Biopharmaceutical Sector

Weekly Update – October 16, 2023

STIFEL | Healthcare

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Strong Partner in a Turbulent Environment

The biopharma industry environment is facing unprecedented challenges amidst a turbulent global economic and geopolitical environment.

Stifel's Global Healthcare Group has remained focused on supporting our clients in achieving their long-term goals throughout the current market downturn.

As shown at right, we remain active across the board. We have supported our clients in achieving notable recent successes in M&A and capital markets transactions.

Stifel's full-service healthcare investment banking practice offers a best-in-class combination of deep sector knowledge, strong industry relationships, and broad product expertise.

Stifel's Global Healthcare Group is comprised of over 100 professionals covering all segments of the healthcare industry. The team, located in New York, San Francisco, London, Mumbai, Toronto, and Montreal, has substantial experience in assisting companies with all types of financing and M&A assignments. The Global Healthcare Group is dedicated to building long-term relationships with its clients through senior level attention. Since the formation of the Global Healthcare Group in Q4 2010, the team have helped raise over $115 billion for almost 300 healthcare companies in over 600 transactions. Over the same period, members of the Global Healthcare Group have advised on over 350 announced M&A transactions, including over 160 cross-border assignments.

$450,000,000

cerevel

Confidentially Marketed Follow-on Offering

Joint Bookrunner

October 2023

$100,000,000

Vistagen

Registered Direct

Joint Bookrunner

October 2023

$80,000,000

bionano

Registered Offering and Private Placement of Convertible Notes

Co-Lead Placement Agent

October 2023

$90,833,010

immunome

morphimmune

Merger Transaction

Advisor to Buyer

October 2023

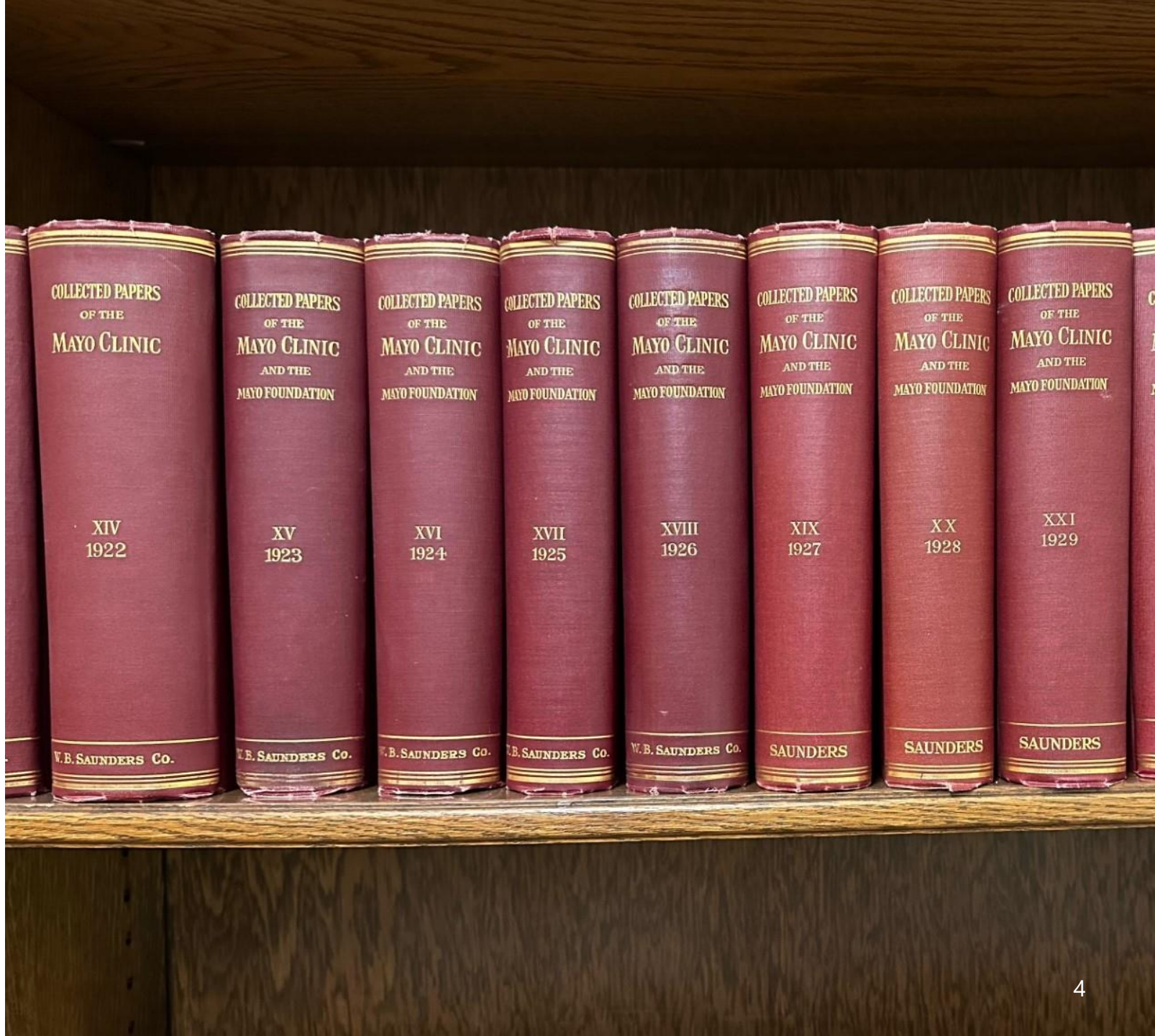
STIFEL | Healthcare

All transaction announcements appear as a matter of record only. Stifel collectively refers to Stifel, Nicolaus & Company, Incorporated and other affiliated broker-dealer subsidiaries of Stifel Financial Corp.

Past Issues / Mailing List

If you are not on the mailing list for this publication and wish to be added, please notify Natasha Yeung (yeungn@stifel.com).

Recent issues in case you missed and want to read:
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Changing Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)



Join Us at These Upcoming Events

Biotech Hangout held its latest event on October 13th.

The next event will be on October 20, 2023.

Please join us.

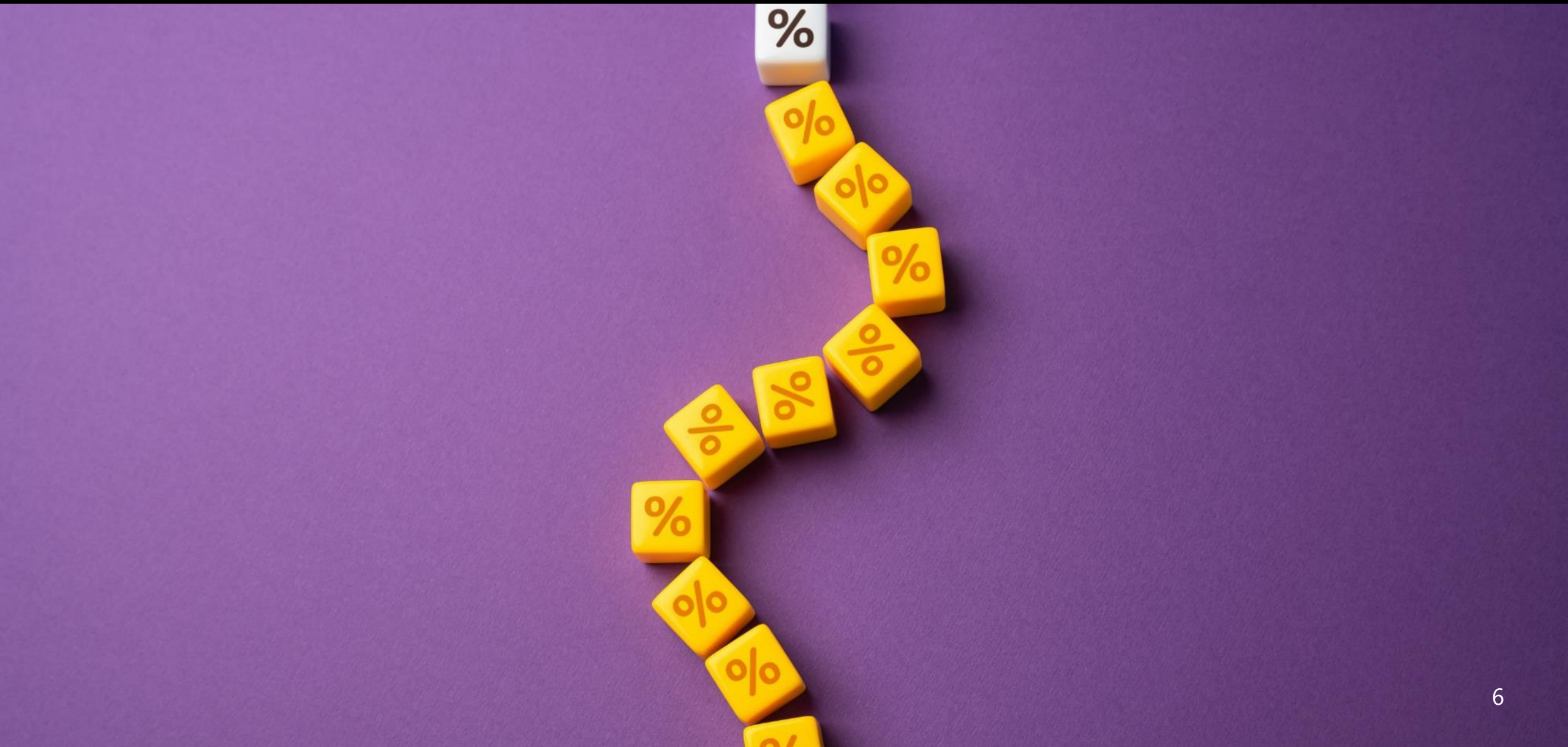
To Learn More
https://www.biotechhangout.com/

BIO-Europe convenes over 5,500 attendees, representing 60 countries and 2,220+ companies, making the event the industry's largest gathering of biopharma professionals in Europe.

