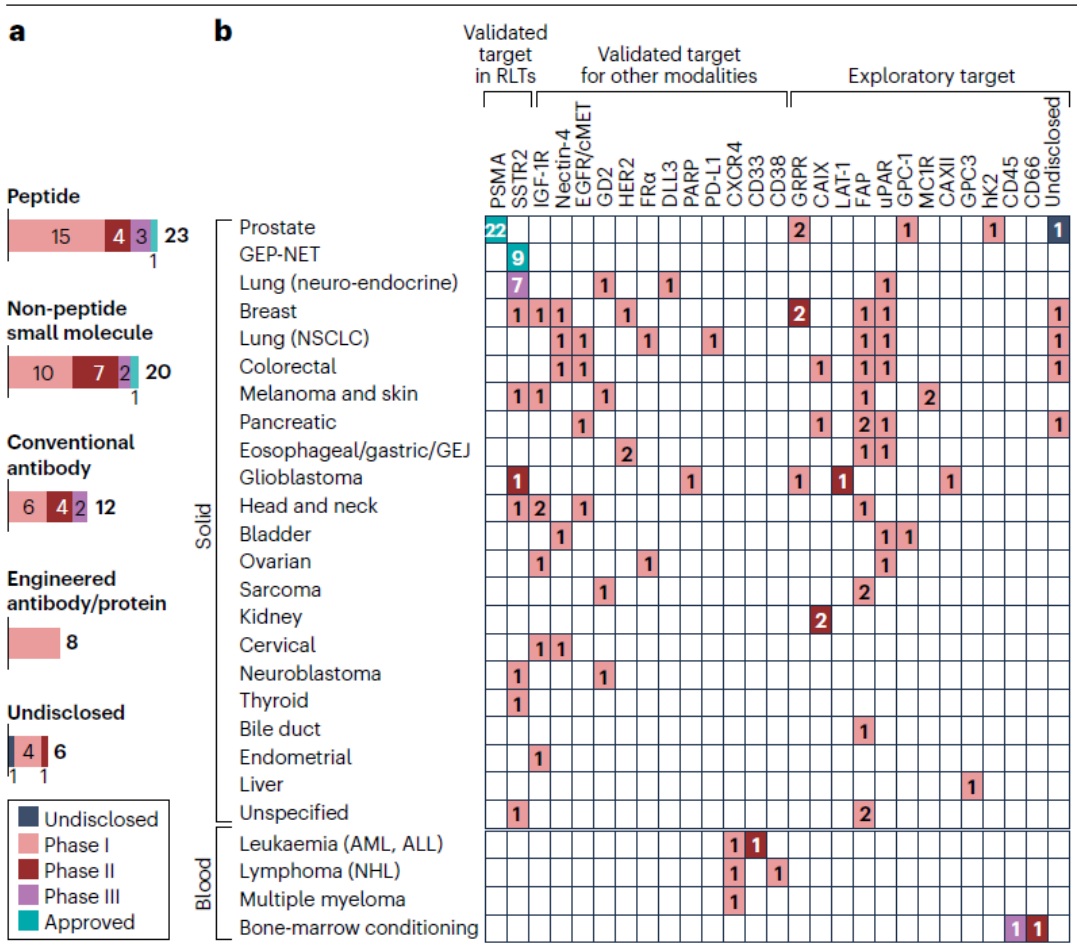


Fig. 2 | Clinical-stage radioligand therapies by targeting moiety, target and tumour type. a, Targeting moieties. **b**, Targets and tumour types. Number and colour represent the number of assets and the most advanced development stage for that tumour–target pair respectively; a single asset can be represented in multiple tumour–target pairs.

Source: https://www.nature.com/articles/d41573-025-00096-w

Paracetamol (acetaminophen) use during pregnancy and autism risk: Evidence does not support causal association

Louwen F, Deuster E, McAuliffe FM, Jacobsson B, Geary M, Fleischman S, Kihara AB., *Int J Gynaecol Obstet.* Sep 30, 2025.

Recent political statements linking paracetamol (acetaminophen) use during pregnancy to autism spectrum disorders have created concern among patients and healthcare providers worldwide. This editorial critically examines the scientific evidence, highlighting that the largest and most methodologically rigorous population-based studies employing sibling control analyses demonstrate no causal association between prenatal paracetamol exposure and neurodevelopmental disorders. While some observational studies have suggested potential weak associations, these findings likely reflect confounding by indication and familial genetic factors rather than actual causal relationships. The most robust evidence comes from a Swedish population-based study of 2.48 million children, which found no increased risk when controlling for familial confounding. Major international medical organizations including ACOG, RCOG, and FIGO, and regulatory agencies including the European Medicines Agency continue to recommend paracetamol as the safest analgesic option during pregnancy when clinically indicated. The established risks of untreated pain and fever during pregnancy significantly outweigh theoretical concerns based on methodologically limited studies. Healthcare providers should continue evidence-based counseling while avoiding unnecessary anxiety about this essential medication in obstetric practice.

Source: https://pubmed.ncbi.nlm.nih.gov/41028913/

The most comprehensive and methodologically sophisticated evidence on this topic comes from a Swedish population-based study published in *JAMA* in April 2024, analyzing 2.48 million children born between 1995 and 2019.[4] This study employed sibling control analysis—a methodology that controls for shared genetic and environmental factors within families—representing the gold standard for addressing confounding in observational research. The Swedish study's findings are clear: when familial confounding was properly controlled for through sibling analysis, there was no evidence of increased risk of autism (hazard ratio 0.98; 95% CI 0.94–1.02), attention-deficit/hyperactivity disorder (ADHD) (hazard ratio 0.98; 95% CI 0.95–1.01), or intellectual disability (hazard ratio 1.01; 95% CI 0.96–1.07) associated with paracetamol use during pregnancy.

This approach is particularly powerful given that siblings of children with autism have approximately a 20% likelihood of also receiving an autism diagnosis.[5] Importantly, when conventional analytical models suggested marginal associations (hazard ratios of 1.05–1.07), these associations completely disappeared in sibling analyses, demonstrating that previously reported associations likely reflect familial confounding rather than causal relationships.[6] Supporting evidence comes from a Japanese population-based study of over 200 000 children; this study also employed

Rethinking Alzheimer's: The Overlooked Role of Tiny Balls of Fat

Stanford Report, Sep 25, 2025 (excerpt)

When, in 1906, Dr. Alois Alzheimer conducted his landmark microscopic inspections of brain tissue from a patient whose dementia would become known as Alzheimer's disease, he observed not two but three defining aberrations. One was amyloid plaques, gummy blobs situated between brain cells and composed largely of the sticky substance A-beta.

… Alzheimer noticed a distinctive third feature in his autopsied patient's brain tissue: tiny oily spheres, not in neurons but within other brain cells called microglia. Unlike amyloid plaques and neurofibrillary tangles, both of which have become objects of intense focus on the part of neuroscientists, not much has been said about these microscopic fatballs.

To find out, Wyss-Coray and his associates used sophisticated but now-common methods to generate, in lab dishware, two batches of brand-new human microglia that were identical except for one thing: They carried different APOE gene variants in their genomes. One batch of microglia was APOE3/3, and the other was APOE4/4. Knowing that A-beta can induce formation of lipid droplets in microglia, the scientists added A-beta fibrils to separate culture dishes, one holding APOE3/3 microglia and the other containing APOE4/4 microglia. There ensued a ho-hum uptick in APOE3/3 microglia's overall lipid-droplet production, but a big jump in that process by their APOE4/4 counterparts.

Next, the scientists sorted their APOE4/4 microglia into lipid-droplet-rich and lipid-droplet-poor fractions and steeped the two collections in separate dishes full of nutrient broth. After 12 hours, they removed broth from both dishes and poured some from each dish, respectively, into one or the other of two other dishes containing lab-generated human neurons. To a third dish containing equivalent neurons, they added pristine nutrient broth unadulterated by microglial exposure. In neurons given broth from lipid-droplet-rich microglia, tau molecules became extremely prone to chemical modifications that are known to speed tau's clumping into neurofibrillary tangles. But this didn't occur to any appreciable extent in neurons bathed in broth from lipid-droplet-poor microglia – and not at all in neurons basking in straight-from-the-bottle, microglia-unsullied broth.

What's more, neurons bathed in the broth in which lipid-droplet-rich APO4/4 microglia had sat died in substantial numbers. This fate befell far fewer neurons steeped in lipid-droplet-poor microglia's bathwater. And there was no effect at all when, instead, the scientists bathed the lab-grown neurons in the broth of A-beta-exposed microglia that had, however, been bioengineered to knock their APOE gene entirely out of working order. Evidently, APOE is essential to something A-beta-annoyed microglia are spewing that harms neurons. What that something is, no one really knows yet. But scientists, including Wyss-Coray, want to find out, because this knowledge could open new avenues to treating or preventing the nerve damage that epitomizes Alzheimer's disease. Other promising therapeutic candidates might be compounds that put the brakes on microglial lipid-droplet formation without compromising all-important lipid production in all the body's hundreds of other cell types.

Source: https://news.stanford.edu/stories/2025/09/alzheimers-treatment-microglia-research

AZ: Working on T-Cell Engagers that Are CD8+ Specific

***Jacob Plieth, ApexOnco: Oncology Pipeline*, Oct 2, 2025 (excerpt)**

AstraZeneca's bold move to make T-cell engagement more precise, initially using a technology the group calls "Titan", has resulted in a new project that uses a fresh approach: AZD6621, a CD8-guided T-cell engager targeting Steap2, has just started its first-in-human study, according to clinicaltrials.gov.

The difference between this and two Titan-based T-cell engagers that entered clinical development over the past year is scientifically intriguing. However, a patent filing and poster at this year's AACR conference have revealed that the differences might merely represent a refinement of Astra's earlier approach, as the aim of the projects is similar.

In a nutshell, that aim is to reduce the propensity of T-cell engagers to cause cytokine-release syndrome (CRS). It's thought that CRS is largely derived from CD4+ (helper) T cells, and the problem might be that typical T-cell engagers like Columvi engage CD4+ as well as CD8+ (cytotoxic) T cells.

Selective CD8 targeting

This is where Titan, or target-induced T-cell activating nanobody, a technology Astra presented preclinically last year, comes in.

According to a LinkedIn post by Astra's senior vice-president Mark Cobbold, Titan aims to increase the specificity of the anticancer response by selectively engaging CD8+ T cells, which are characterised by the presence of the CD8 co-receptor, and make up a relatively small population of T cells.

While typical T-cell engagers comprise a bispecific antibody that hits a tumour-associated antigen plus CD3, the latter to engage T cells, a Titan-based project uses a multispecific approach. This involves designing a molecule with domains against the T-cell receptor (TCR) and the CD8 co-receptor, as well as two tumour-targeting domains.

The first Astra project that used this design was the anti-CD20 molecule AZD5492, which entered the clinic a year ago, and this was followed by AZD9793, which targets GPC3.

Now comes the anti-Steap2 project AZD6621, whose prostate cancer trial began this month. This molecule was apparently patented last year, and the patent filing also describes it as a CD8-guided T-cell engager, but one with an affinity-optimised CD3-binding domain instead of one targeting TCR.

Source: https://www.oncologypipeline.com/apexonco/astras-clash-t-cell-engager-titans

Regulators of CD8+ T Cell Exhaustion

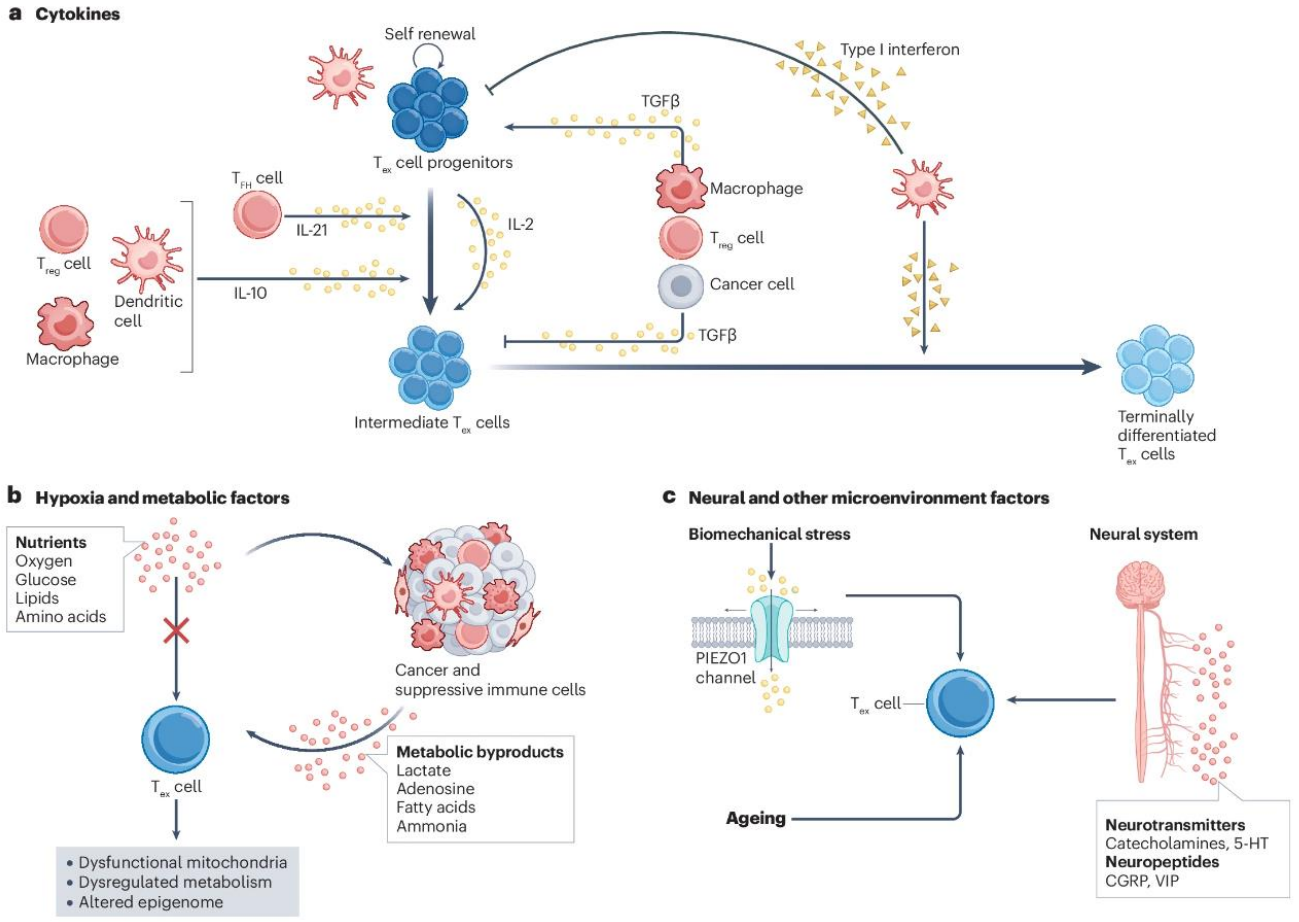
Qinli Sun and Chen Dong, Nature Immunology, Oct 1, 2025 (excerpt)

T cell exhaustion, as a result of persistent antigenic stimulation during chronic infection and cancer, represents an intricate and highly regulated differentiation process. Characterized by a progressive loss of T cell function, exhaustion is a major contributor to the failure to control infections and cancer. Recent work in this field has revealed the critical role of both environmental factors and intracellular regulators in this process; however, its complexity requires a multifaceted approach for a more complete understanding.