To Learn More
https://informaconnect.com/bioeurope/

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

Macro Update



Gradual Slowdown in Inflation Continues

Marley Jay, *CNBC*, October 11, 2023 (excerpt)

Inflation leveled off to 3.7% in September compared to a year ago, extending a gradual slowdown in consumer prices, even as it slowed to 0.4% from 0.6% in August.

The Bureau of Labor Statistics released its latest round of price data Thursday morning. Experts had expected it to show that overall prices for consumers rose 3.6% from a year ago, and by 0.2% compared to August.

Source: https://www.nbcnews.com/business/economy/inflation-september-2023-how-economy-looks-now-consumer-price-index-rcna119776

Investors Are Calling It: The Federal Reserve May Be Done Raising Rates

Joe Rennison and Jeanna Smialek, *New York Times*, October 11, 2023 (excerpt)

Investors are betting that the Federal Reserve, which has raised interest rates to their highest levels in 22 years, may finally be finished.

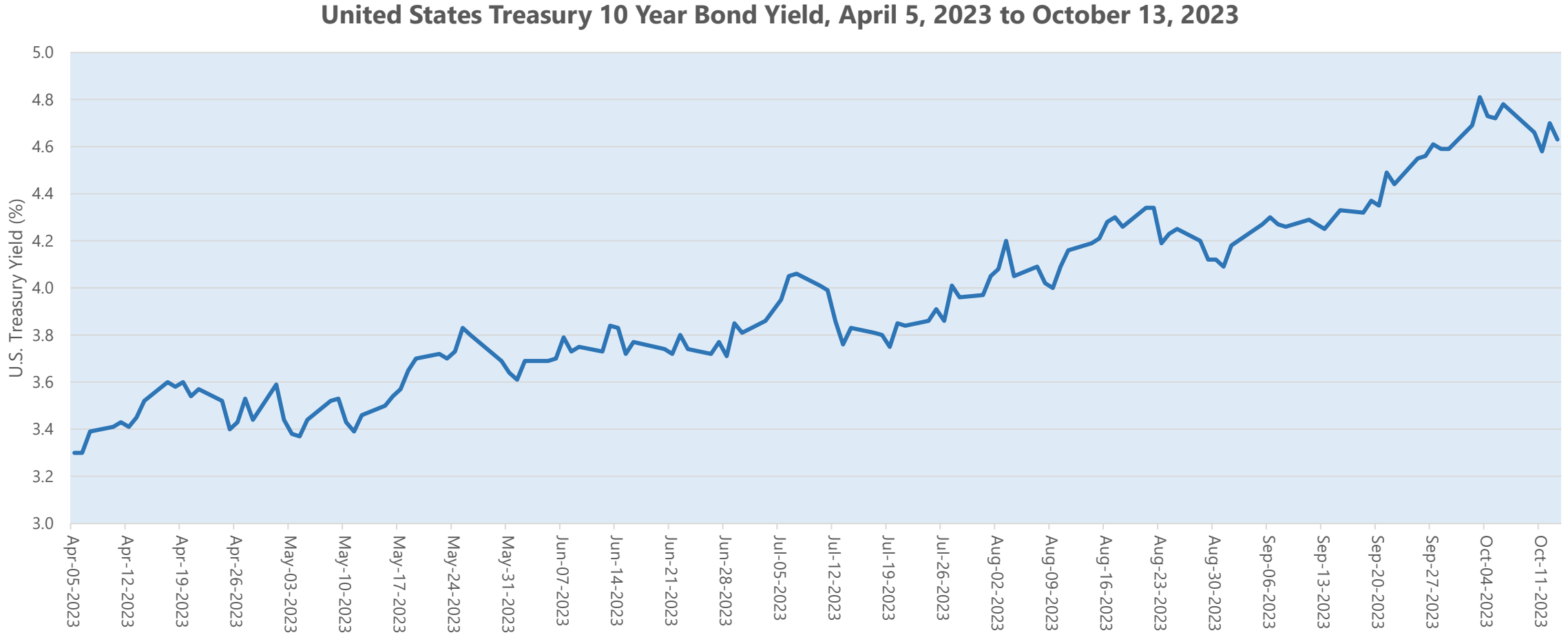
Several top Fed officials have indicated in recent days that the central bank's effort to cool the economy through higher borrowing costs is being amplified by recent market moves that are essentially doing some of that job for them.

In particular, attention has focused on a run-up in interest rates on U.S. government debt, with the yield on the 10-year Treasury bond briefly touching a two-decade high last week. That yield is incredibly important because it acts as the market's foundation, underpinning interest rates on many other types of borrowing, from mortgages to corporate debt, and influencing the value of companies in the stock market.

Source: https://www.nytimes.com/2023/10/11/business/wall-street-interest-rates-federal-reserve.html

Long Bond Yields Started Dropping Two Weeks Ago

The yield on U.S. Treasuries has marched straight up for the last six months. But starting two weeks ago, bond yields started coming down and are now down 18 basis points from their peak point. This should portend well for long duration assets such as biotech.



Growing Negative Sentiment in Biotech

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

Negative Biotech Sentiment

We have had the occasion to speak with numerous investors and biotech CEO's in the last two weeks and can share that sector sentiment is nearing a low point. A summary of views was shared as well on last week's "Biotech Hangout."

The XBI peaked at 173.99 on February 8, 2021 – roughly a year into the Pandemic. It's now been nearly 1,000 days since that point – 2.7 years to be exact.

And the XBI is down 60% from peak and is not showing any signs of a rebound. In past market downturns, things had picked up easily by this point.

Optimists on last week's "Biotech Hangout" episode were noting that we must be at the bottom.

It does feel that way and yet last week's market developments were troubling.

The reason is that the market kept falling even though the fundamentals had shifted. We are not only far away from peak inflation but now, interest rates – the ultimate biotech fundamental – have turned south.

When rates have gone up in past weeks, biotech has reliably fallen, but somehow the opposite doesn't seem to hold.

Sentiment (continued)

We do not claim to be great readers of charts but our look this week at volume on ETFs, like the XBI, would suggest that there is some type of “local distress” in the market at present. That is, someone big is selling biotech stocks – in quantity.

This could be one or more parties that are negative on the sector. This could be a fund that is in a period of forced liquidation. Or, possibly, one or more generalist funds or a group of retail investors that are giving up on the sector.

The nature of the capital markets is that anonymous trading is possible. Thus, we will never know exactly who is selling and why.

What we can say is that, in many conversations with market participants in recent weeks, there is an **ebbing of optimism** – the sense that this market will turn soon or is turning now. We have heard this from many biotech CEOs and investors.

Last week’s events, of course, saw Mirati be acquired which was a major boon for hedge funds like Tavistock, Avoro, EcoR1 and RTW.

On the other hand, negative news sent Akero’s stock down 70% and 89Bio instantly joined suit. 89Bio went from $16.03/share to $7.62 without any company specific news. In total, $4 billion in equity value was wiped out on the news of these two FGF21 companies.

Sentiment (continued)

A read of the holder's lists of these two companies is very different.

Three well-known long only mutual fund groups took much of the hit for the bad news.

Last week also saw a major setback at Alnylam with its CRL in cardiomyopathy of ATTR amyloidosis. Alynlam's ownership list also features many prominent long-only funds.

None of this is good as we need these long-only funds to thrive in our sector for long-term prosperity to take hold.

This **cresting of negative sentiment** and poor market conditions may portend that long-awaited capitulation is upon us.

A market bottom is often marked by forced selling from funds that can no longer survive prevalent conditions. We saw this in the 2003-2005 period as many now long-forgotten funds (e.g., Amerindo) failed emerge alive from the turn-of-century downturn.

Conversations with fund managers identify many groups that are "cutting back exposure" until the new year.

Perhaps this survivalist instinct is healthy given the circumstances.

The current geopolitical circumstances and uncertain macro picture creates substantial downside risk in the months ahead.

Sentiment (continued)

We recently spent time with a major fund manager in biotech who worries that the prevalent investment style of many specialist funds is facing an **existential threat.**

He notes that the sheer number of companies in high-risk life sciences areas such as biotech, diagnostics, tools, devices, HCIT etc. has grown massively in recent years.

The **average duration** of the cash flows of these companies has also grown. That is, there are a lot more preclinical or early clinical companies around today than, say in 2005 or 2015.

These earlier stage companies have thrived due to a large influx of MD/Ph.D. fund managers that are event driven rather than fundamentals driven. Capital flows have been quite positive as the event driven investment approach has generated good returns.

The core idea is that one can generate alpha by using scientific analysis to identify which trials will work and which will not, which drugs are for real and which are not – and then bet accordingly.

The problem, according to this fund manager, is that the success of this style of event investing in long duration stocks assumes that there are enough long-term fundamentalist investors in the market to allow these investors to trade in and out of stocks around events.

Some are arguing that the event investing style underlying today's biotech investment market is facing an existential threat.

Sentiment (continued)

Think of **motorcyclists zooming in and around slow traffic** on a roadway.

This investor notes that there have always been long-term fundamentalist funds that are playing for the cash flows that are implied by success in our sector.

This investor further indicated that we are now seeing the assumptions underlying the event investing style erode with the consequence that many relatively unseasoned fund managers are waking up to realize that they are in an uncharted land. One where event-based traders are basically betting against each other – which creates an unproductive and unhealthy **zero-sum dynamic** – such as that which played out last week with names like Akero and Mirati. This investor noted that a key assumption underlying the **event style investing game** was the ongoing need for pharma to buy biotech stocks. He argued that this fundamental is alive and well but that, unfortunately, there are just too many biotech names relative to the bid from pharma. Pharma can't bail out the entire market.

Another person likened this last week to a bar where 100 people of one gender showed up but there were only 3 people of the opposite gender there – creating an unbalanced environment for people to meet someone of the opposite sex.

Sentiment (continued)

We do think that the fund manager's story about the current market resonates with current circumstances.

Generalists have been leaving the market and the "smarter" long-only funds have been taking their lumps. We have observed that successful trial outcomes have been associated with less of an upside bump lately, while bad news has caused stocks to get completely savaged (witness 89Bio last week).

This is a sign of an imbalance of event traders relative to fundamentalists in the market.

This fund manager had a **dark outlook** – noting that the science-heavy event approach to investing was threatened by current circumstances and that we could see a major restructuring of the buyside and sector if current market conditions persist.

He argues that we are going to see more and more flow of capital into companies that have "real businesses" and that we will need to see companies consolidate and structure their operations for a world where profitability will matter and that one cannot run a company with negative cash flows forever. He further noted that we are likely to see boards recognize that scientifically oriented management teams will need to be augmented by management that have operational skills and understand real cost management.

This manager does anticipate a sector rebirth amidst an historical bioscience renaissance.

Just not one where we will have hundreds upon hundreds of companies that expect to burn cash indefinitely.

A very different view of the market has been presented by RA Capital. Their key point is that the **scientific innovation economy is a massive long-term driver of value**, and while they praise efficiency, RA would likely argue that sometimes companies need to burn money for quite awhile to be able to reach their potential.

Indeed, they have argued that today's biotech capital formation "infrastructure" is sufficient to sustain the bio innovation economy.

RA Capital has written several reports in which they note that there are biotech companies that have specialist investor sponsorship and others that do not. Their argument has been that there are enough specialist investors around to sponsor companies with strong science and quality drug development programs.

The data put together by RA Capital has indeed been persuasive and supports the notion that despite the sector wreckage, the innovation system has been functioning well.

Sentiment (continued)

Some would argue that today's biopharma capital formation system functions reasonably well in routing money to companies with high upside potential.

The underlying point that the capital formation system is functioning well enough suggests that companies that *should get money* can do so, even if valuations are less than ideal.

We are sympathetic to this depiction of the market as it comports with the obvious fact that few companies with negative enterprise values today have robust positive clinical datasets for a drug that addresses a major unmet medical need.

It also is consistent with the fact that, overwhelmingly, companies that get bought in pharma M&A are sponsored by specialist funds and that specialist funds often pile into secondary offerings after companies report positive data.

As we see it, the challenge is a different one: the growing **bifurcation** of the market. That is, there are fewer companies today with enough of a valuation to bring in the scale of capital to support a broad drug development agenda.

As shown in forthcoming pages, the size of the market's "good neighborhood" has been steadily shrinking in recent months. If you will, the hurdle to be able to access that specialist fund money has been rising and valuations have been dropping. From what we can see, the number of biotech companies with good stories that are not able to access capital on sensible terms has been rising.

Sentiment (continued)

One market observer put it this way to us last week:

"The bifurcation of the haves and have nots is a key aspect of the today's biotech market and is becoming ever more evident. Sentiment remains terrible as 'have not' stocks are getting pounded into the ground while the 'haves' are struggling to just stay in place."

These public market challenges obviously feed back into the entire ecosystem.

There hasn't been an IPO yet in the month of October.

Private investment volumes are dropping despite robust amounts of money available in private funds and the like.

On a positive note, the most important fundamental does seem to be shifting. The Fed does indeed appear to be getting ready to pause rates.

If inflation can stay at bay, we would expect to observe further drops in long-bond yields, which we suspect, have been pushed up substantially by speculation.

Ultimately, a shifting macro environment will be a major positive – and this could start to play out relatively quickly if the macro circumstances continue to improve.

There is growing bifurcation in the biotech ecosystem between the "haves" and the "have nots".

Biopharma Market Update

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

Biotech Stocks Flat Last Week

The XBI was down last week despite positive inflation news. Unlike past weeks, interest rates have started to decline.

Biotech Stocks Down Last Week

Return: Oct 6 to Oct 13, 2023

Nasdaq Biotech Index: -0.6%
Arca XBI ETF: -3.6%
Stifel Global Biotech (EV): -2.7%*
S&P 500: 0.4%

Return: Jan 1 to Oct 13, 2023

Nasdaq Biotech Index: -6.8%
Arca XBI ETF: -16.1%
Stifel Global Biotech: -15.6%*
Stifel Global Biotech (adjusted): -9.6%*
S&P 500: +12.7%

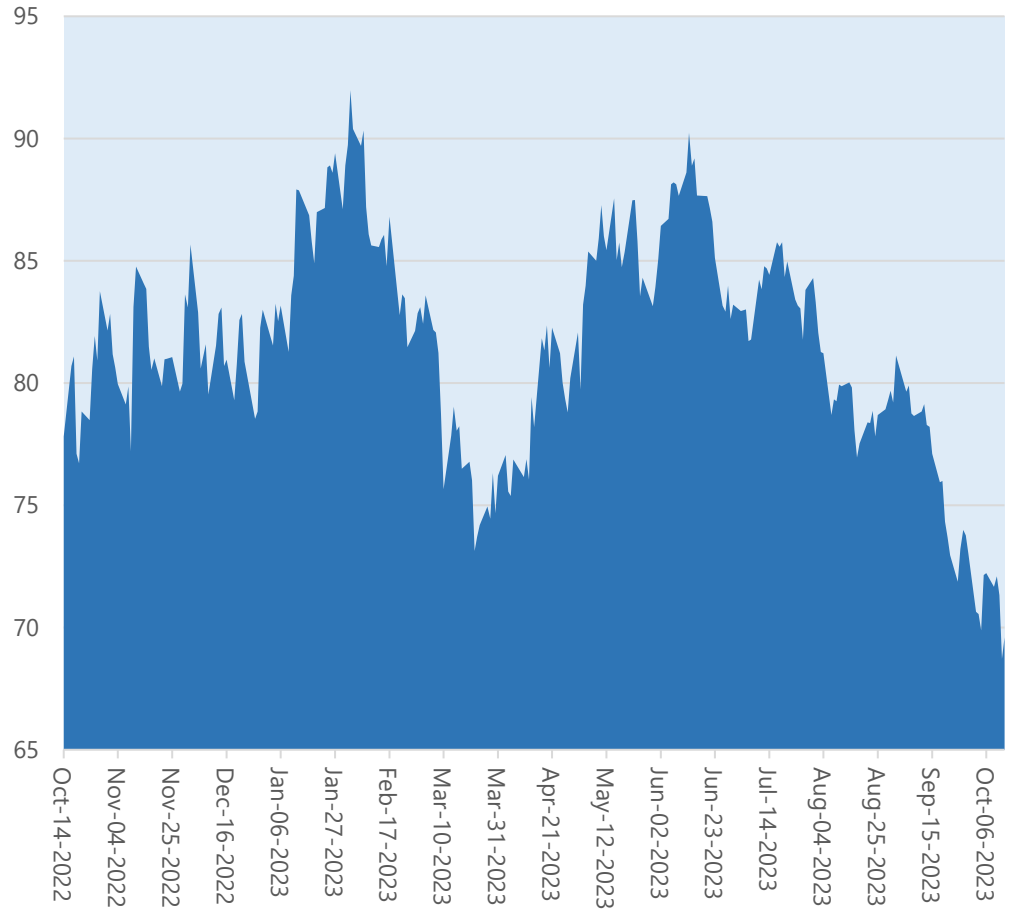
VIX Up

Oct 21: 29.7%
Jan 20: 19.9%
May 26: 18.0%
July 21: 13.6%
Sep 23: 17.2%
Sep 29: 17.3%
Oct 6: 17.4%
Oct 13: 19.3%

10-Year Treasury Yield Down

Oct 21: 4.2%
Jan 20: 3.48%
May 26: 3.8%
July 21: 3.84%
Sep 23: 4.44%
Sep 29: 4.59%
Oct 6: 4.78%
Oct 13: 4.63%