A critical aspect that requires further investigation is the spatial regulation of T cell exhaustion, particularly the role of microenvironmental cells in the specific niches such as tumour sites or chronically infected tissues. In particular, the formation, maintenance and differentiation of Tex cell progenitors within distinct tissue microenvironments remain underexplored. Understanding how these environmental factors influence the exhaustion process will be key to developing strategies that target Tex cells within tissue-specific contexts. Moreover, significant barriers remain in translating promising preclinical findings into successful therapeutic outcomes in human patients, which are far more complex and heterogeneous than animal models. A deeper exploration of how therapeutic interventions can reprogramme Tex cells in the clinical setting is crucial.

Fig. 2: Microenvironmental regulation of CD8$^+$ T cell exhaustion.

From: Regulators of CD8$^+$ T cell exhaustion



Source: https://www.nature.com/articles/s41577-025-01221-x/

Regulators of CD8+ T Cell Exhaustion (continued)

Fig. 3: Transcriptional regulation of T_{ex} cell development and differentiation.

From: Regulators of CD8$^+$ T cell exhaustion

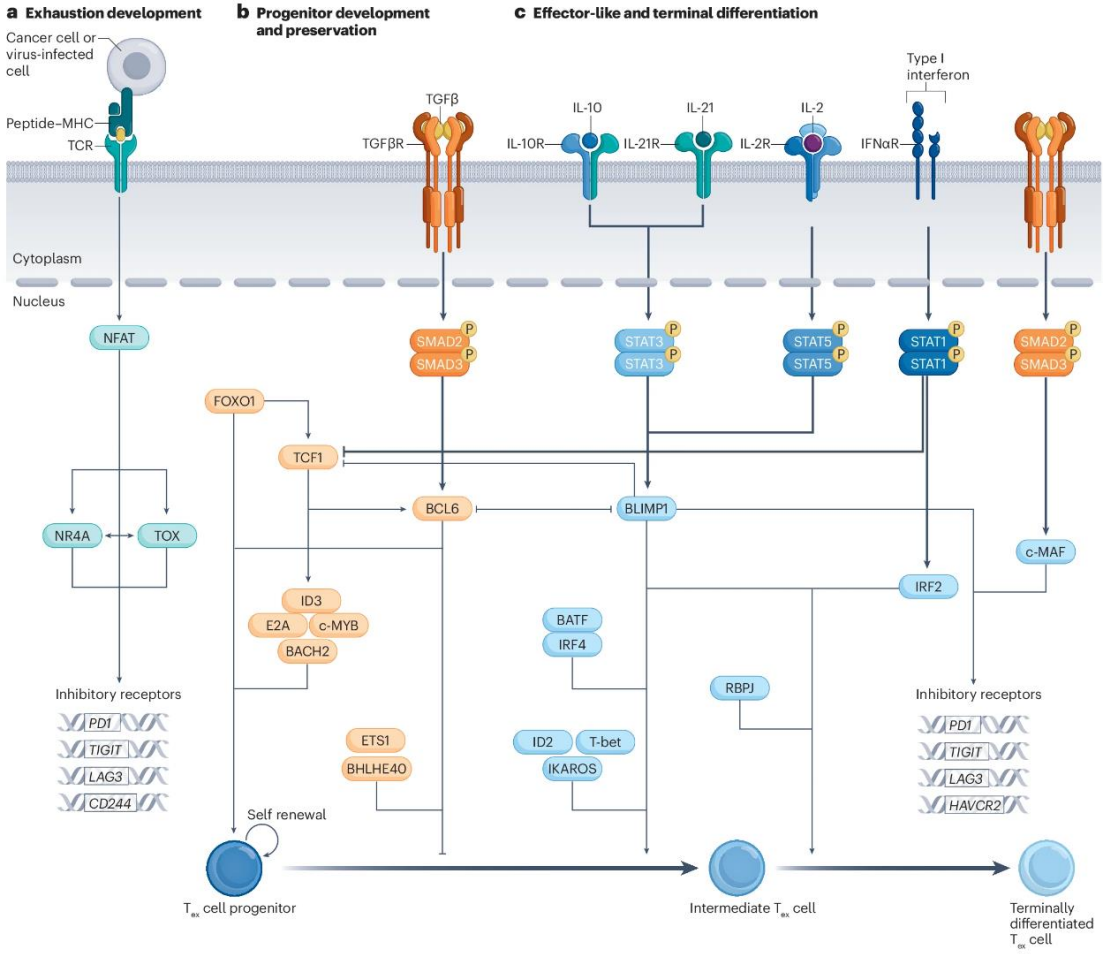
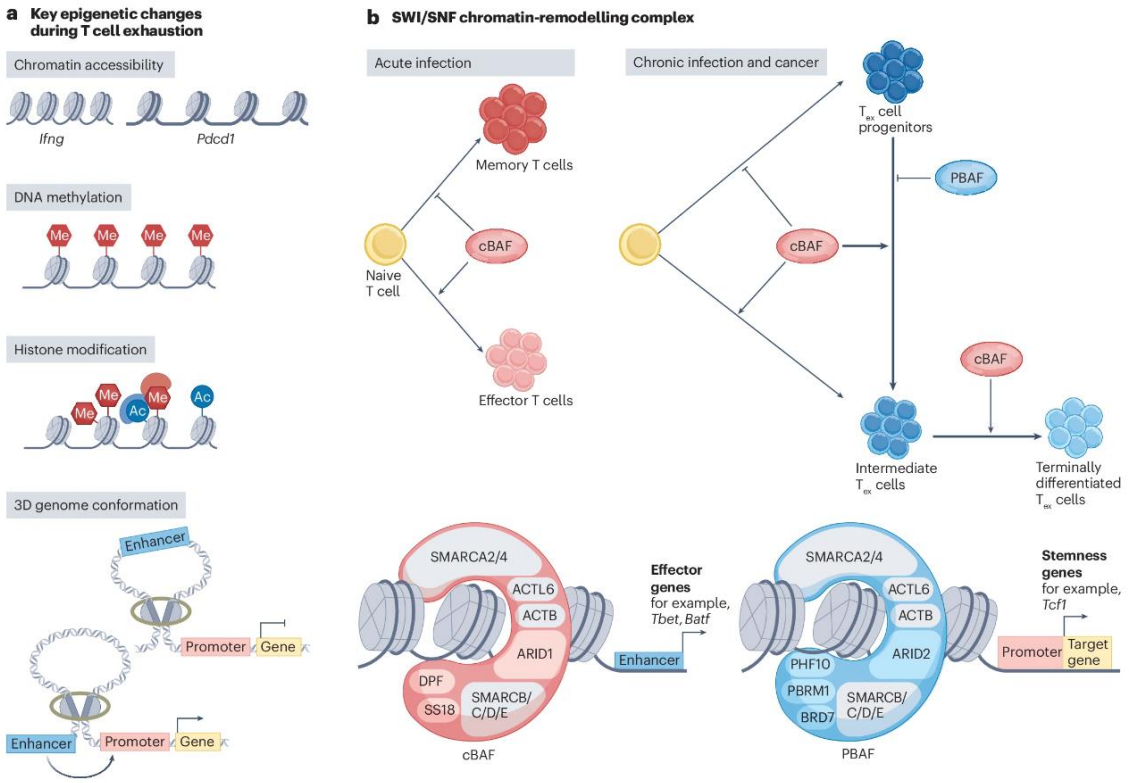


Fig. 4: Epigenetic regulation of CD8$^+$ T cell exhaustion.

From: Regulators of CD8$^+$ T cell exhaustion



Source: https://www.nature.com/articles/s41577-025-01221-x/

Proteotoxic Stress Response Drives T Cell Exhaustion and Immune Evasion

***Yi Wang et.al., Nature*, Oct 1, 2025 (excerpt)**

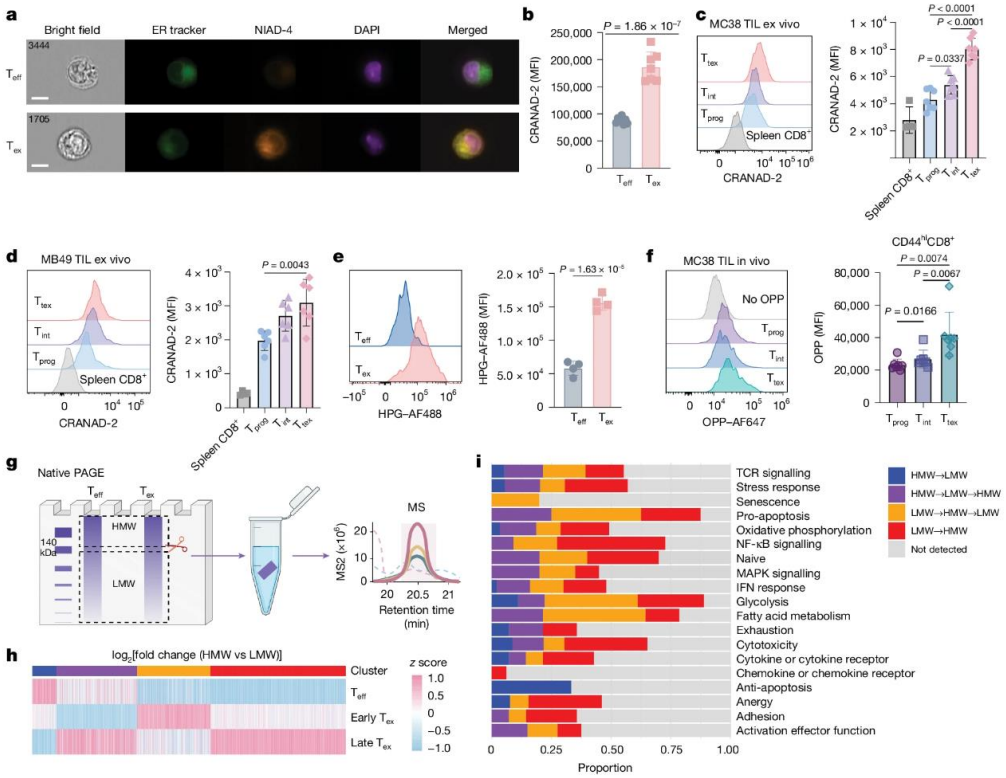
Chronic infections and cancer cause T cell dysfunction known as exhaustion. This cell state is caused by persistent antigen exposure, suboptimal co-stimulation and a plethora of hostile factors that dampen protective immunity and limit the efficacy of immunotherapies.

The mechanisms that underlie T cell exhaustion remain poorly understood. Here we analyse the proteome of CD8+ exhausted T (Tex) cells across multiple states of exhaustion in the context of both chronic viral infections and cancer. We show that there is a non-stochastic pathway-specific discordance between mRNA and protein dynamics between T effector (Teff) and Tex cells. We identify a distinct proteotoxic stress response (PSR) in Tex cells, which we term Tex-PSR.

Contrary to canonical stress responses that induce a reduction in protein synthesis, Tex-PSR involves an increase in global translation activity and an upregulation of specialized chaperone proteins. Tex-PSR is further characterized by the accumulation of protein aggregates and stress granules and an increase in autophagy-dominant protein catabolism. We establish that disruption of proteostasis alone can convert Teff cells to Tex cells, and we link Tex-PSR mechanistically to persistent AKT signalling. Finally, disruption of Tex-PSR-associated chaperones in CD8+ T cells improves cancer immunotherapy in preclinical models. Moreover, a high Tex-PSR in T cells from patients with cancer confers poor responses to clinical immunotherapy. Collectively, our findings indicate that Tex-PSR is a hallmark and a mechanistic driver of T cell exhaustion, which raises the possibility of targeting proteostasis pathways as an approach for cancer immunotherapy.

Fig. 2: Chronic TCR stimulation disrupts proteostasis during T cell exhaustion.

From: Proteotoxic stress response drives T cell exhaustion and immune evasion



Source: https://www.nature.com/articles/s41586-025-09539-1

Mapping the Plasma Metabolome to Human Health and Disease in 274,241 Adults

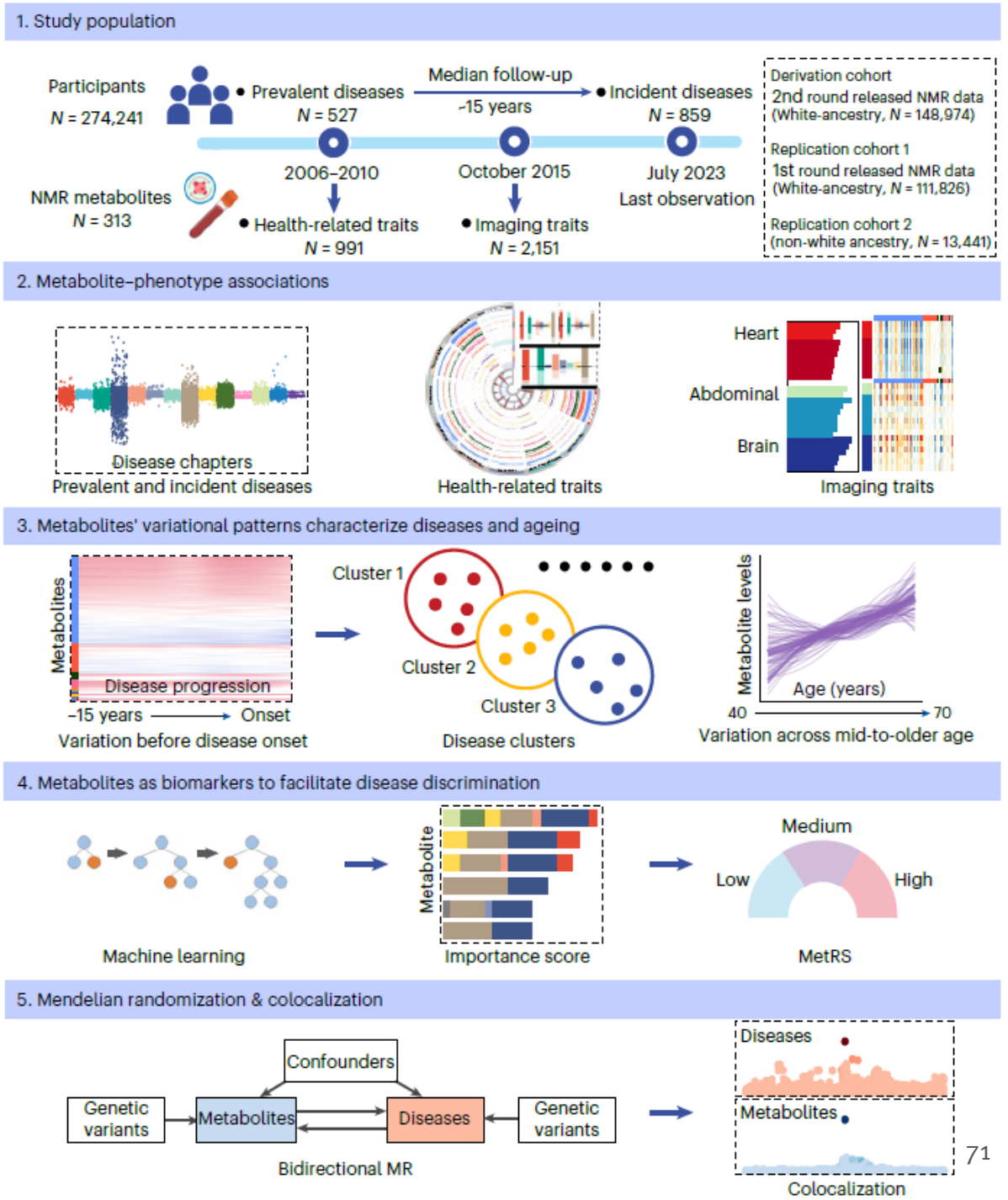
***Jia You et.al., Nature*, Sep 19, 2025 (excerpt)**

A systematic characterization of metabolic profiles in human health and disease enhances precision medicine. Here we present a comprehensive human metabolome–phenome atlas, using data from 274,241 UK Biobank participants with nuclear magnetic resonance metabolic measures. This atlas links 313 plasma metabolites to 1,386 diseases and 3,142 traits, with participants being prospectively followed for a median of 14.9 years. This atlas uncovered 52,836 metabolite–disease and 73,639 metabolite–trait associations, where the ratio of cholesterol to total lipids in large low-density lipoprotein percentage was found as the metabolite associated with the highest number (n = 526) of diseases.