XBI, Oct 14 2022 to Oct 13, 2023

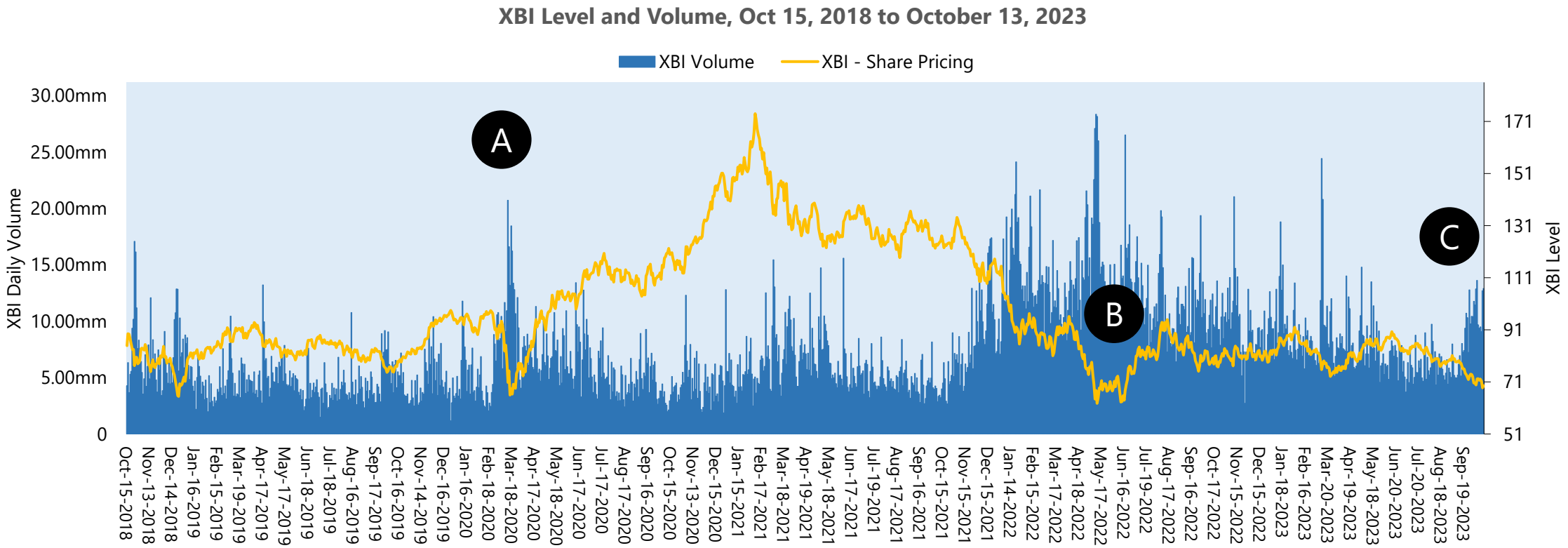


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

High XBI Volume in Last Month

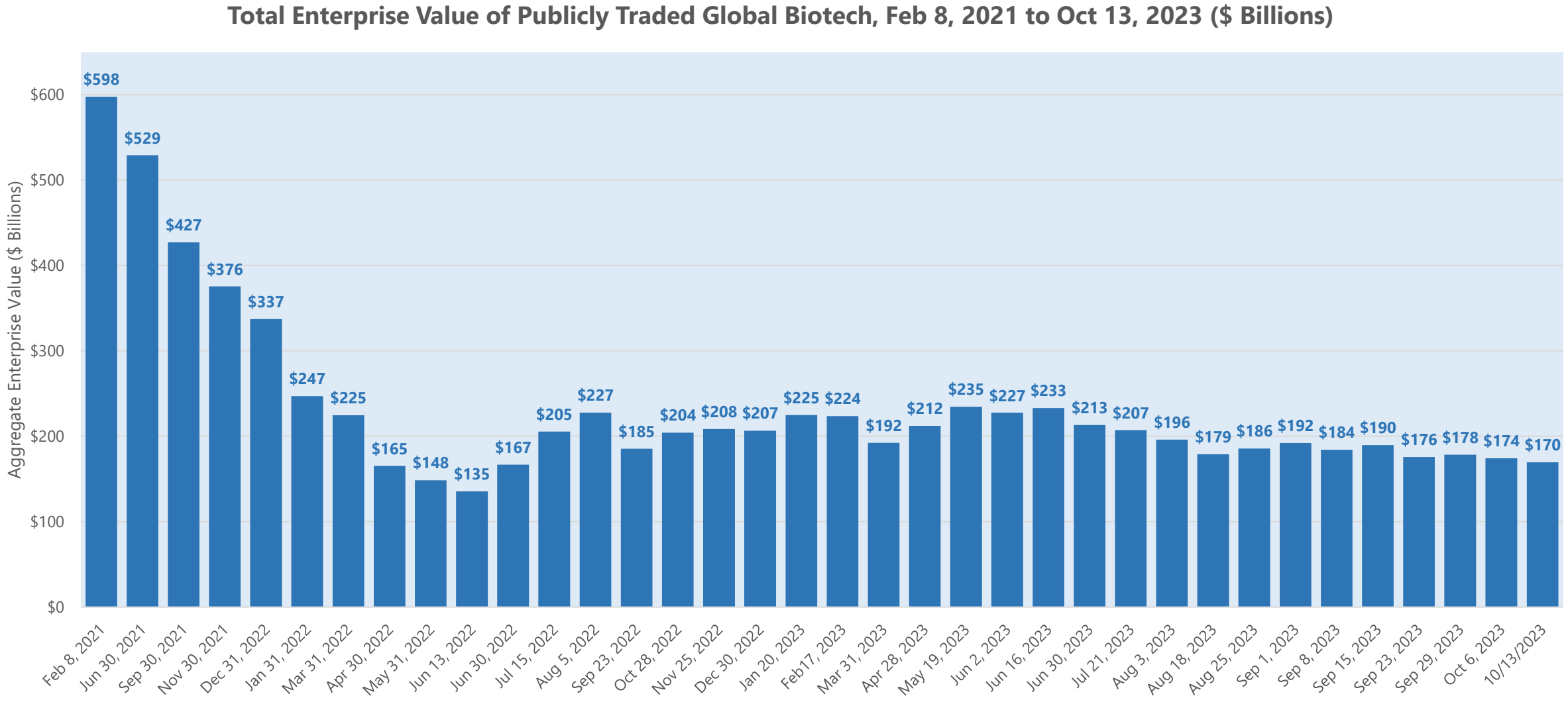
The XBI is a readily tradeable ETF that broadly reflects value movements in the innovation part of the biopharma economy – particularly biotech stocks. As a result, it is often used for hedging activities in periods of distress (especially short-selling while liquidating stocks). One will note very high levels of XBI trading volume when the market plunged at the start of the Pandemic (A), during last Summer's "mini biotech crash" (B) and, now again, in the last several weeks (C). While trading volumes have doubled recently, they are not at the levels seen last Summer. Nonetheless, we surmise that there is significant distress leading to hedging activity this month.



Source: S&P CapitalIQ.

Total Global Biotech Sector Value Down Last Week

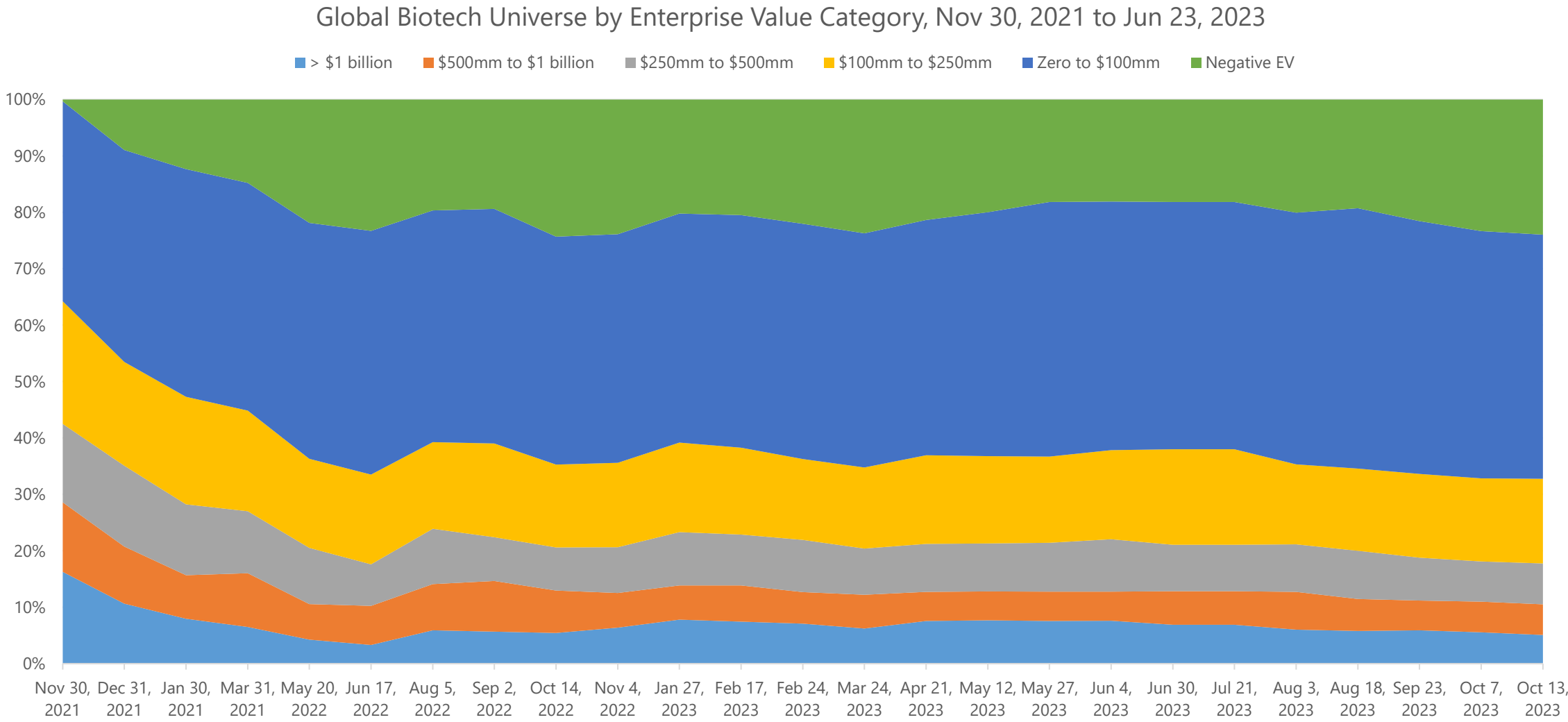
The total value of the global biotech sector fell by 2.7% last week and is now down over 10% for the year.