In addition, we found that more than half (57.5%) of metabolites showed statistical variations from healthy individuals over a decade before disease onset. Combined with demographics, the machine-learning-based metabolic risk score signified the top 30 (around 10%) metabolites as biomarkers, yielding favourable classification performance (area under the curve › 0.8) for 94 prevalent and 81 incident diseases.

Finally, Mendelian randomization analyses provided support for causal relationships of 454 metabolite–disease pairs, among which 402 exhibited shared genetic determinants. Additional insights can be gleaned via an accessible interactive resource (https://metabolome-phenome-atlas.com/).

Source: https://www.nature.com/articles/s42255-025-01371-1



Manifold Bio: Barcoded Biologics

***Elliott Hershberg*, Sep 28, 2025 (excerpt)**

In biology, great technologists have a way of measuring the unmeasurable. And Manifold had done just that.

They had fifty antibody medicines, each carefully designed to traffic across the blood-brain barrier and dissolve the plaques thought to drive the progression of Alzheimer's disease.

But testing each antibody would require over five hundred monkeys. Even if they could procure this many animals, the cost—both financially and ethically—would be enormous.

Instead, Manifold ran the study with a molecular sleight of hand. Using their protein barcoding system, they resolved the distribution of each drug in the body in parallel, requiring an order of magnitude less animals. And what they saw was incredible.

As Jack Scannell observed in 2012, despite all of these extraordinary developer tools, "the number of new drugs approved per billion US dollars spent on R&D has halved roughly every 9 years since 1950, falling around 80-fold in inflation-adjusted terms."

In one of his "diagnoses" for this decline in efficiency, Scannell points to "The 'basic research–brute force' bias." We have a tendency to over-invest in the discovery technologies that can be rapidly scaled and industrialized. But the ability to be scaled doesn't necessarily correlate with a tool's ability to help successfully predict a drug outcome.

Manifold Bio has a vision to change that.

Founded in 2019 during the onset of the COVID pandemic, Manifold got started with nothing more than a small team and an idea. What if we could point our exponentially improving DNA technologies at the bottlenecks that come after we find drug starting points? What if we could test massive numbers of drug candidates in a single animal experiment?

Fast forwarding to the present moment, this is no longer just theory.

Using sophisticated molecular engineering, Manifold has built a drug discovery platform capable of screening over 100,000 antibodies in the type of in vivo experiments in organisms that would typically test one antibody. Narrower screens can resolve over 1,000 antibodies in the body at a resolution so precise it would be like detecting a single grain of sugar in over 120 Olympic-size swimming pools.

Along the way, Manifold has raised over $70M, recruited word-class drug discovery talent, and developed a pipeline of promising drug candidates that aim to precisely target one of the most challenging organs to develop biologics for: the brain.

Just like the industry's evolution, Manifold's story involves a number of crucial—and often serendipitous—insights and pivots stacking on top of each other to arrive at their current position.

Source: https://centuryofbio.com/p/manifold

Manifold Bio (continued)

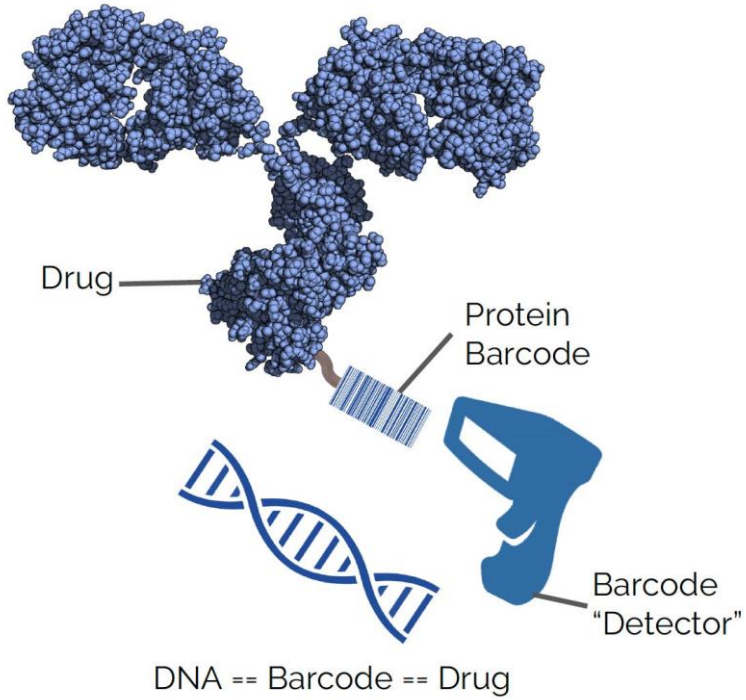
Using ML², they'd screen a massive number of antibodies against a massive number of antigens in a giant all-by-all experiment. By screening every antibody against every antigen, they could find antibody-antigen pairs that were highly specific to each other.

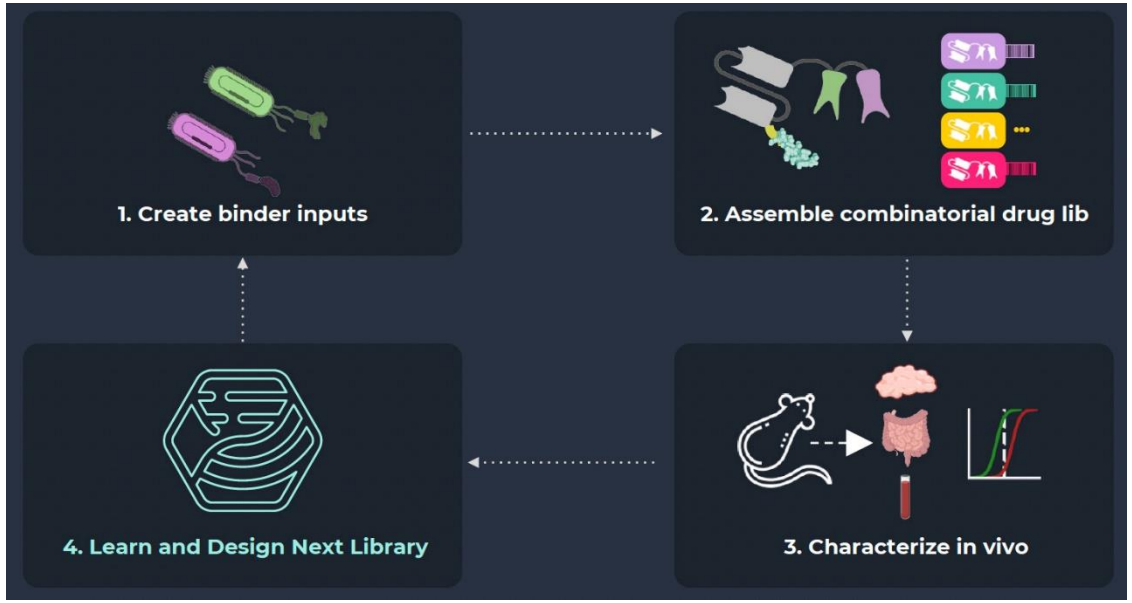
It would be like building a big set of lock-and-key pairs.

Now, what if they could discretely put the key (antigen) on an antibody they wanted to track?

And what if they attached DNA to the lock (antibody) that would bind it?

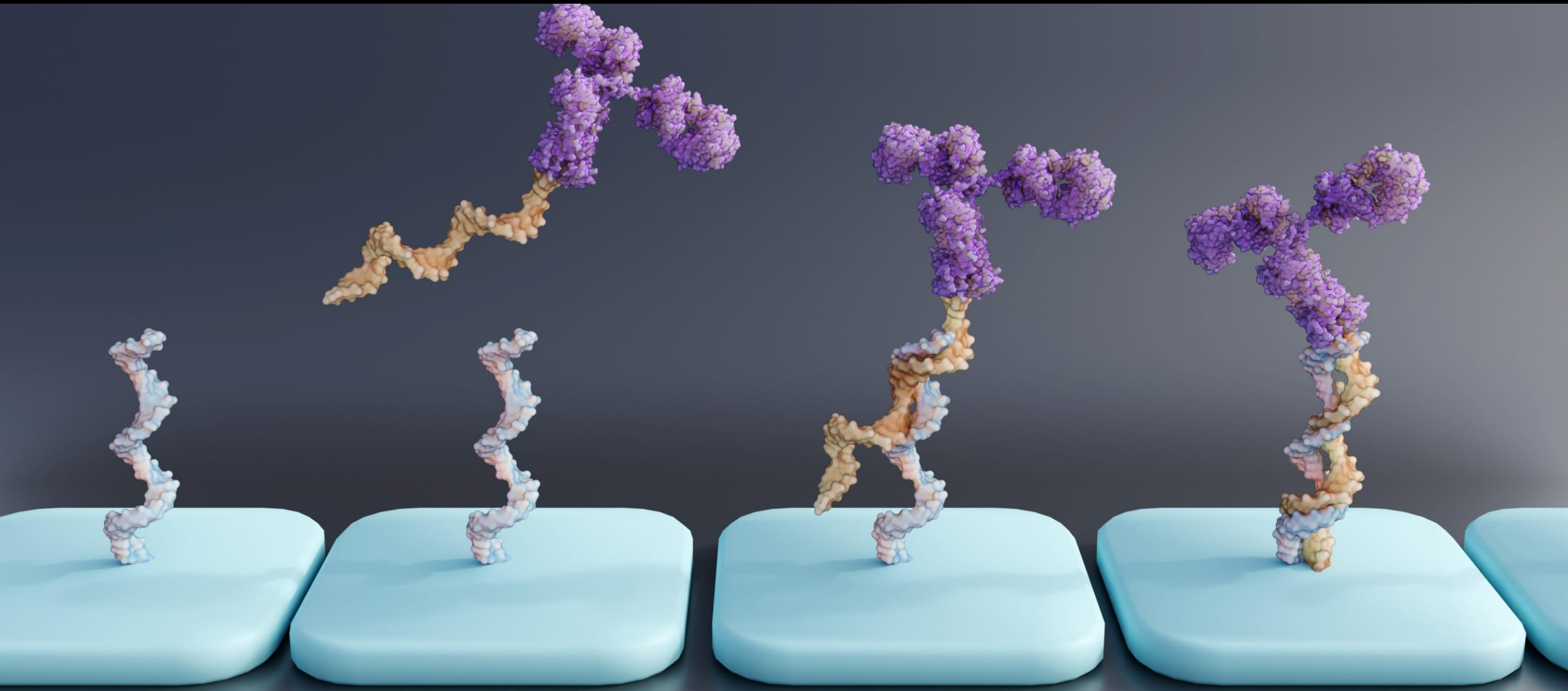
This would convert antibody measurement into a DNA barcode detection problem just like for AAV.





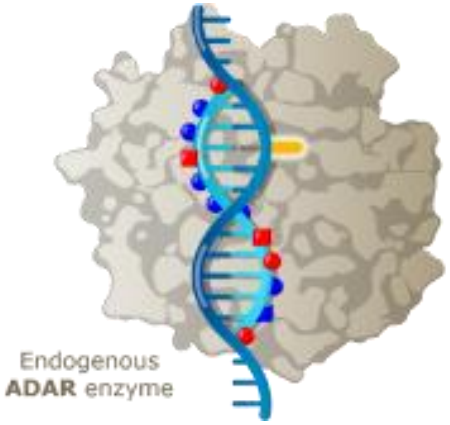
Source: https://centuryofbio.com/p/manifold