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

Total Global Biotech Sector Neighborhood Shifting

The number of global biotech companies worth more than $1bn continues to drop while the population of those with negative enterprise value and values less than $100mm is shooting up. The market is ever more bifurcated.



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

Amid a Rough Year for Life Sciences, Cormorant Delivers Healthy Returns

Stephen Taub, Institutional Investor, Oct 11, 2023

Most life sciences and biopharma hedge funds are having another rough year. They are either losing money or are up just a few percentage points.

But not Cormorant Asset Management, which has been operating below the radar of many hedge fund watchers.

In the first nine months of this year, the firm headed by Bihua Chen has posted a 20 percent gain in its hedge fund, the Cormorant Global Healthcare Master Fund, according to two people, including an investor. Last year, it was up around 18 to 19 percent, according to the investor.

Chen founded Cormorant in 2013. Earlier in her career, she worked at Izzy Englander's multistrategy hedge fund giant, Millennium Management. She also founded BC Capital, working at the firm from 2005 to 2010.

Cormorant focuses on biotech, medical technology, and life sciences companies and currently manages $3 billion, according to Chen's published bio.

The firm's hedge fund, which manages about $1 billion, invests essentially all of its assets in the health care and life sciences industries, according to a regulatory filing. No more than 10 percent of assets are invested in private companies, according to the investor.

Cormorant has no doubt been heavily boosted by its largest long position, MoonLake Immunotherapeutics, which accounted for nearly one-quarter of Cormorant's U.S.-listed long assets at the end of the second quarter…

Meanwhile, Cormorant is currently raising money for its fifth private fund, Cormorant Private Healthcare Fund V. The fund will focus on early-stage biotech and medtech companies, according to an investor.

It has already received $330 million in commitments, and Cormorant is hoping to raise a total of $400 million by the time it closes the fundraising about six months from now, says the investor.

So far this year, Cormorant has been one of the most active hedge fund firms with venture capital arms in the private markets. It has already made 16 new private investments, compared with 20 last year, according to Crunchbase.

Source: https://www.institutionalinvestor.com/article/2cb1clqihmcvwini18agw

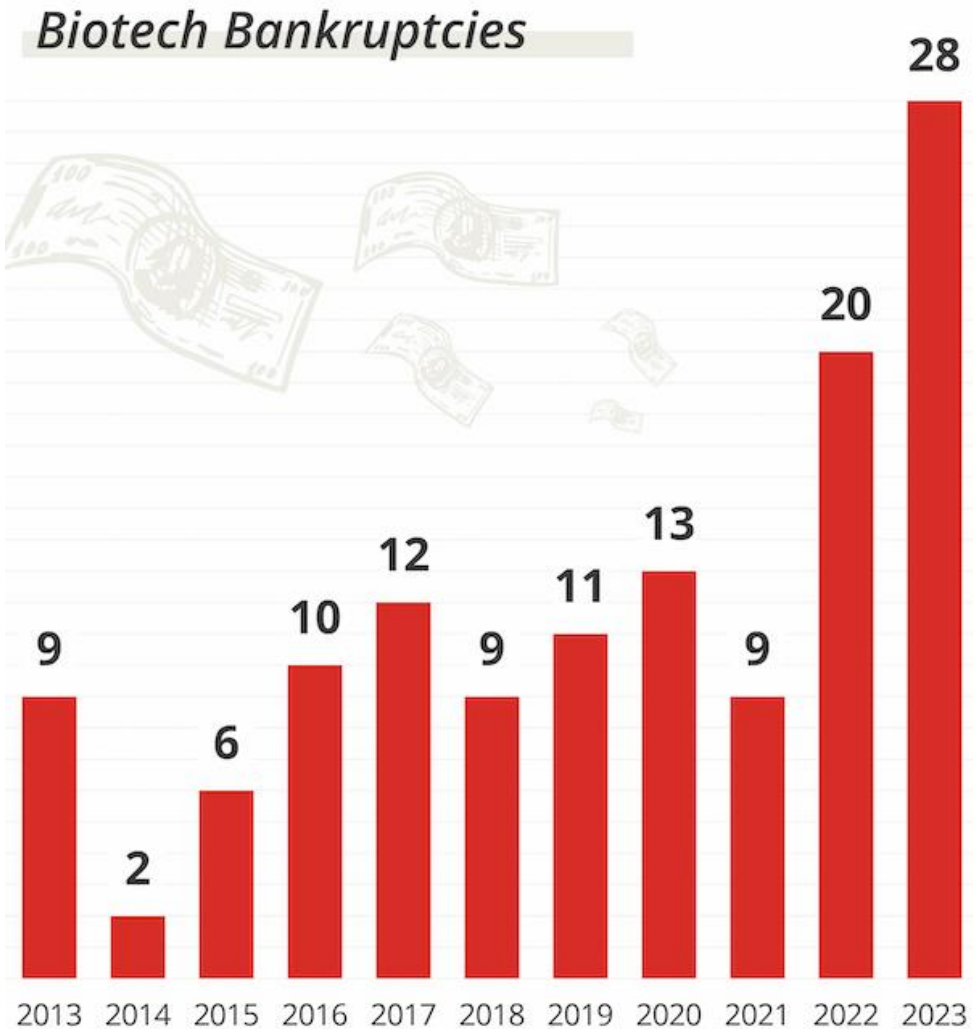
Biotech Bankruptcies Skyrocket

Ana Mulero, Biospace, Oct 11, 2023 (excerpt)

Bankruptcy among biotechs is on the rise, with a spike in the number of cases in the past couple of years, highlighting struggles to secure financing and recover financially.

This year has seen a record high 28 biotech bankruptcies so far, SEC filings show. And more will come by year's end, according to James Cassel, chairman and co-founder of Miami-based investment banking firm Cassel Salpeter & Co., which helps companies through bankruptcy processes. The most recent filing came from Infinity Pharmaceuticals on Sept. 28. The company entered a merger agreement with MEI Pharma in February to advance three clinical oncology candidates, only to have the agreement fail in July, which resulted in Infinity laying off 78% of its workforce and declaring bankruptcy.

Last year saw a total of 20 biotech bankruptcy cases, compared with 2021's total of nine, which was consistent with historical trends.



Source: https://www.biospace.com/article/biotech-bankruptcies-skyrocket/

Biotech Venture Capitalist Says Bad Industry Outlook Will Continue

Mary Goldman, *Axios*, Oct 12, 2023 (excerpt)

Unproductive investments a few years back led to the biotechnology sector's current bleak capital market, Stephen Berenson, managing partner at Flagship Pioneering, told Dan Primack at Axios BFD Thursday.

The big picture: A string of late-stage trial failures around 2021 contributed to the public market's current skepticism of biotech, he said. And that poor market outlook is likely to continue for a while.