RNA Therapeutics Update

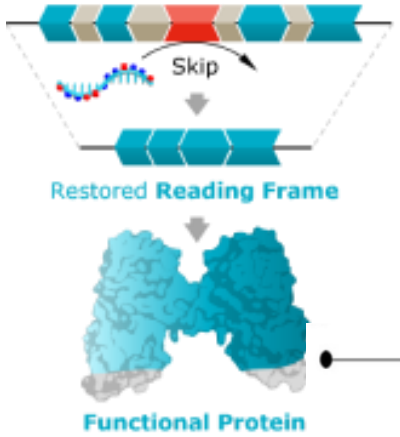


Key Approaches for RNA Therapeutics

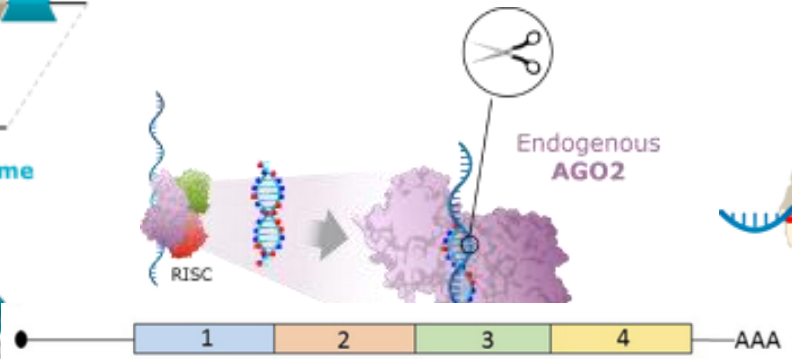
RNA Editing



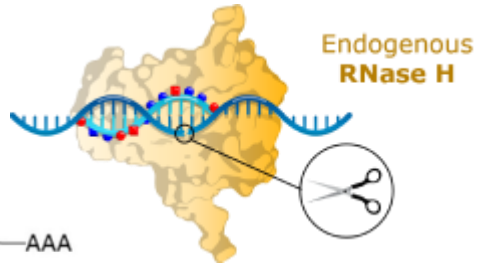
RNA Splicing



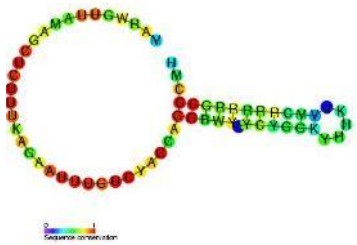
RNAi Silencing



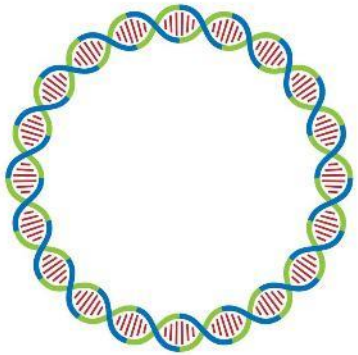
ASO Silencing



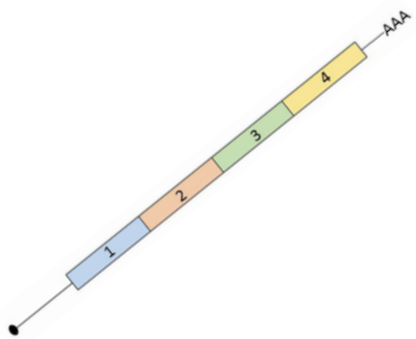
snRNA / U7 RNA



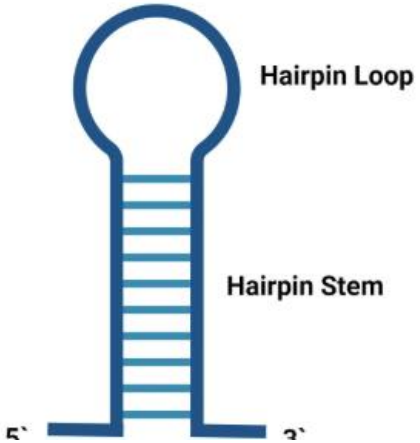
Circular RNA



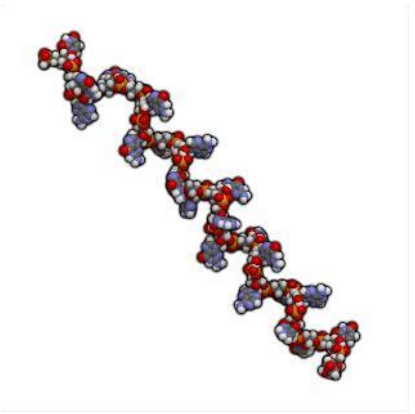
Linear mRNA



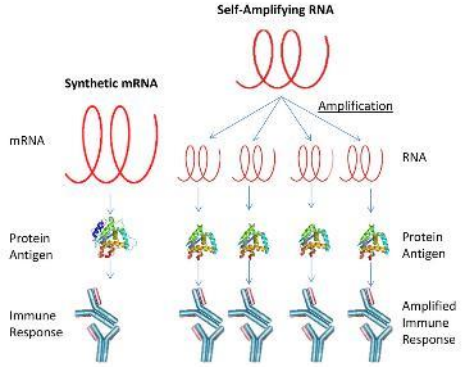
Short Hairpin RNA



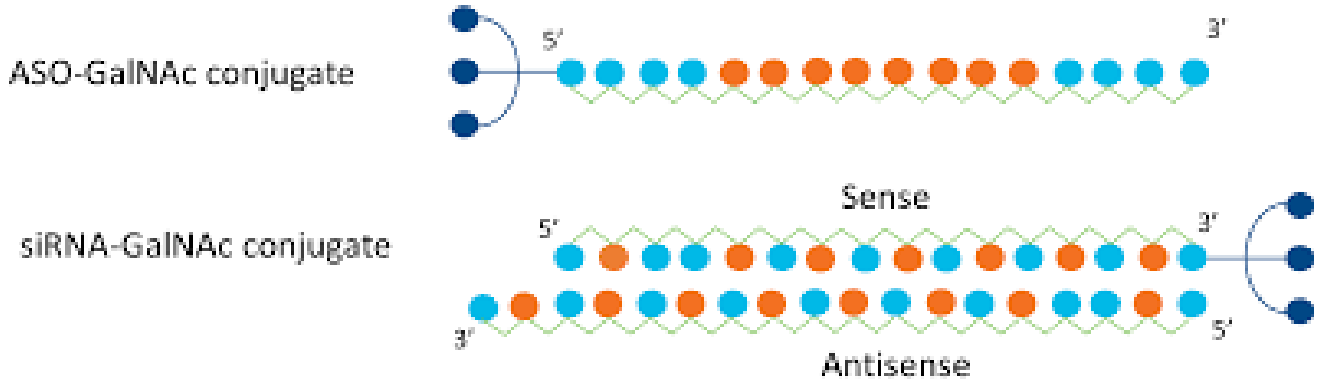
microRNA



saRNA

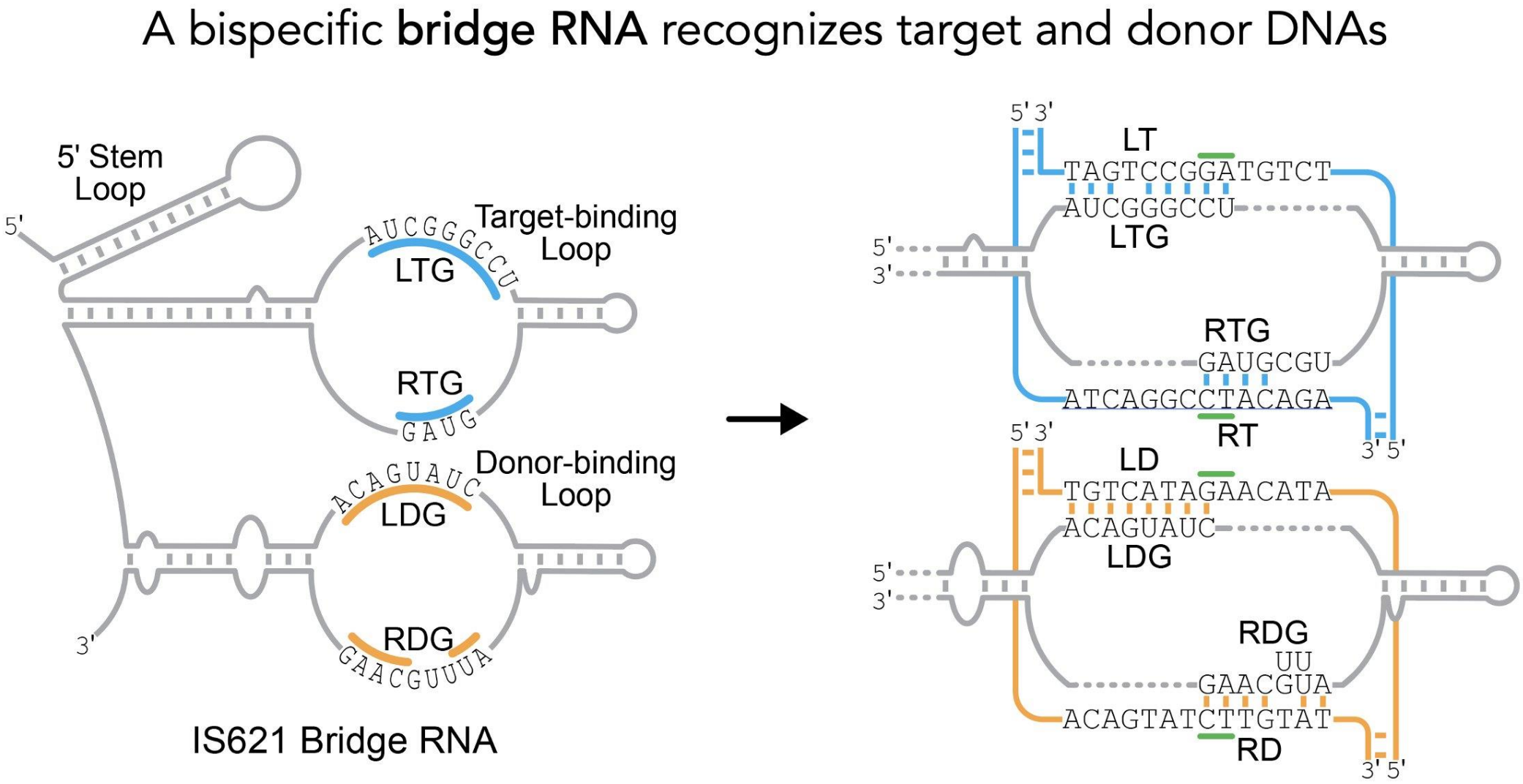


ASO vs. RNAi



Feature	ASOs (Antisense Oligonucleotides)	siRNAs (Small Interfering RNAs)
Mechanism	Binds single-stranded RNA to degrade via RNase H or modulate splicing	Forms RNA-induced silencing complex (RISC) for mRNA cleavage
Location of action	Primarily nucleus or cytosol	Cytoplasm
Stability	Generally more susceptible to nuclease degradation	More stable with proper modification
Delivery	Often direct delivery (e.g., intrathecal) or conjugated	Conjugated (e.g., GalNAc) or LNP-formulated
Off-target effects	More prone to off-target hybridization	Off-target effects via seed region and immune activation