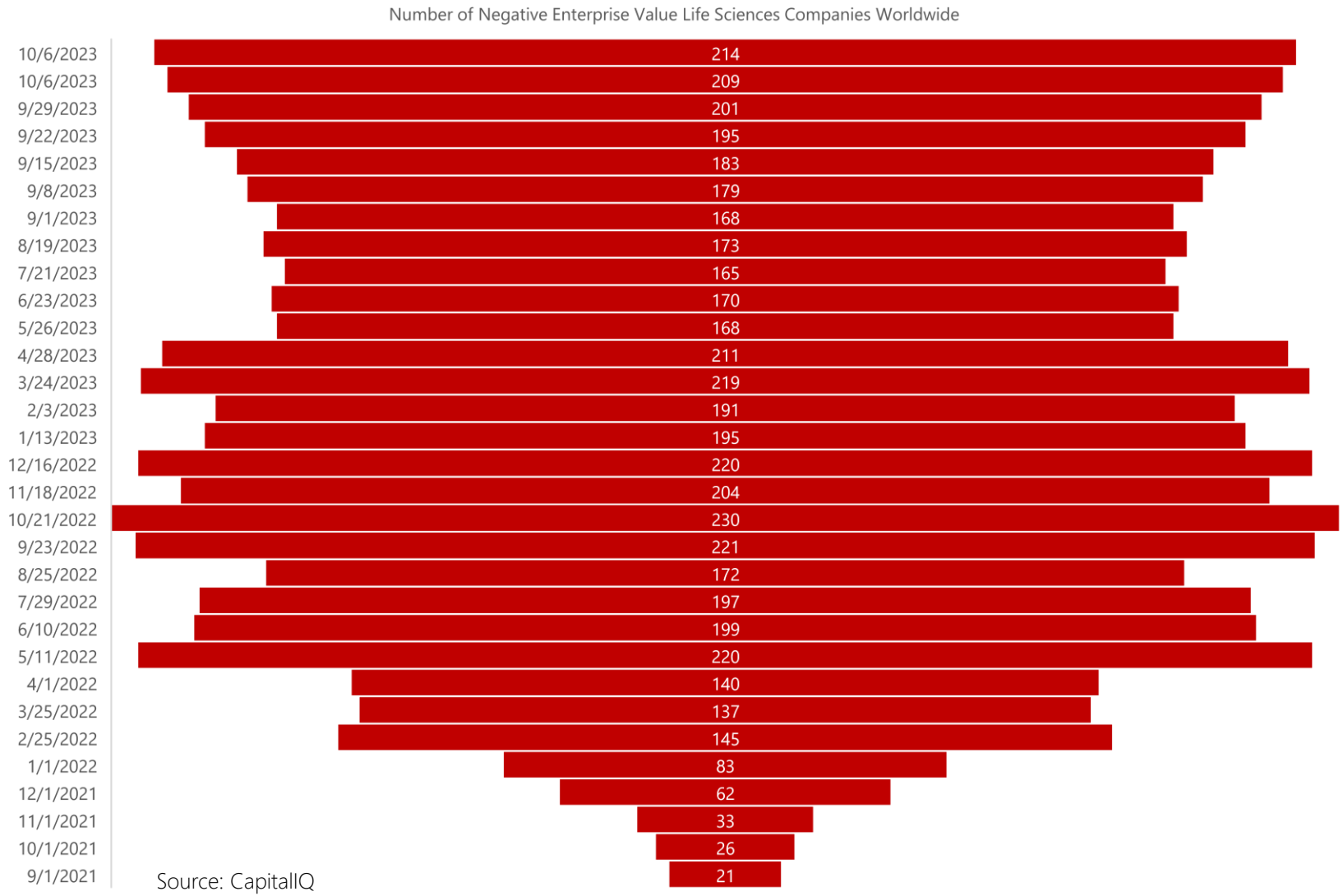
Context: The IPO market for biotech fell 93% in 2022 from the year prior, according to EY.

What he said: "Companies are going to run out of money unless they're able to prove their value propositions to some constituency, whether it's investors, pharma, merger partners, you name it," said Berenson, a board member for Moderna.

Source: https://www.axios.com/2023/10/12/flagship-pioneering-moderna-bfd

Stephen Berenson

Number of Negative Enterprise Value Life Sciences Companies Rose to 214 in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide rose from 209 a week ago to 214 last Friday.

Public Life Sciences Sector Value Flat Last Week

The total enterprise value of the publicly traded life sciences sector was flat last week (+$3 billion). The sectors that dropped the most were medical devices, life science tools, biotech and diagnostics. Commercial pharma was up 1.4%.

Sector	Firm Count	Enterprise Value (Oct 13, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$81,210	0.4%	1.3%	-1.4%
Biotech	814	$169,574	-2.7%	-10.4%	-5.1%
CDMO	40	$160,239	1.0%	-3.2%	-6.4%
Diagnostics	83	$222,109	-2.5%	-8.1%	2.8%
OTC	31	$28,022	-1.0%	-9.0%	0.0%
Commercial Pharma	723	$5,812,356	1.4%	-1.6%	11.0%
Pharma Services	40	$202,542	1.6%	-0.4%	13.1%
Life Science Tools	53	$620,704	-3.3%	-9.9%	-11.4%
Devices	181	$1,447,556	-3.4%	-8.5%	0.6%
HCIT	11	$22,928	1.2%	-0.3%	8.0%
Total	**2057**	**$8,765,529**	**0.0%**	**-3.8%**	**6.4%**

Source: CapitalIQ

A Very Strong Week for Novo Nordisk (And Lilly, By Implication)

novo nordisk

company announcement

Novo Nordisk raises sales and operating profit outlook for 2023

Bagsværd, Denmark, 13 October 2023 – Novo Nordisk today announced that the sales and operating profit growth at constant exchange rates (CER) for the first nine months of 2023 and that the full-year sales and operating profit outlook at CER have been raised.

In the first nine months of 2023, Novo Nordisk's sales increased by 33% and operating profit increased by 37% both at CER.

Profit and loss (CER)	Third quarter 2023	First nine months 2023
Sales growth	38%	33%
Operating profit growth (EBIT)	47%	37%

The sales outlook for 2023 is updated, primarily reflecting higher full-year expectations for Ozempic® volumes sold in the US and gross-to-net sales adjustments for Ozempic® and Wegovy® in the US.

Outlook 2023 (CER)	Expectations 10 August	Expectations 13 October
Sales growth	27-33%	32-38%
Operating profit growth (EBIT)	31-37%	40-46%

Novo Nordisk's full disclosure of the financial results for the first nine months of 2023 will be published on 2 November 2023.

StockWatch: Novo Nordisk Shares Soar as Ozempic Aces Phase III CKD Trial

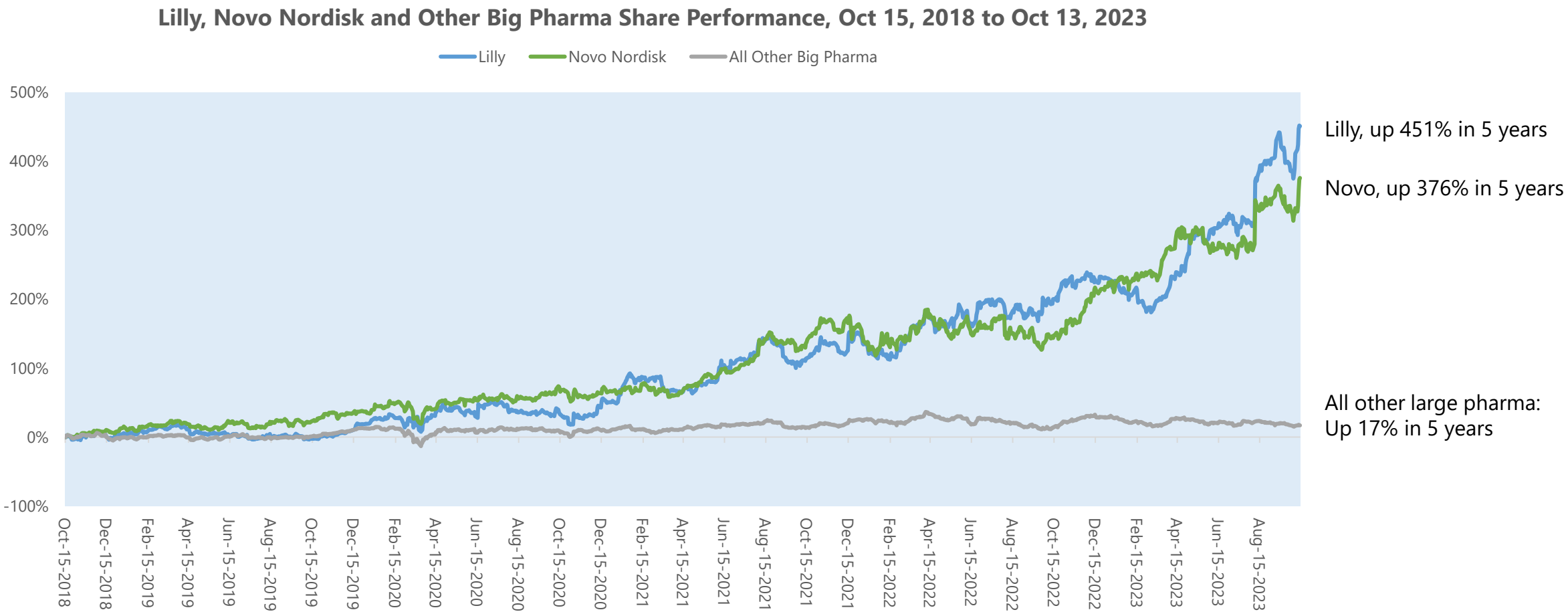
GenEng News, Oct 12, 2023

Novo Nordisk continued its year-long stock surge this week when it halted a Phase III trial early due to undisclosed efficacy results suggesting that its blockbuster adult type 2 diabetes drug Ozempic® (semaglutide)—which shares the same active ingredient as its obesity drug Wegovy® (semaglutide injection)—is also an effective treatment for chronic kidney disease (CKD). Novo Nordisk announced an early halt to its Phase III FLOW trial (NCT03819153), designed to compare semaglutide with placebo in the progression of renal impairment in people with type 2 diabetes and chronic kidney disease. The company cited a recommendation from the study's independent Data Monitoring Committee (DMC) following results from an interim analysis that were not shared in a press release announcing Novo Nordisk will begin closing the trial.

Sources: https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html, https://www.genengnews.com/gen-edge/stockwatch-novo-nordisk-shares-soar-as-ozempic-aces-phase-iii-ckd-trial/

Lilly and Novo Nordisk Outperformance Continued Last Week

Lilly shares rose another 10% last week while Novo shares rose by 7% on the back of raised guidance from Novo and positive data in CKD with semaglutide. An equal weighted index of other large pharmas was up 0.4% last week. Lilly is now up 451% in the last five years versus 17% for all big pharma as a group. With an enterprise value last Friday at close of $563 billion, Lilly is the world's 10th largest public company by value.



Lilly, up 451% in 5 years

Novo, up 376% in 5 years

All other large pharma:
Up 17% in 5 years

Source: CapitalIQ. The other large pharma group includes AbbVie, Amgen, Bayer, Bristol-Myers, Gilead, GSK, Merck, Novartis, Pfizer, Roche and Sanofi.

‘Miracle Drug’ Euphoria: Experts Warn Widespread Use of Weight Loss Medicine Faces Major Hurdles

Anna Gleason, CNBC, Oct 14, 2023

Two experts see major challenges facing the adoption of new obesity drugs. Dr. Kavita Patel, a physician and NBC News medical contributor, believes fresh data from Novo Nordisk on Ozempic’s ability to delay the progression of chronic kidney disease is among the strongest supporting evidence for secondary uses of the drug.

However, she considers data supporting the use of obesity drugs for other conditions including Alzheimer’s and alcohol addiction as underdeveloped.

“Those trials … are nowhere near as robust as the data we have on [Novo Nordisk trial] FLOW, on sleep apnea, cardiovascular risks, on diabetes control — double-blind placebo, randomized controlled trials that are incredible,” she told CNBC’s “Fast Money” on Wednesday. “We have a long way to go for that. I’ve seen a lot of miracle drugs before.”

Novo Nordisk halted FLOW on Tuesday. According to the company’s press release, it happened more than a year after an interim analysis showed that Ozempic could treat chronic kidney disease in Type 2 diabetic patients. As of Friday’s close, Novo Nordisk is up 9.82% since its announcement. Its obesity drug maker competitor Eli Lilly is up 5.16% in the same period.

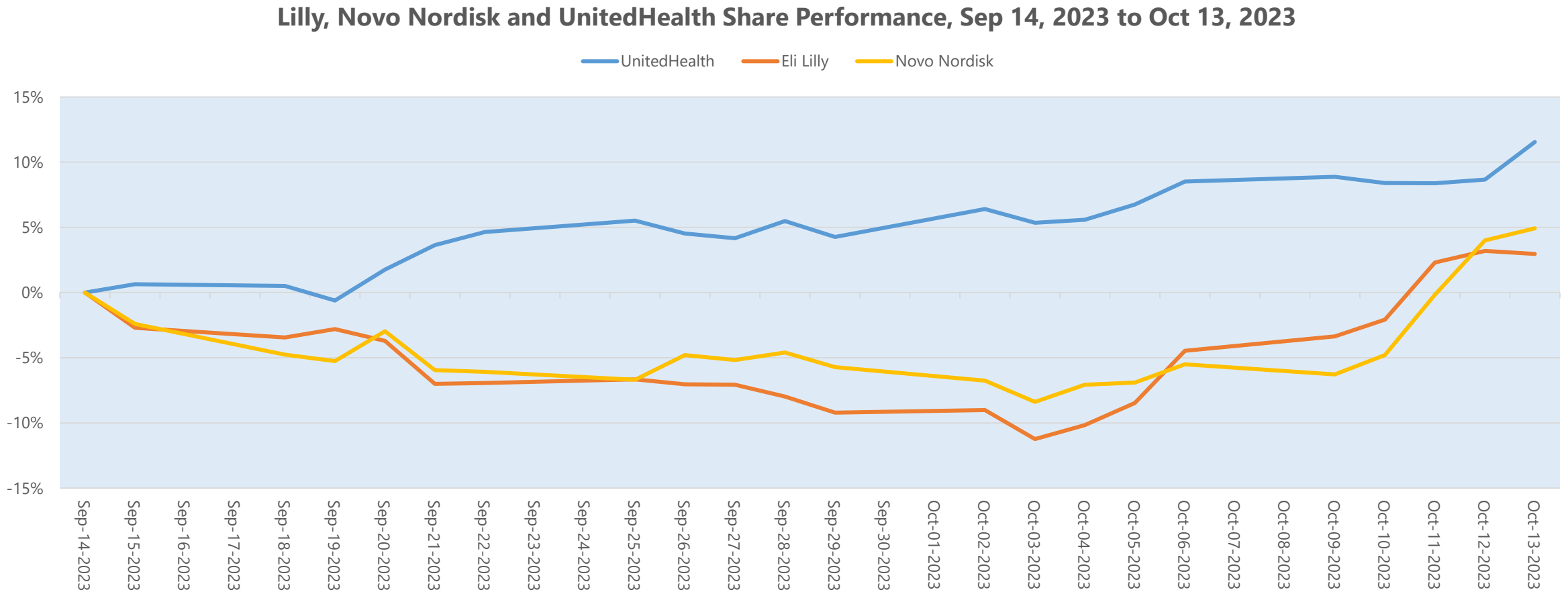
Patel believes efficacy is just one of the major hurdles the medication needs to clear before it can be approved for uses outside of diabetes management.

“We know this drug works really well in diabetics. But there are so many barriers to getting there —including cost, adherence, prescriber rate,” said Patel, who also served as a Whit House Health Policy Director under President Obama. The growth trend may not be sustainable for Novo Nordisk and Eli Lilly, based on current supply constraints that have left patients unable to secure dosages.

Source: https://www.cnbc.com/2023/10/14/obesity-medicine-euphoria-warning-experts-tackle-miracle-drugs.html

United Health Also Performing Well This Year

We see the quest to be the first trillion-dollar health company involving a three-way battle between Lilly, Novo and UnitedHealth. United Health is the largest health insurer and private health provider in the US. Its shares have outperformed Lilly and Novo in the last month and are up 11.5%. United's enterprise value of $523 billion is now way ahead of Novo and within 8% of Lilly. As highlighted in past weekly issues, this is a battle of pharma innovation versus business model innovation in care delivery and payment. While we love Lilly's portfolio, we continue to think that UnitedHealth has a very good chance to become the first trillion-dollar healthcare company.



Source: CapitalIQ.

UnitedHealth Group Reports Third Quarter Results

UnitedHealthcare reported last week that they generated $34 billion in cash flow in the first nine months of 2023. They are on track to generate $46 billion in cash flow this year.

Earnings Release, October 13, 2023

UnitedHealth Group (NYSE: UNH) reported third quarter 2023 performance led by broad-based growth at Optum and UnitedHealthcare.

"As a result of our colleagues' steadfast focus on helping people access and receive the care they need, we are well-positioned to help even more people and continue to generate strong, diversified growth in the coming years," said Andrew Witty, chief executive officer of UnitedHealth Group.

Growth in the third quarter was driven by the continuing increase in the number of people served by Optum and UnitedHealthcare and the broadening scope of services offered. The company strengthened the range of its full year 2023 net earnings outlook to $23.60 to $23.75 per share and adjusted net earnings to $24.85 to $25.00 per share.

Cash flows from operations for the third quarter 2023 were $6.9 billion or 1.1x net income.

Nine-months to date, **cash flows were $34.3 billion** or 2.0x net income and adjusted for CMS payment timing were $22.4 billion or 1.3x net income. The company returned over $11.5 billion to shareholders through the first nine months of 2023 through dividends and share repurchases. Return on equity of 28% in the quarter reflected the company's consistent, broad-based earnings and efficient capital structure.

Source: https://www.unitedhealthgroup.com/newsroom/2023/2023-10-13-uhg-reports-third-quarter-results.html

Comments from the CEO of UnitedHealthcare

"Our teams and capabilities are aligned around five enterprise growth priorities to carry that mission forward [including] Accelerating the transition to Value-Based, Comprehensive Care Delivery, strengthening alignment across all participants to provide patients with the highest quality and best outcomes at the lowest costs."

"Looking to 2023 and beyond, we are confident in our ability to sustain this momentum and determined to build upon it – delivering on our long-term goal to grow earnings per share by 13% to 16%. We will continue to generate distinctive returns for our shareholders by delivering greater value for all stakeholders."

"In most cases, we're really now, despite our size, only scratching the surface of the opportunities that lay ahead."