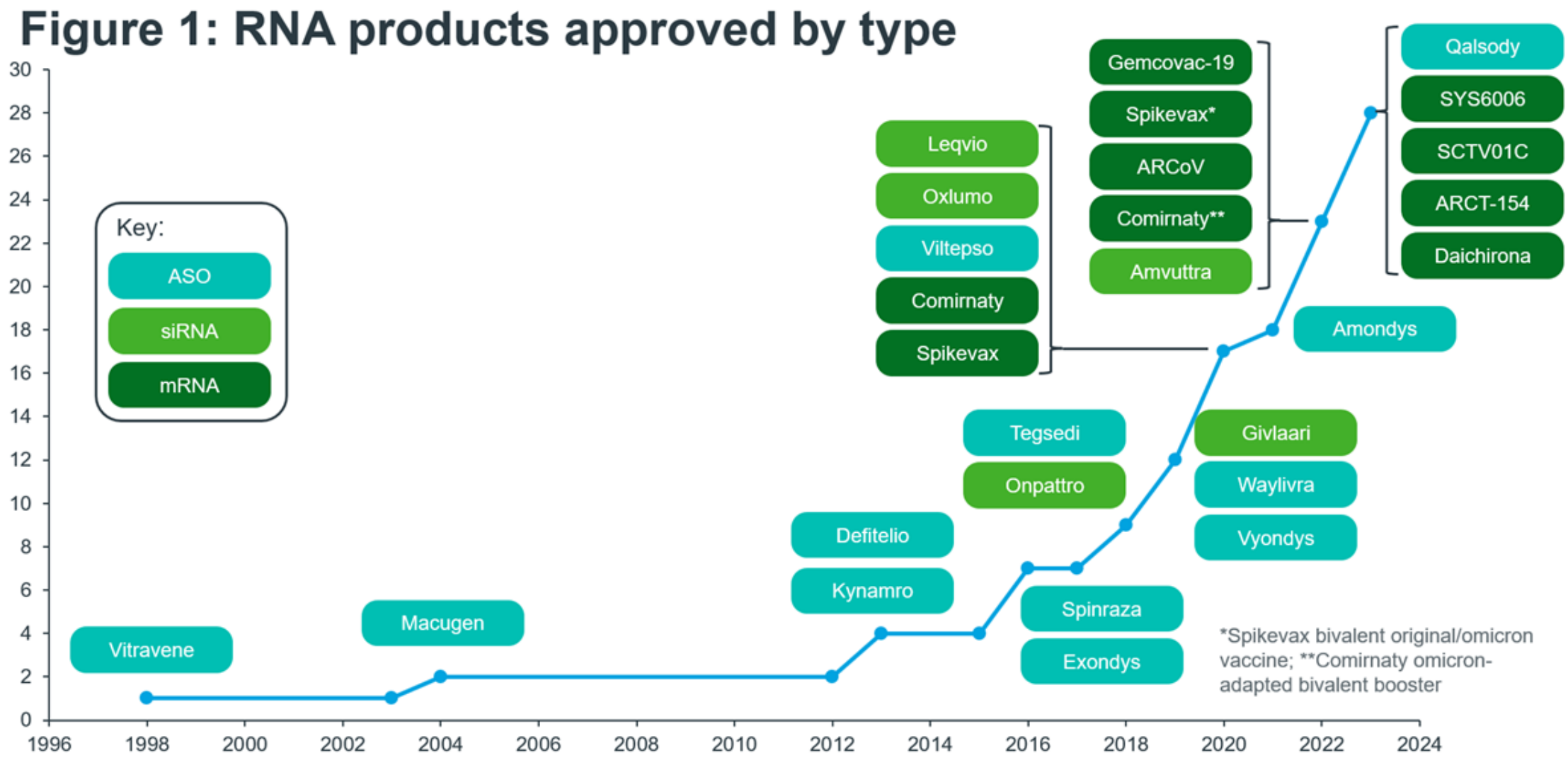
Bridge RNA Facilitates Multispecifics



We Are Learning How to Target Specific Tissue Types

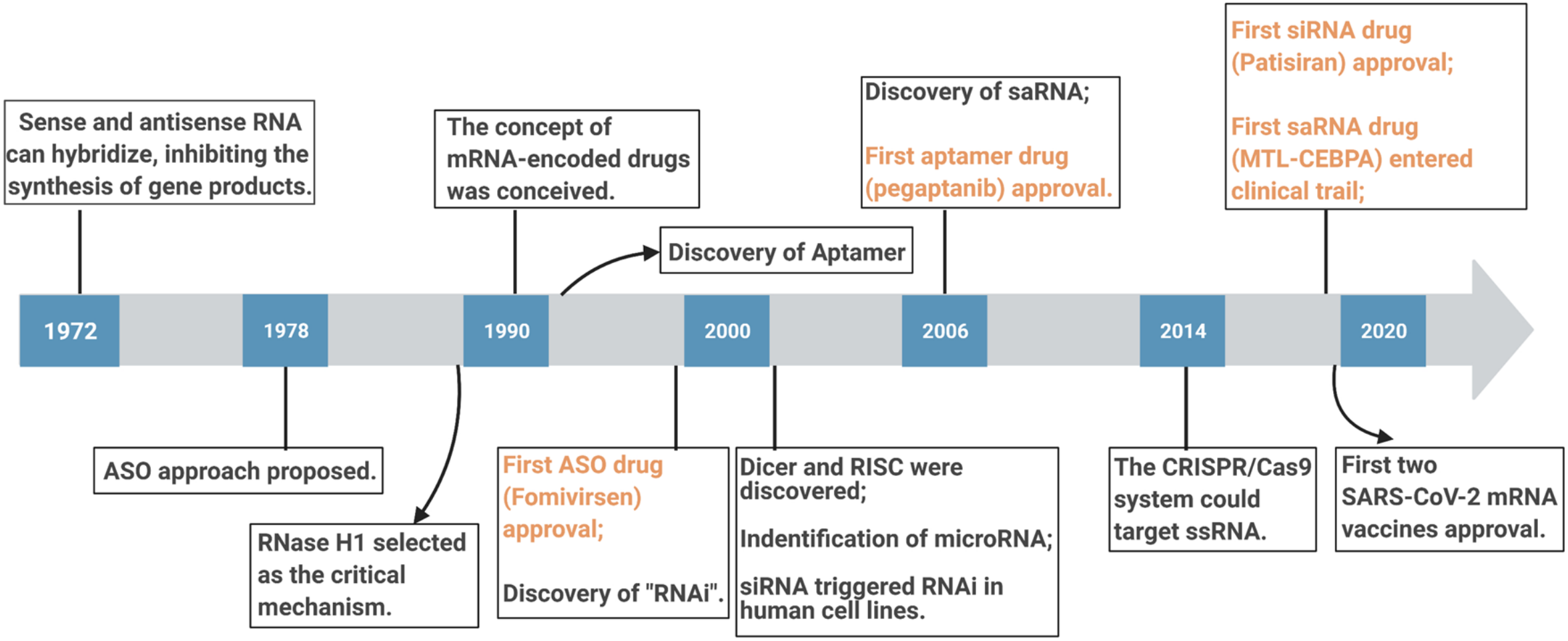
Target Tissue	Delivery Challenge	Targeting Strategy / Ligand	Mechanism	Key Developers / Examples	Clinical Stage
Liver	High uptake needed; must avoid off-target tissues	GalNAc (triantennary N-acetylgalactosamine)	Binds ASGPR receptor on hepatocytes	Alnylam, Ionis, Dicerna, Arrowhead	Widely approved (Leqvio, Givlaari, etc.)
CNS (brain / spinal cord)	Blood-brain barrier (BBB) blocks systemic entry	TfR-targeted proteins / ligand-conjugated RNAs	Receptor-mediated transcytosis across BBB	ADARx, Denali (TV platform), Biogen, Sanofi	Clinical (biologics); preclinical (ASOs)
CNS (Brain)	Blood-brain barrier (BBB) blocks systemic entry	Cell-penetrating peptides (CPPs), brain-homing peptides	Passive or active transport, BBB modulation	Atalanta, Entrada, Aro Bio, City Therapeutics	Preclinical/Early Phase 1
CNS (Brain)	BBB blocks entry	Engineered LNPs	BBB-penetrant or focused lipid chemistry	Acuitas, Arcturus, Versantis	Preclinical
Muscle / Heart	Poor endocytosis, high perfusion, no GalNAc-equivalent	Antibody-Oligo Conjugates (AOCs)	Targets muscle-specific receptors (e.g., TfR1)	Avidity, Dyne, Entrada	Phase 1–2 (AOC 1001)
Muscle / Heart	Poor endocytosis, high perfusion, no GalNAc-equivalent	Peptide-Oligo Conjugates (POCs)	Tissue-homing peptides (integrins, etc.)	PepGen, Ionis (neuromuscular)	Preclinical/Phase 1
Kidney	No obvious receptors for delivery	Kidney recycling receptors (like ASPGR)	Receptor-mediated uptake	Judo Bio	Preclinical

IQVIA: Multiple RNA Product Approvals



Source: https://www.iqvia.com/blogs/2023/11/rna-therapeutics-rewriting-the-script-of-medical-treatments

History of RNA Drug Development

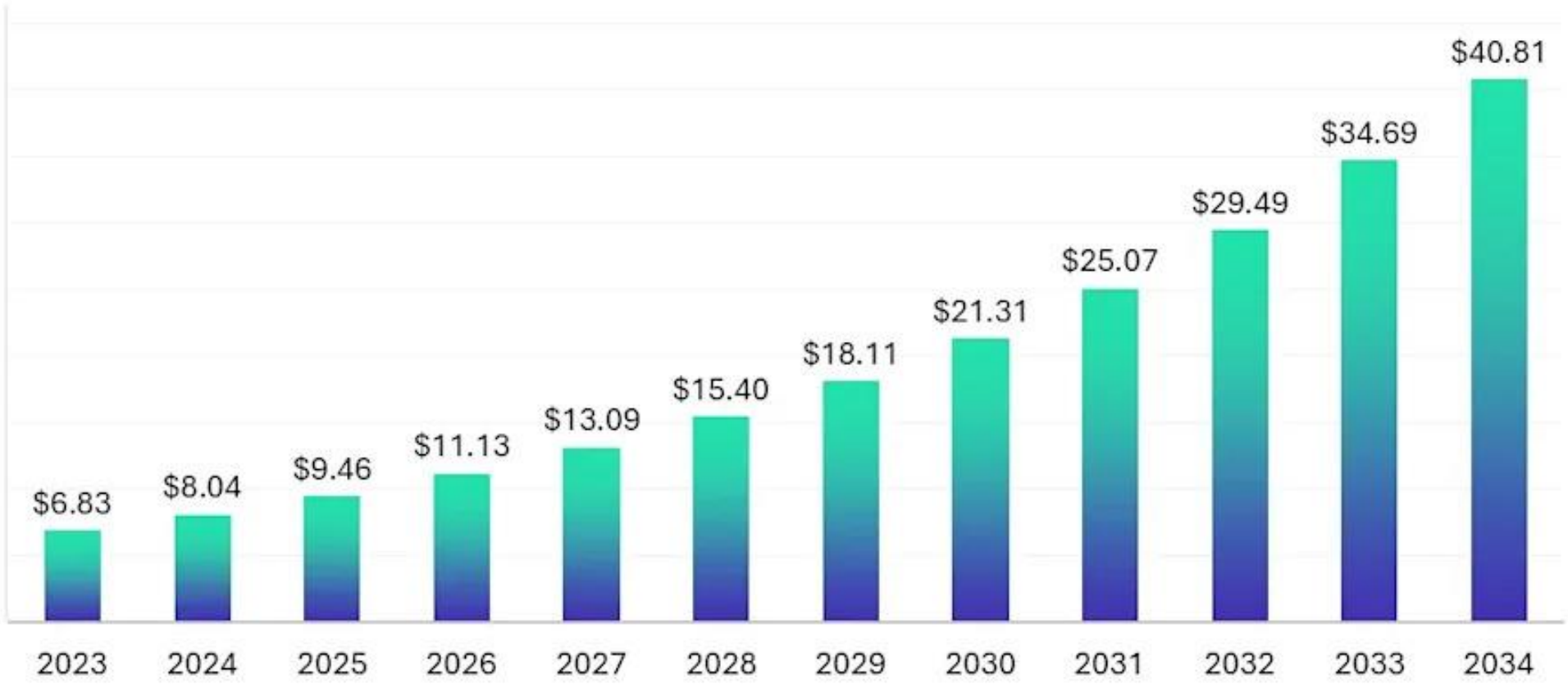


Source: https://www.nature.com/articles/s41419-022-05075-2

Large Market Opportunity for RNA Therapies

Towards HEALTHCARE

RNA Based Therapeutic Market Size 2023 to 2034 (USD Billion)



https://www.towardshealthcare.com/

Top Fifteen Publicly Traded RNA Therapeutics Pure Play Companies

Company Name	Ticker	Year Founded	Core Technology	Lead Program	Stage of Development of Lead Program	Enterprise Value (Oct 3, 2025, $mm)	Market Cap (Oct 3, 2025, $mm)	Comment
Alnylam	ALNY	2002	RNAi	Amvuttra / ATTR Amyloidosis	Commercial	$59,700	$59,818	The RNAi pioneer with 5 marketed products; big potential in ATTR cardiomyopathy.
IONIS	IONS	1989	ASO	Olezarsen / FCS	Commercial	$10,713	$11,022	Long-time leader in RNA modulation; multiple marketed ASO drugs (Spinraza, Tegsedi, etc.).
BIONTECH	BNTX	2008	mRNA	BNT122 / cancer vaccine	Commercial	$9,192	$25,360	Focused on cancer and applications of Mrna
AVIDITY BIOSCIENCES	RNA	2012	RNA Conjugates	AOC 1001 / Myotonic dystrophy type 1	Phase 2	$5,574	$6,752	Targets muscle and rare diseases (AOC 1001, 1044). Uses antibody-guided siRNA delivery.
arrowhead pharmaceuticals	ARWR	2003	RNAi	Plozasiran / Hypertrigliceridemia	Phase 3	$4,806	$4,994	Liver and extrahepatic delivery (AIM™ platform); partnerships with Amgen, Takeda, Horizon.
moderna	MRNA	2010	mRNA	mRNA-1083 / COVID-19 + flu vaccine	Commercial	$4,321	$11,085	mRNA vaccine leader
OliX Pharmaceuticals	KOSDAQ: A226950	2003	RNAi	OLX101A / Hypertrophic Scar	Phase 3	$1,312	$1,327	RNAi therapeutics for dermal, ophthalmic, and pulmonary diseases
Dyne THERAPEUTICS	DYN	2017	RNA Conjugates	DYNE-101 / Myotonic dystrophy type 1	Phase 2	$1,295	$1,858	Focused on myotonic dystrophy and Duchenne muscular dystrophy; early daa
WAVE LIFE SCIENCES	WVE	2012	RNAi	WVE-006 / AAT Deficiency	Phase 2	$960	$1,138	Works on stereopure oligos and RNA editing using ADAR mechanisms.
STOKE THERAPEUTICS	STOK	2014	RNA splice modulation	Zorevunersen / Dravet Syndrome	Phase 3	$940	$1,300	TANGO platform for splice modulation with RNA therapies. Upregulates gene expression for severe diseases.
ARCTURUS therapeutics	ARCT	2013	RNAi	ARCT-154 / Covid + Flu Vaccine	Phase 3	$443	$613	Works on mRNA vaccines and therapeutics, including self-amplifying mRNA.
KORRO BIO	KRRO	2018	RNA editing	KRRO-110 / AAT Deficiency	Phase 1	$434	$359	RNA editing for the treatment of rare and highly prevalent diseases in the United States
PepGen	PEPG	2018	RNA splice modulation	PGN-EDO0051 / DMD	Phase 2	$353	$296	RNA therapies for severe neuromuscular and neurologic diseases
ProQR	PRQR	2012	RNA editing	AX-0810 / Cholestatic Disease	Phase 1	$258	$137	Uses axiomer platform to design RNA therapies for rare diseases
SILENCE THERAPEUTICS	SLN	1994	RNAi	SLN 360 / Lipoprotein(a)	Phase 2	$122	$236	Hepatic and cardiovascular targets; partnerships with AstraZeneca and Hansoh.

Source: Stifel Analysis and S&P CapitalIQ

Fifteen Largest Private Financings for RNA Therapeutic Biotechs, 2021 to 2025

Company	Financing Date	Amount Raised ($mm)	Series	Lead Investor	Core Technology	Stage at Financing	Main Therapeutic Area
ReNAgade Therapeutics	05/23/2023	$300	Series A	MPM BioImpact	Circular RNA	Discovery Stage	Unknown
Orbital Therapeutics	04/26/2023	$270	Series A	ARCH Venture	In Vivo CAR-t via RNA	Discovery Stage	Autoimmune
ReCode Therapeutics	10/21/2021	$250	Series B	Pfizer Venture	Targeted delivery of genetic medicines	Pre-IND	Pulmonary
ADARx Pharmaceuticals	08/09/2023	$200	Series C	Bain Capital LS	RNAi for deep protein knock down	Pre-IND	Endocrine
Borealis	08/22/2024	$180	Series A	Versant	RNA therapeutics for kidney disease	Discovery Stage	Renal
AiRNA	04/01/2025	$155	Series B	ARCH / Forbion	RNA editing for rare disease	Discovery Stage	Rare Disease
Strand Therapeutics	08/07/2025	$153	Series B	Kinnevik	Self-amplifying RNA platform	Discovery Stage	Cancer
City Therapeutics	10/08/2024	$135	Series A	ARCH Venture	Next-generation RNAi	Discovery Stage	Not Applicable
alltrna	08/09/2023	$109	Series B	Flagship	Transfer RNA	Discovery Stage	Stop Codon Disease
Immorna	03/01/2023	$100	Series A	GL Ventures	mRNA delivered in vivo CAR-t	Phase 1	Cancer
judobio	10/07/2024	$100	Series A	Atlas Venture	RNA Therapy for the Kidney	Discovery Stage	Other
Atalanta Therapeutics	01/28/2025	$97	Series B	EQT Life Sciences	RNAi for neuroscience	02 Preclinical / IND	Neurologic
ascidian	10/13/2022	$90	Series A	Apple Tree Partners	RNA editing	Pre-IND	Ophthalmic
AiRNA	09/19/2023	$90	Series A	ARCH Venture Partners	Fin - VC / Private Equity	Discovery Stage	Other
ARTHEx biotech	05/03/2023	$87	Series B	Columbus Venture	Fin - VC / Private Equity	Phase 2	Musculoskeletal

Source: DealForma and Stifel Research

Illustrative Interesting Company: Orbital

Orbital Therapeutics Presents Non-Human Primate Data for In Vivo CAR-T Therapy with Potential Best-in-Class Profile for Autoimmune Disease

Full B Cell Depletion Achieved in Blood, Spleen, and Lymph Nodes in Non-Human Primate Study

Data Supports the Nomination of OTX-201, a Novel In Vivo CAR-T Therapy, as Orbital's First Product Candidate

Company Plans to Advance OTX-201 Toward Clinical Development for B Cell-Driven Autoimmune Diseases in 1H'26

CAMBRIDGE, Mass. – July 22, 2025 – Orbital Therapeutics, a biotechnology company pioneering a new generation of RNA medicines that reprogram the immune system *in vivo* to treat disease at its source, today announced encouraging preclinical results supporting the development of its lead RNA immunotherapy candidate, OTX-201, at the 5th Annual mRNA-Based Therapeutics Summit in Boston, held July 21–23, 2025. Specifically, in a non-human primate study, Orbital's *in vivo* CAR-T approach achieved full B cell depletion in blood, spleen, and lymph nodes, which is required for an effective immune system reset in autoimmune disease. Based on preclinical findings to date, Orbital is advancing OTX-201 through IND-enabling studies and plans to begin clinical development in the first half of 2026. OTX-201 comprises an optimized circular RNA encoding a CD19-targeted CAR delivered via targeted lipid nanoparticles (LNPs) with in vivo administration.

Source: https://www.orbitaltx.com/orbital-therapeutics-presents-non-human-primate-data-for-in-vivo-car-t-therapy-with-potential-best-in-class-profile-for-autoimmune-disease/

Illustrative Interesting Company: Myeloid

Creating all-human single stranded RNA therapies that avoid immunogenic responses to in vivo therapies.

The first in vivo platform delivering repeat dosing, lineage flexibility, and scalable patient access

	MYELOID Therapeutics, Inc.	Other mRNA-LNP Platforms (capstan therapeutics, abbvie)	In Vivo Lentiviral CARs (interius, Kite, EsoBiotec, AstraZeneca)	Ex Vivo CAR-T (KYMRIAH (tisagenlecleucel), YESCARTA (axicabtagene ciloleucel))
Repeat Dosing	Yes	Limited	No	No
Transient CAR Expression	Yes, 8+ days	Yes, <5 days	No	No
Stable CAR Expression	Yes	No	Yes	Yes
Selective Programming	Yes	Limited	Limited	Yes
Scalability	Yes	Yes	Limited	No
Manufacturing cost	Low	Low	Medium	High
Accessibility	High	High	Medium	Low
Concept to Clinic Time	<12 months	2+ years	3+ years	4+ years

Source: https://myeloidtx.com/

Illustrative Interesting Company: Arrakis

Arrakis is planning to be in the clinic next year with a small molecular modulator of RNA.

Arrakis rSM platform build is complete: Lead program is novel RNA-targeted genetic medicine for DM1

THE FUTURE OF TARGET DISCOVERY IS RNA
RNA is **upstream of all biology** and the first explicitly RNA-targeted therapeutics are now in the market, but most RNA targets are **out of reach** of today's modalities

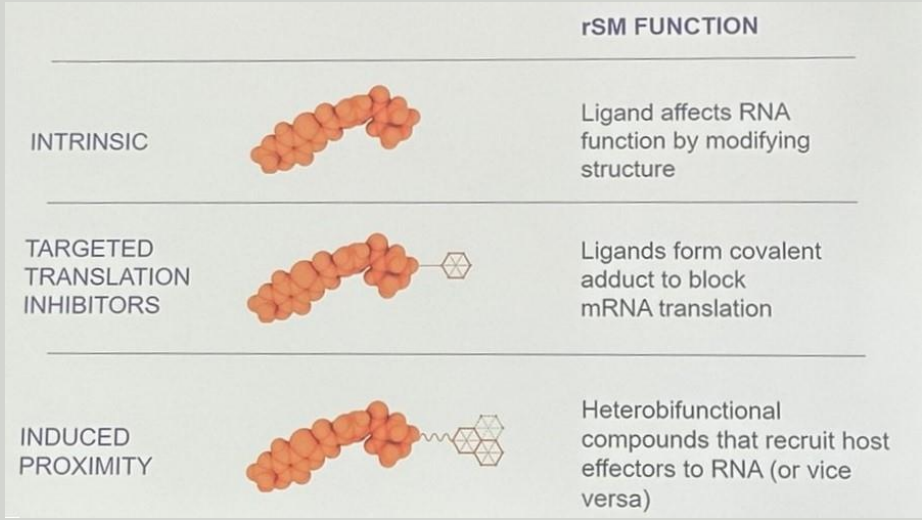
COMPREHENSIVE TECH STACK FOR RNA LIGAND DISCOVERY
Arrakis and its partners have invested $300M+ in building a highly differentiated platform for discovering **drug-like small molecule ligands** for RNA targets

FIRST LEAD PROGRAM FOR DM1 EXEMPLIFIES POTENTIAL OF THE PLATFORM
Arrakis RNA-targeted small molecules **address genetic root** of disease, displace MBNL1, disrupt nuclear foci and correct splicing defects in patient-derived cells, and **fully reverse myotonia** in animals following **oral delivery**; IND target 2H2026

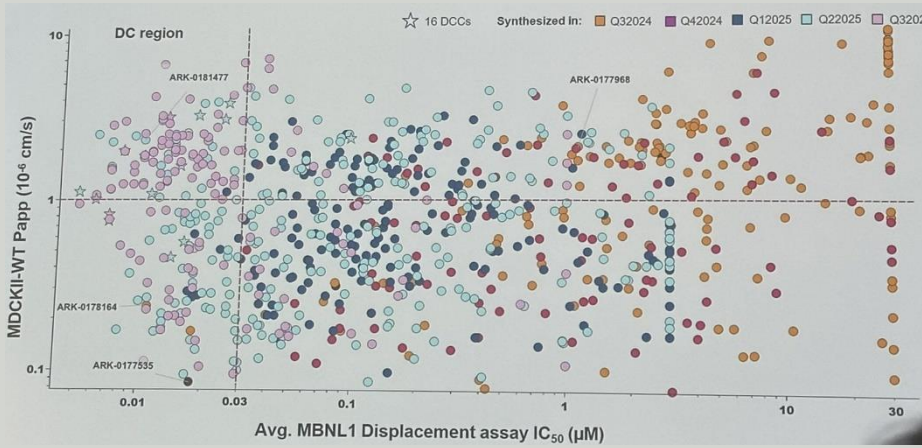
NEXT FRONTIER IS TRANSCRIPTOME-WIDE DRUG DISCOVERY
Arrakis is **expanding its reach** to the full transcriptome by extending the principle of **covalency** to achieve translational blockade of specific mRNA targets

©ARRAKIS THERAPEUTICS 2025 | 2

Multiple Approaches for Small Molecule RNA Drugs



Sophisticated Medicinal Chemistry Program



Source: Arrakis, Presentation, Zurich Switzerland, September 2025

RNAi Therapies Covering More Common Diseases

More Usage of RNAi for Common Diseases

Yes, this trend is expected to accelerate. Historically, **siRNA therapies** were limited to rare diseases due to delivery constraints and manufacturing costs. However, the success of **Leqvio (inclisiran)** for hypercholesterolemia and promising data from **Zilebesiran** (hypertension, Alnylam) and **Olpasiran** (Lp(a), Amgen) show that **chronic, prevalent diseases** can be effectively targeted if the dosing interval is long (e.g., twice-yearly), safety is high, and endpoints are clear. The platform's ability to **silence genes with high specificity and durability** makes it attractive for common diseases—particularly where **long-acting pharmacology** offers clinical or adherence advantages.

We are Learning to Get the Costs Down

The historical cost of a GALNAC therapy was over $1500 per dose.

Today, the lowest COGS that is reasonably being discussed is $200 (roughly) a dose for inclirisan.

We recently ran into a company in china that is creating **fast followers** in the RNAi field and is focused on getting the **COGS of this approach down dramatically** for cardiometabolic applications.

This cost-effective approach could enable this class of medicines for broader use. They believe that they can get cost down to less than $30 a dose using either of two China CDMOs.

Example: Big Excitement in RNA Therapies for Obesity

We are also excited by the new wave of RNA interference (RNAi) and nucleic acid therapies that silence genes which influence fat accumulation and metabolism. Arrowhead Pharmaceuticals leads with ARO-INHBE, an siRNA targeting *INHBE*, the gene encoding Activin E. Preclinical primate studies showed up to ~79% sustained protein reduction, with effects lasting at least 90 days, supporting quarterly dosing. Arrowhead has begun a Phase 1/2a study testing ARO-INHBE alone and in combination with tirzepatide to see if Activin E knockdown can amplify fat loss while sparing lean mass.

The company is also advancing ARO-ALK7, which targets ALK7, Activin E's receptor, into early human studies. Alnylam Pharmaceuticals is developing ALN-2232, another siRNA aimed at *ACVR1C* (ALK7), and a separate INHBE candidate, both in preclinical and early clinical stages with first-in-human trials expected in late 2025. Meanwhile, Wave Life Sciences has introduced WVE-007, a GalNAc-siRNA targeting INHBE that, in animal models, combined with semaglutide to more than double weight loss compared to semaglutide alone—an encouraging sign for future combination regimens.

Beyond siRNA, interest is rising in **microRNA** and **long non-coding RNA** (lncRNA) therapies. Resalis Therapeutics has begun a Phase 1 trial of RES-010, a lncRNA therapy designed to improve metabolic health in overweight adults, with first data expected in 2026. Together, these programs highlight how nucleic acid therapeutics could become powerful, durable complements—or alternatives—to incretin-based drugs in the next generation of obesity treatment.

Illustrative Interesting Company: Corsera Health

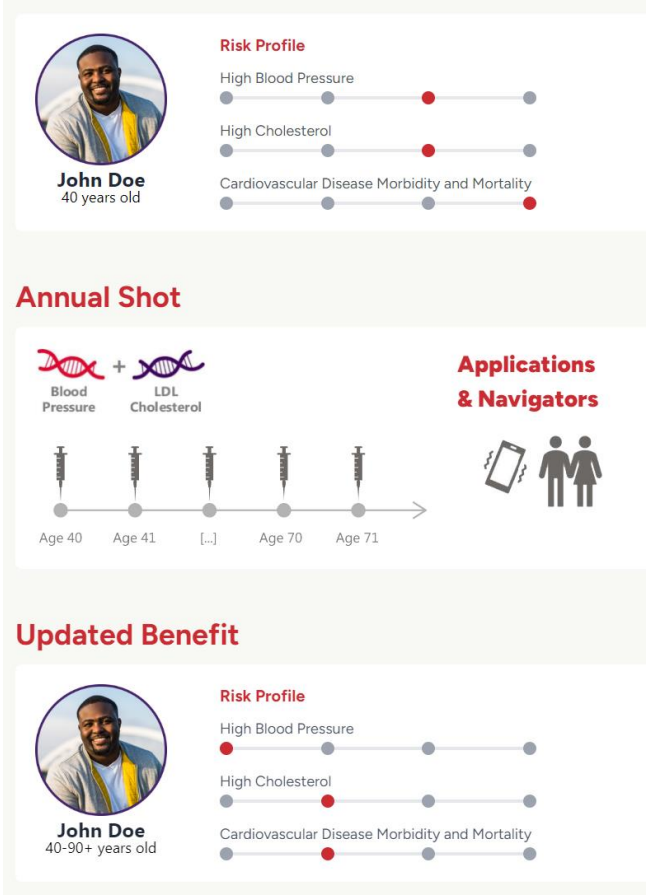
Multiple programs under development with a PSCK9 / AGT as the core pipeline item. The idea is that one annual shot can control a patient's blood pressure and cholesterol – hence reducing the key drivers of CVD.

High blood pressure and high LDL cholesterol are major drivers of cardiovascular disease and leading causes of global morbidity and mortality. Yet in current practice, treatment often begins only after these conditions have already developed. By then, years of exposure to disease-causing proteins may have caused irreversible harm, significantly increasing the short-term risk of cardiac events—damage that earlier intervention could have helped prevent. (ESC Congress 2025)

Treating these conditions typically requires multiple daily medications or frequent injections, creating a significant treatment burden.

At Corsera Health, our product development is powered by a robust scientific discovery engine enabling the development of preventive RNAi medicines. These are highly potent and specific siRNA molecules designed to be made at scale efficiently, and to silence the genes that drive these conditions. These include targets such as proprotein convertase subtilisin/kexin type 9 (PCSK9) and angiotensinogen (AGT)—both of which play critical roles in the insidious onset and progression of cardiovascular disease.

The development of these molecules is central to our prevention strategy, which integrates our predictive analytics with a once-annual dual-targeting intervention.



Source: https://corserahealth.com/science

We are Just Getting Started with RNA Technologies

Craig Mello and Darryl Conte, *Nature*, September 2024

The diversity of RNA silencing phenomena suggests that other interesting findings await discovery. For example, the existence of an inheritance mechanism for the transmission of RNAi in *C. elegans* raises the question of whether natural small RNAs are transmitted in germ cells or other developmental cell lineages in other animals, including humans. Extrachromosomal inheritance of silencing patterns by means of small RNAs could provide sophisticated layers of gene regulation, at both post-transcriptional and chromatin modifying levels. These small RNAs may be important in stem-cell maintenance and development, and differential localization of such RNAs may have a role in the generation of cellular diversity. The past ten years have seen an explosion in the number of noncoding RNAs found to orchestrate remarkably diverse functions.

These functions include: sequence-specific modification of cellular RNAs guided by small nucleolar RNAs; induction of chromosome wide domains of chromatin condensation by the mammalian noncoding RNA Xist (X-inactive specific transcript); autosomal gene imprinting and silencing by noncoding mammalian *Air* (antisense IgF2r RNA); and finally sequence-directed cleavage and/or repression of target mRNAs and genes by miRNAs and siRNAs, discussed here and in the accompanying reviews. Some have likened this period to an RNA revolution. But considering the potential role of RNA as a primordial biopolymer of life, it is perhaps more apt to call it an RNA 'revelation'. RNA is not taking over the cell — it has been in control all along. We just didn't realize it until now.

Craig Mello

Darryl Conte

Source: https://www.nature.com/articles/nature02872

Primary Care and Preventive Medicine

Just 4% of U.S. Healthcare Spend Goes to Primary Care

Jessica Chang, Bianca Silva Gordon, Catalina Desouza, Healthcare Cost Institute, September 17, 2025

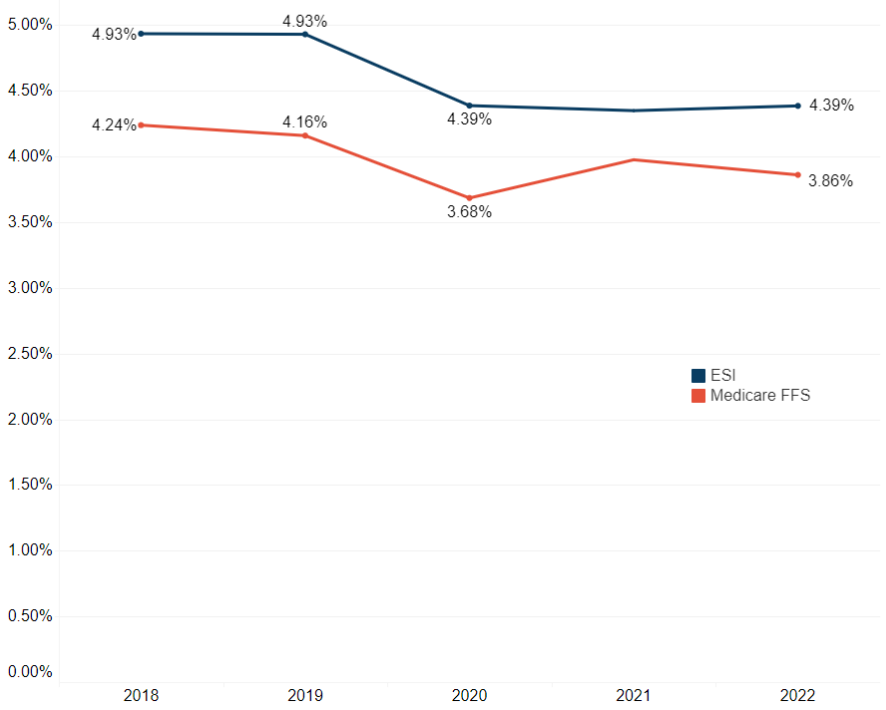
Primary care offers patients a critical connection point to the health care system. With contact, continuity, comprehensiveness, and coordination as its base1, primary care has been shown to improve health outcomes and population health, reduce health disparities, and save health care dollars. Despite the virtues and benefits of primary care, it seems to be getting harder to access. In 2025, there were 7,901 primary care health professional shortage areas. A recent report found that primary care physicians per capita declined between 2012 and 2021, and fewer trainees chose to pursue primary care than specialty care over the same period.

In response, a number of states are innovating to increase investment in primary care. By one estimate, nearly 20 states have taken action to improve primary care with initiatives ranging from defining and measuring primary care to setting specific primary care spending targets.

This analysis assesses what portion of total health care spending is dedicated to primary care, in alignment with many of the primary care spending targets that are expressed as a percentage of total health care spending. We defined the percentage of primary care as the portion of ambulatory spending rendered by primary care providers (PCPs) relative to total medical and prescription spending among people with Employer-Sponsored Insurance (ESI) and Medicare Fee-for-Service (FFS) between 2018 and 2022.

Approximately 4% of spending went to primary care in 2022. Nationally, among people with ESI, primary care made up 4.39% of total medical and prescription spending in 2022. Primary care spending in Medicare FFS was lower than ESI, at 3.86% of total spending.

Figure 1: Trend in National Share of Primary Care Spending to Total Medical and Prescription Spending between ESI and Medicare FFS (2018-2022)



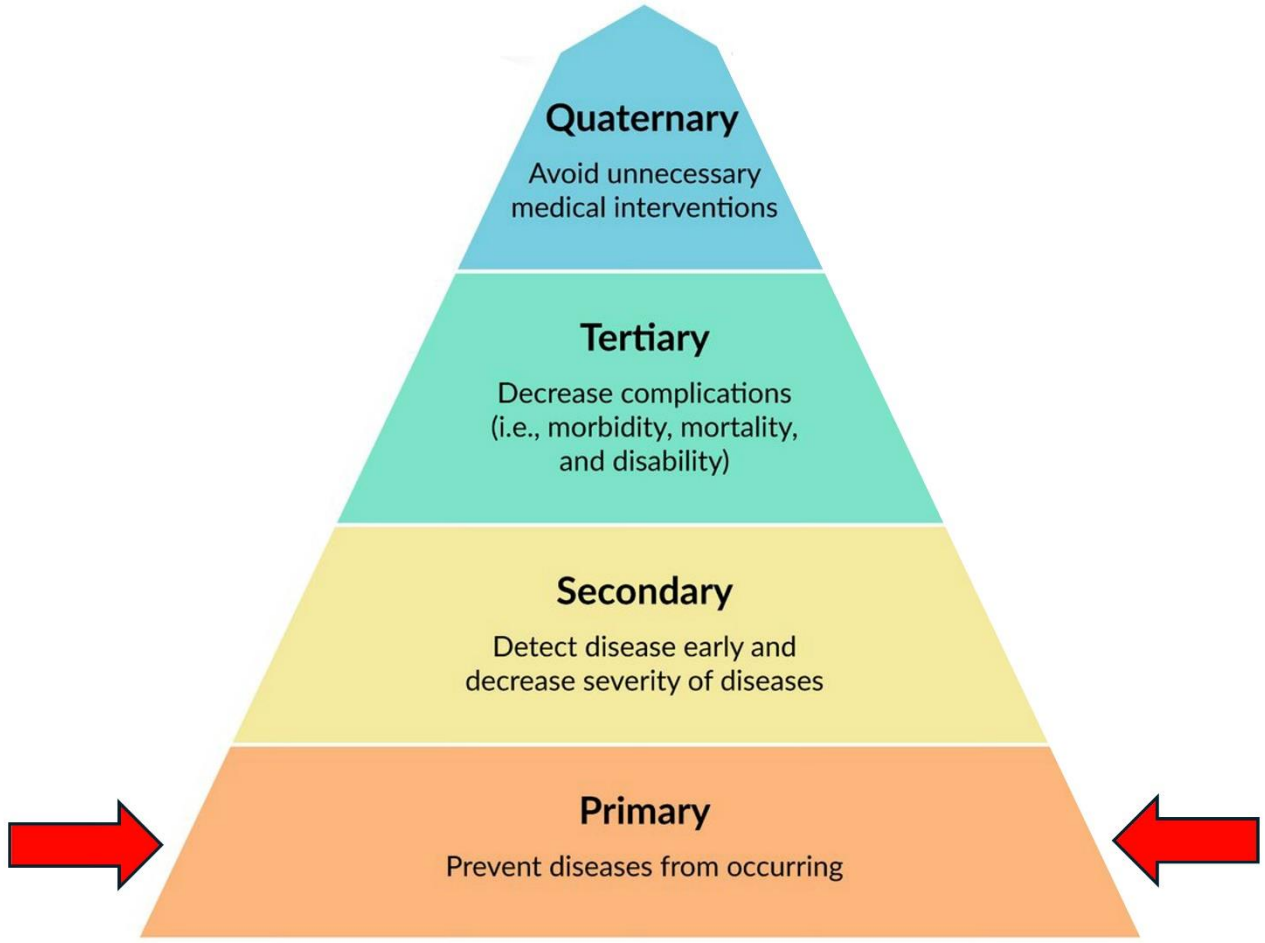
Source: https://healthcostinstitute.org/hcci-originals-dropdown/all-hcci-reports/4-of-health-spending-goes-to-primary-care

It's Time for Primary Prevention in Medicine

Eric Topol, *Substack*, Sep 17, 2025 (excerpt)

Primary Prevention means a disease or condition is averted. The term was coined and introduced by Leavell and Clark in the late 1940s. Now, about 75 years later, we've yet to achieve any substantive primary prevention with the notable exception of vaccinations that prevent infectious diseases. Of the 3 major age-related diseases that I focused on in SUPER AGERS—cardiovascular, cancer, and neurodegenerative—we have not prevented the latter two. Remember screening for cancer (such as mammography, colonoscopy, PSA, or total body MRI as some have advocated without adequate data) is a secondary prevention, with the objective of finding cancer at an early stage. Nothing meaningful has yet been shown to prevent neurodegenerative diseases. While there has been some preemption of cardiovascular disease with the use of lipid panels and cholesterol lowering drugs, heart attacks (and heart disease) and strokes remain the number 1 and 3 medical causes of death in the United States, respectively. And heart disease deaths are ticking up, adjusted for age.

Instead our healthcare now is centered on treating these diseases, which has limited success for many cancers and even less, thus far no disease-modifying impact, for neurodegenerative diseases (Alzheimer's and Parkinson's). No less, there's the profound economic benefit of primary prevention for reducing the cost of such treatments, such as tailored oncology drugs or support of people with dementia in long-term care facilities. I hope this brief review will convince you that primary prevention is a great and largely unfulfilled need, that in light of recent advances it should be given the highest priority. The key problem is that we haven't had the ability to do it. Until now.



Source: https://erictopol.substack.com/p/dawn-of-a-new-era-of-primary-prevention

Topol Article (continued)

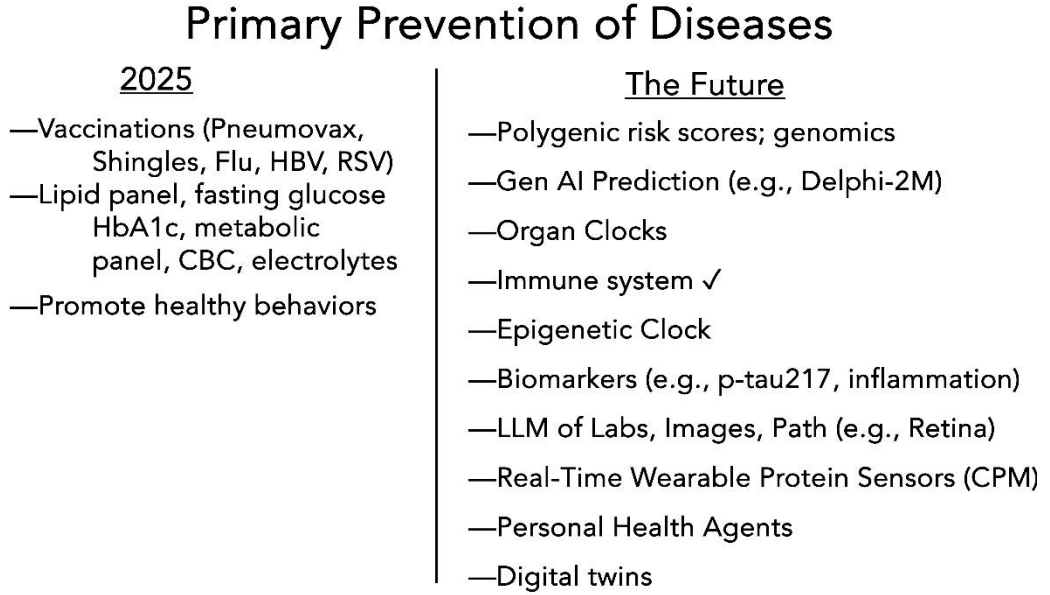
As I presented in SUPER AGERS, we now have the means for defining high-risk individuals for the major age-related diseases. By using multimodal A.I. to integrate all the layers of a person's data, we'll be able to know whether a person is at high-risk and get an impression of the temporal arc of when a disease will appear (clinically manifest). Below is the example for cancer. We've already seen a number of studies demonstrating A.I. partitioning of high-risk and early detection of pancreatic cancer (among other cancer types) with much less depth of data than presented here. As you know, this is a highly fatal cancer which, in over 90% of cases, is only currently diagnosed at late, metastatic stages.

Alzheimer's is the most dreaded disease for most people. Following a similar template as above for cancer (presented in SUPER AGERS), we will be starting a large randomized trial soon to prevent Alzheimer's in people at high-risk due to their family history, APOE4 status, and polygenic risk score. Now that we have blood biomarkers that are modifiable like p-tau217, we're in a powerful position to move forward.

Concluding Remarks

Here's the contrast. At left in the chart is state-of-the-art "primary prevention" today. Even that short list is not followed by a large proportion of primary care physicians or their patients. With the exception of preventing infectious diseases, it has little, certainly insufficient impact to prevent non-communicable, ,major age-related diseases.

Source: https://erictopol.substack.com/p/dawn-of-a-new-era-of-primary-prevention



At right in the chart above, the future, with many layers of new data that are already available (like p-tau217, polygenic risk scores, genomics). And many that will be available soon, such as organ clocks, an immune system clock and comprehensive assessment, A.I. of the retina, your images, and labs (trends in your "normal" lab values without an asterisk can be quite meaningful with A.I., as I previously reviewed). Eventually CPM and digital twin information resources (learning from nearest neighbor in our species) will be added to take primary prevention to an even higher level. We're at the dawn of primary prevention. Not only are there many new layers of data—organ clocks, biomarkers, genomics, biosensors—but we have multimodal A.I. and agentlc A.I. to analyze the data. For the first time, we are seeing a large health model (Delphi-2M) that has learned the grammar and language of health, tokenizing it to predict diseases with temporal anchoring. We've gotten used to large language models that predict the next word in a sentence, but just imagine how powerful a large health model (LHM) will be when all the other layers of data beyond those utilized in Delphi-2M are integrated. Yes, 0.76 AUC performance for prediction across all diseases isn't great, but this is just the beginning. From Delphi-2M, we learned that person's health story can be projected 20 years ahead. This represents a jump from my prior piece on precision medical forecasting. Future models will keep improving on precise medical forecasting.

We Need a Primary Care Buildup

Fred Pelzman, *Medpage Today*, Sep 29, 2025 (excerpt)

Well, the autumnal equinox has come and gone, and the leaves have started to turn and fall on the streets of New York City.

Along with this changing of the seasons have come a flurry of inquiries from senior residents at internal medicine (IM) residencies across the region and beyond, starting to look for advice about jobs.

At this point, it does my heart good -- it warms me -- when I hear that senior residents, despite practicing in residency clinics and practices across the country, still have a yearning, and the intention, to practice primary care outpatient medicine.

Here at our tertiary/quaternary care academic medical center, the push is obviously towards specialized care, and many of the IM residents, including those on the residency's primary care track, end up applying for fellowships. It's true that we need lots of cardiologists, gastroenterologists, nephrologists, infectious disease specialists, rheumatologists, and all the rest. But it feels to me, and I know you've heard me say this before, that what our country really needs -- seemingly now more than ever -- is an incredibly strong base of people practicing primary care outpatient medicine.

Residents historically practice in dramatically underserved settings, and end up managing a lot of incredibly complex patients with multiple comorbidities and high needs, countless social stressors, and challenges in their social determinants of health and health literacy that prevent them from getting the best care regardless of the efforts of those around them trying to do what's right for them.

Our residents see challenging patients discharged from hospital with little or no continuity or follow-up with specialists, and patients sent home from prolonged hospitalizations with no one assuming responsibility for their care. Without our residents, the best-laid plans of discharge summaries often go awry. Having a great primary care doctor at the helm can make a difference, but we need to create a better environment where people will beg to enter this field, where the unmitigated joy of taking care of people will make everything else pale by comparison.

Right now, we're just not quite there. The chores and challenges of the patient population; the limited support in terms of personnel and resources and access to specialty and subspecialty care; and the administrative, bureaucratic, and insurance company barriers that are put up in front of even the most well-meaning and strong-willed doctor and patient trying to get everything done makes working in the outpatient setting at times frustrating, and for obvious reasons, sometimes an unattractive career choice.

It's my vision, and my goal, over the next few years to inspire the people who can help reallocate resources at our institution to rethink outpatient primary care; to throw resources, innovation, and technology at these outpatient settings such that practicing adult internal medicine, pediatrics, ob/gyn, and psychiatry in these resident clinics -- and in the faculty practices in which those residents then move on to -- will be a dream come true, something to aspire to, not a stressful place that leads to burnout and dissatisfaction.

Source: https://www.medpagetoday.com/opinion/patientcenteredmedicalhome/117686

Commonwealth Fund Study Released Last Week Focuses on Administrative Burden

Administrative Burden in Primary Care: Causes and Potential Solutions, Briefing, Oct 2, 2025

Issue: Primary care physicians (PCPs) provide services that address a wide range of patient needs and conditions. As a result, PCPs have substantial care management responsibilities and face greater administrative burden — like prior authorization requests and quality measure reporting requirements — than specialists do. These tasks distract PCPs from patient care, contribute to demoralization and burnout, and exacerbates the PCP workforce shortage.

Goals: To identify the causes of and potential solutions to administrative burden in primary care. Methods: Environmental scan and interviews with 12 PCPs and primary care organization leaders.

Key Findings and Conclusions: PCPs face growing administrative burden owing to complex insurance rules, implementation of value-based payment, poor usability of electronic health record (EHR) systems, and an overload of care quality measures. Chronic underinvestment in primary care, meanwhile, has made it harder for PCPs to hire support staff. Streamlining documentation, simplifying regulations, improving EHR usability, and reducing inbox overload could greatly ease this workload. Embedding forms in EHRs, easing prior authorizations, and refining value-based care metrics could help as well. Artificial intelligence, if deployed carefully, also could potentially ease burden. Improving PCP compensation could help offices hire additional staff to take on administrative tasks, allowing physicians to focus on patient care.

Source: https://www.commonwealthfund.org/publications/issue-briefs/2025/oct/administrative-burden-primary-care-causes-potential-solutions

"Primary care physicians identified EHR documentation and information retrieval, inbox management, nonclinical forms, and prior authorization as having the greatest impact on their administrative burden. Those in management roles also cited contract negotiations and billing, while reporting requirements for quality measures and value-based payment models were concerns across all roles. Multiple stakeholders — including health care organizations, government agencies, regulators, and EHR vendors — could help reduce the administrative workload for primary care physicians."

AI Scribes Can Help Reduce Administrative Burden

Olson KD, Meeker D, Troup M, Barker TD, Nguyen VH, Manders JB, Stults CD, Jones VG, Shah SD, Shah T, Schwamm LH. Use of Ambient AI Scribes to Reduce Administrative Burden and Professional Burnout. *JAMA Netw Open*, October 2, 2025; 8(10):e2534976.

This quality improvement study is, to our knowledge, the first large, multicenter preintervention and postintervention evaluation to assess the association of ambient AI scribes with clinician experience. After 30 days with the ambient AI scribe, 74% lower odds of participants experiencing burnout was found. Controlling for organizational and demographic factors, the proportion of participants reporting burnout decreased from 51.9% to 38.8%. Compared with baseline, implementation of the ambient AI scribe was associated with increased attention on patients, clinician confidence that patients understood care plans from reading the notes, and agreement that additional patients could be added to the clinic schedule if urgently needed, all while reducing note-related cognitive task load and the time spent documenting after hours.

Table 3. Comparison of Secondary Outcome Measures Before and After Use of the Ambient AI Scribe

Outcome	No. of participants	Mean (SE) score[a]			*P* value
		Baseline	Follow-up	Difference	
Burnout	186	4.59 (0.15)	4.12 (0.15)	0.47 (0.12)	<.001
Note-related cognitive task load					
Any	243	7.10 (0.09)	4.46 (0.12)	2.64 (0.13)	<.001
Temporal demand	249	7.01 (0.11)	4.35 (0.13)	2.66 (0.16)	<.001
Effort	248	7.31 (0.12)	4.71 (0.13)	2.60 (0.15)	<.001
Mental demand	254	6.84 (0.12)	4.38 (0.15)	2.46 (0.15)	<.001
Documentation after hours	263	4.95 (0.18)	4.05 (0.16)	0.90 (0.19)	<.001
Focused attention on patients	253	6.51 (0.16)	8.56 (0.11)	−2.05 (0.18)	<.001
Comprehensible care plans	254	7.34 (0.13)	7.79 (0.13)	−0.44 (0.17)	.005
Agreeable to add urgent patients	230	6.21 (0.21)	6.72 (0.20)	−0.51 (0.24)	.02
No. of additional patients (1 to ≥4)	91	2.19 (0.11)	2.16 (0.11)	0.02 (0.11)	.58

Abbreviation: AI, artificial intelligence.

[a] Unadjusted preintervention and postintervention paired *t* tests transformed to 10-point scales.

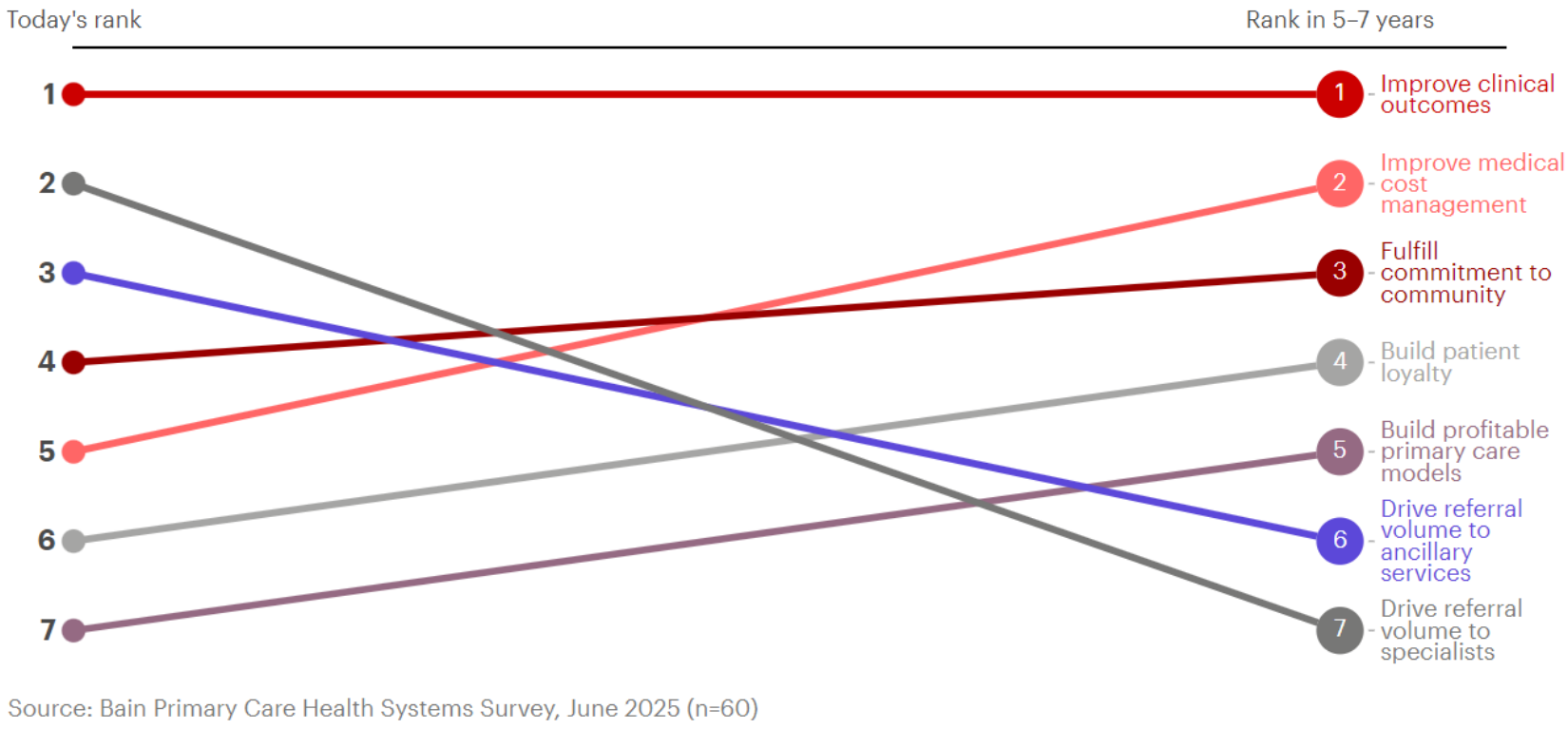
Source: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2839542

Why Health Systems Are Expanding Primary Care

Erin Morrissette, MD and Cate Miller Goldstein, Bain, Sep 25, 2025

Primary care is a critical and growing pillar of health system strategy. In a recent Bain survey, 77% of health system executives said they plan to expand their footprint by adding more practices and employing more primary care physicians in the next five to seven years.

Why? Patient outcomes remain paramount, as leaders recognize that primary care is essential to delivering consistent, high-quality care. Beyond improving clinical outcomes, however, the rationale for expansion reflects a strategic shift. Health systems are moving away from prioritizing primary care as an engine for referrals and ancillary revenue, instead focusing on its role in cost management and the patient experience.

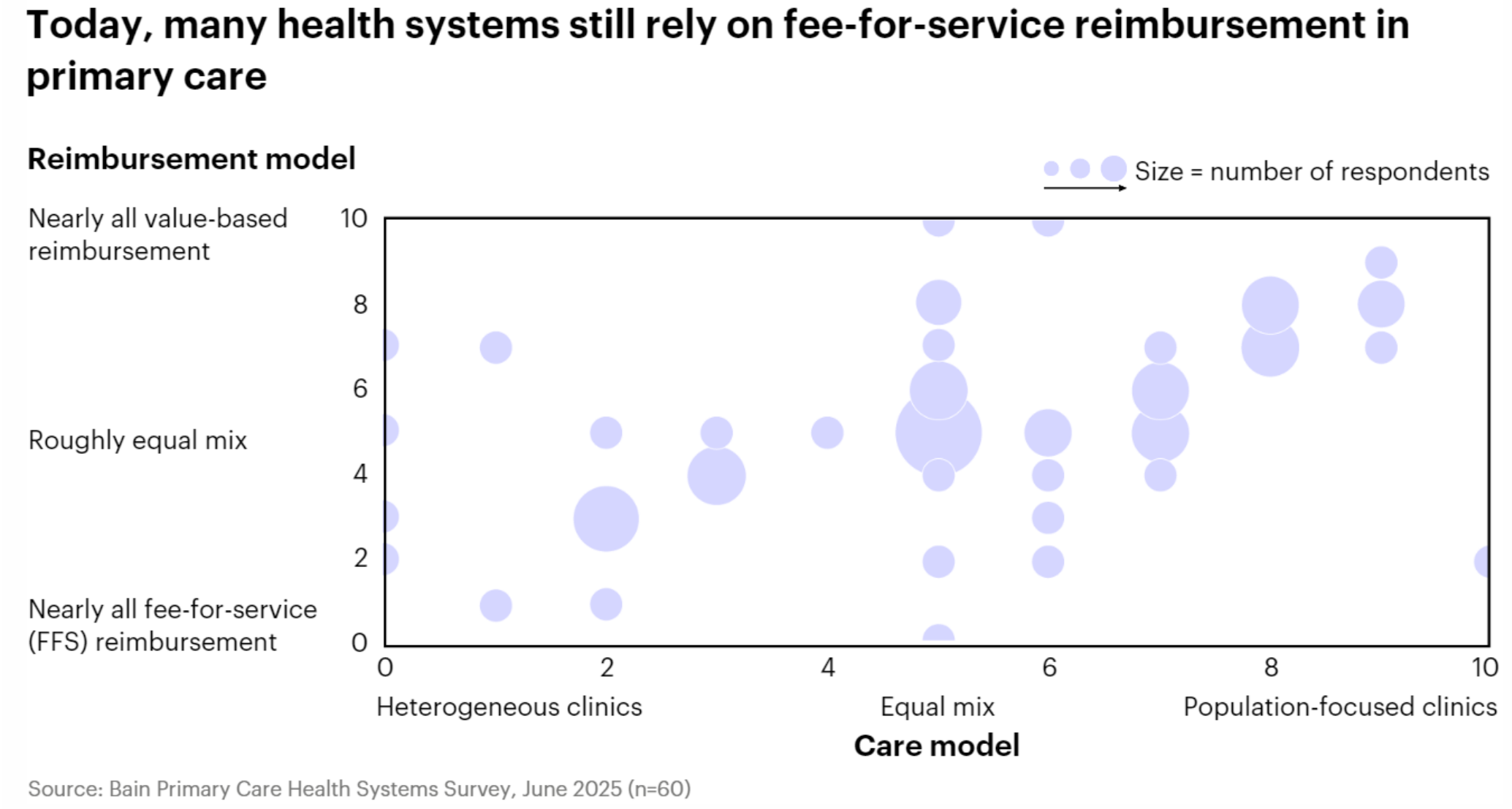


Source: Bain Primary Care Health Systems Survey, June 2025 (n=60)

Source: https://www.bain.com/insights/why-health-systems-are-expanding-primary-care-snap-chart/

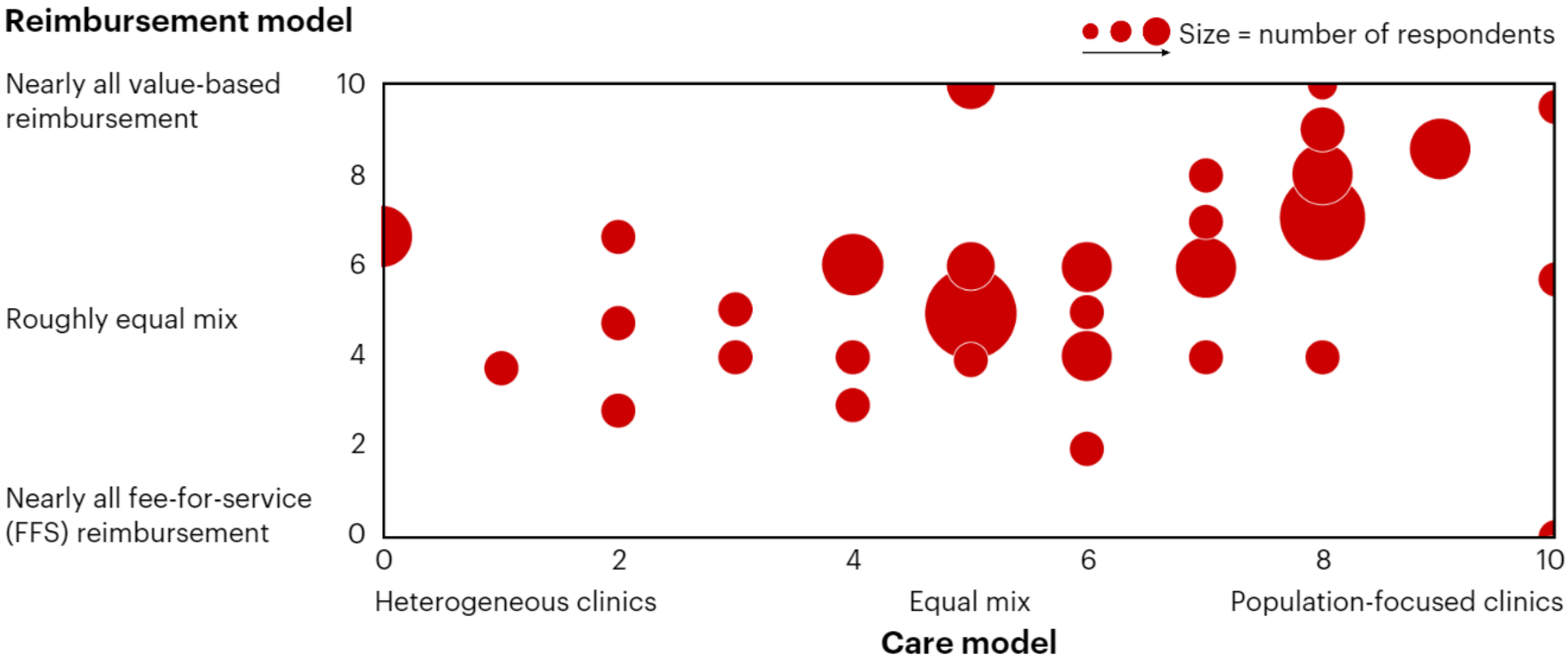
Fee for Service Model is Still Predominant in U.S. Healthcare

Bain Study of Primary Care, Sep 25, 2025



Source: https://www.bain.com/insights/primary-care-2030-health-systems-move-toward-value-based-models-snap-chart/

But executives expect a shift toward value-based and population-focused approaches



Source: Bain Primary Care Health Systems Survey, June 2025 (n=60)

Source: https://www.bain.com/insights/primary-care-2030-health-systems-move-toward-value-based-models-snap-chart/

Disclosure

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