Sir Andrew Witty
Chief Executive Officer
UnitedHealthcare Group

Sources: https://www.unitedhealthgroup.com/investors/conference.html, https://www.startribune.com/unitedhealth-and-cvs-the-unexpected-goliath-vs-goliath-battle/600241535/

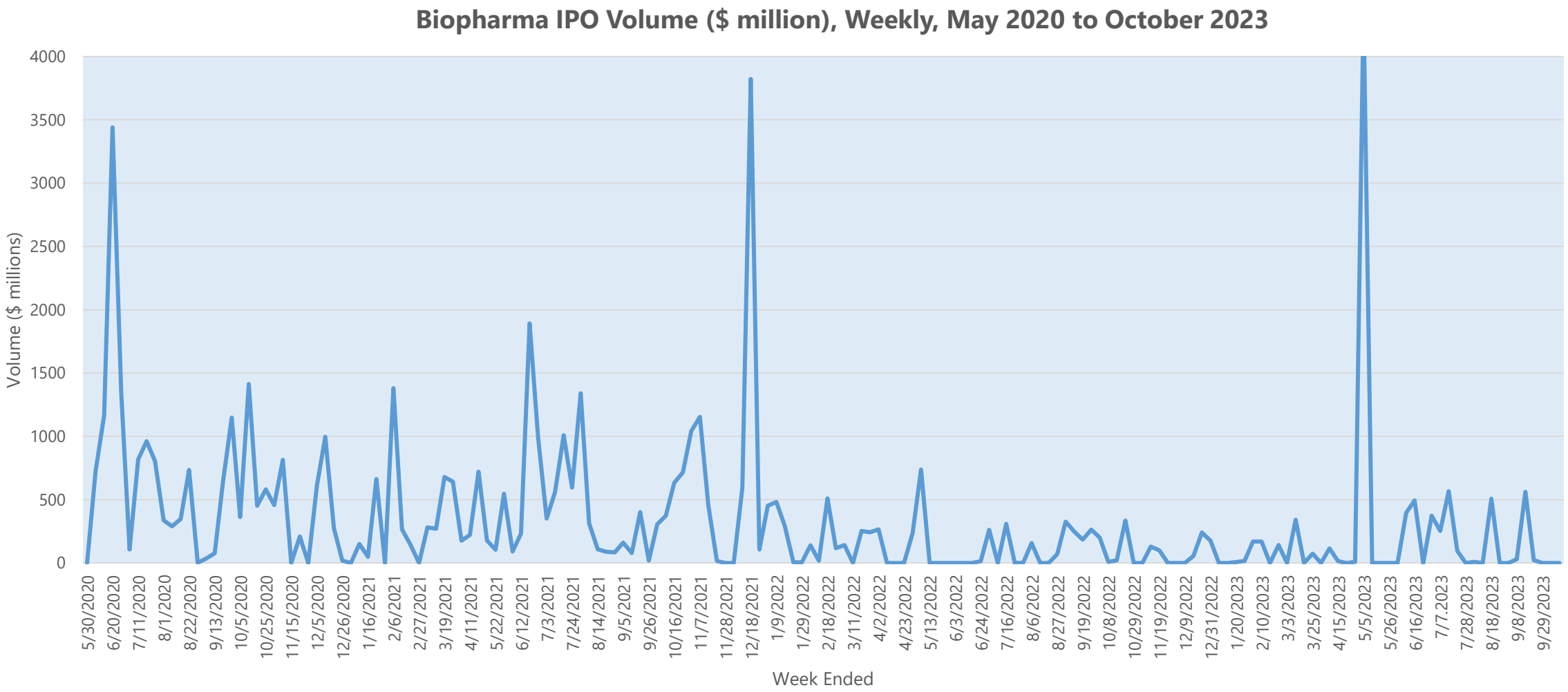
Comment on UnitedHealth Business Model Versus That of a Pharma

1. UnitedHealth has a very powerful business model: become the leading Medicare insurer and, simultaneously, build out the largest health insurance footprint in the United States in Medicaid, employer and individual segments.
2. Compete wherever possible for value-based care contracts where a broad platform would be useful.
3. Focus on maximizing risk-adjustment factor (RAF) value of each beneficiary using analytics on incoming data feeds and send out nurse practitioners to the homes of high risk Medicare beneficiaries who miss their Annual Wellness Visits. This is extremely profitable.
4. **An important element is the integration of physician care and associated services in Optum.** The reasons are many. First, one can direct insureds to Optum sites where physician incentives are aligned with the insurer. Second, care in itself is a good business and synergies gained from the data platform in treating so many millions of patients can prove to be quite helpful.
5. A further value element is the **adoption of standardized care algorithms from mining claims data.** It is not unusual to find that one way to delivering care is less expensive while good for patients. Once this is done it can be adopted by all 70,000 physicians who work for United.
6. The integration of a PBM has obvious value to both government and employer customers. United can focus on delivering the best pharmaceuticals to maximize customer healthcare outcomes while control overall payor spend with an integrated PBM.
7. This business model has high long-term growth and allows the vertically-integrated payvidor to build a strong consumer brand, build a data moat and, potentially, lock in consumers.
8. **Pharma models are radically different** – involving high R&D spend, relatively low returns on R&D and finite monopolies, impacted by generic competition and 20-year patent lives.

Capital Markets Environment

IPO Market Quiet

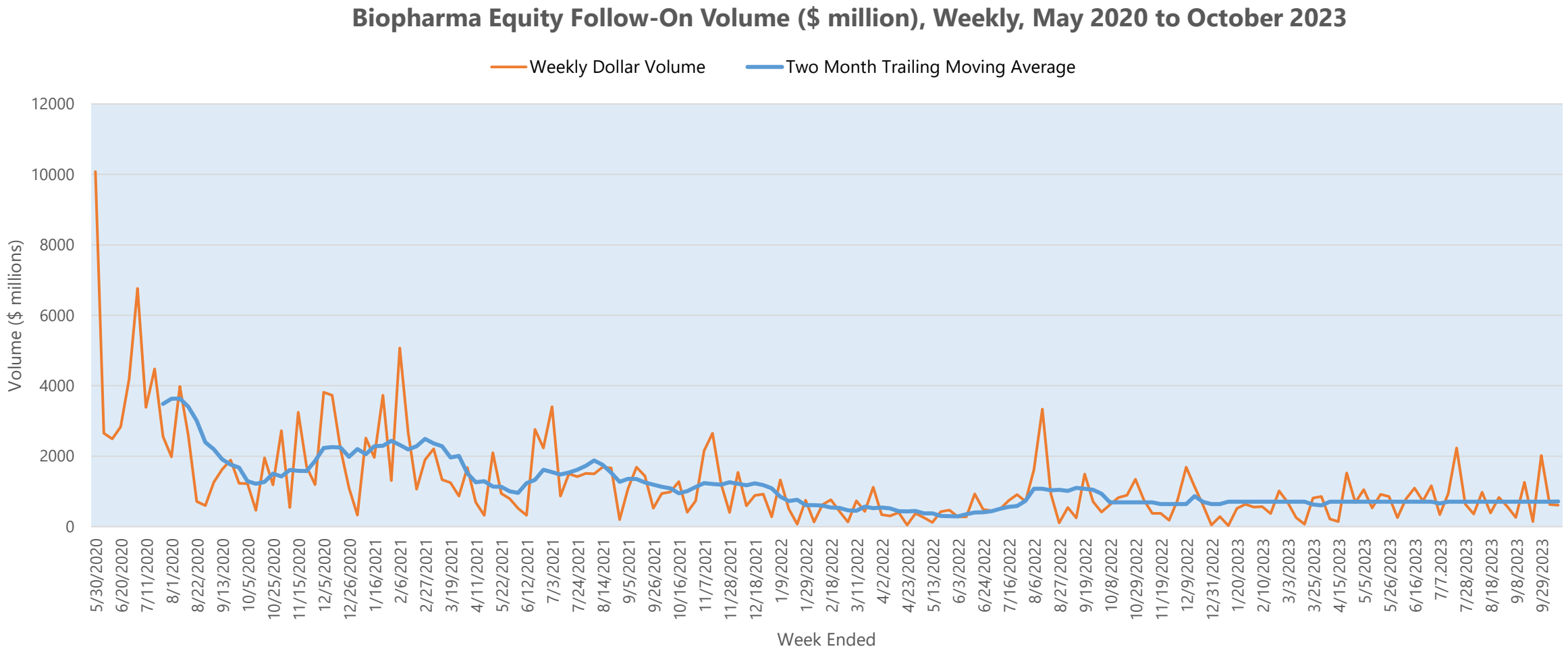
There have been no IPOs yet in the month of October.



Source: Data from CapitalIQ and Stifel research.

Last Week Was Soft for Follow-On Offerings

Last week saw $612 million in follow-on volume. The largest transaction was a $450 million raise by Cerevel.



Source: Data from CapitalIQ and Stifel research.

Cerevel Announces Pricing of Public Offering of Common Stock

CAMBRIDGE, Mass., Oct. 11, 2023 (GLOBE NEWSWIRE) -- Cerevel Therapeutics Holdings, Inc. (Nasdaq: CERE), a company dedicated to unraveling the mysteries of the brain to treat neuroscience diseases, announced today the pricing of its previously announced underwritten public offering of 19,728,189 shares of its common stock at a public offering price of $22.81 per share, or approximately $450 million of shares of its common stock. In addition, Cerevel granted the underwriters a 30-day option to purchase up to an additional 2,959,228 shares of its common stock at the public offering price, less underwriting discounts and commissions. The offering is expected to close on October 16, 2023, subject to customary closing conditions.

$450,000,000

cerevel

Confidentially Marketed Follow-on Offering

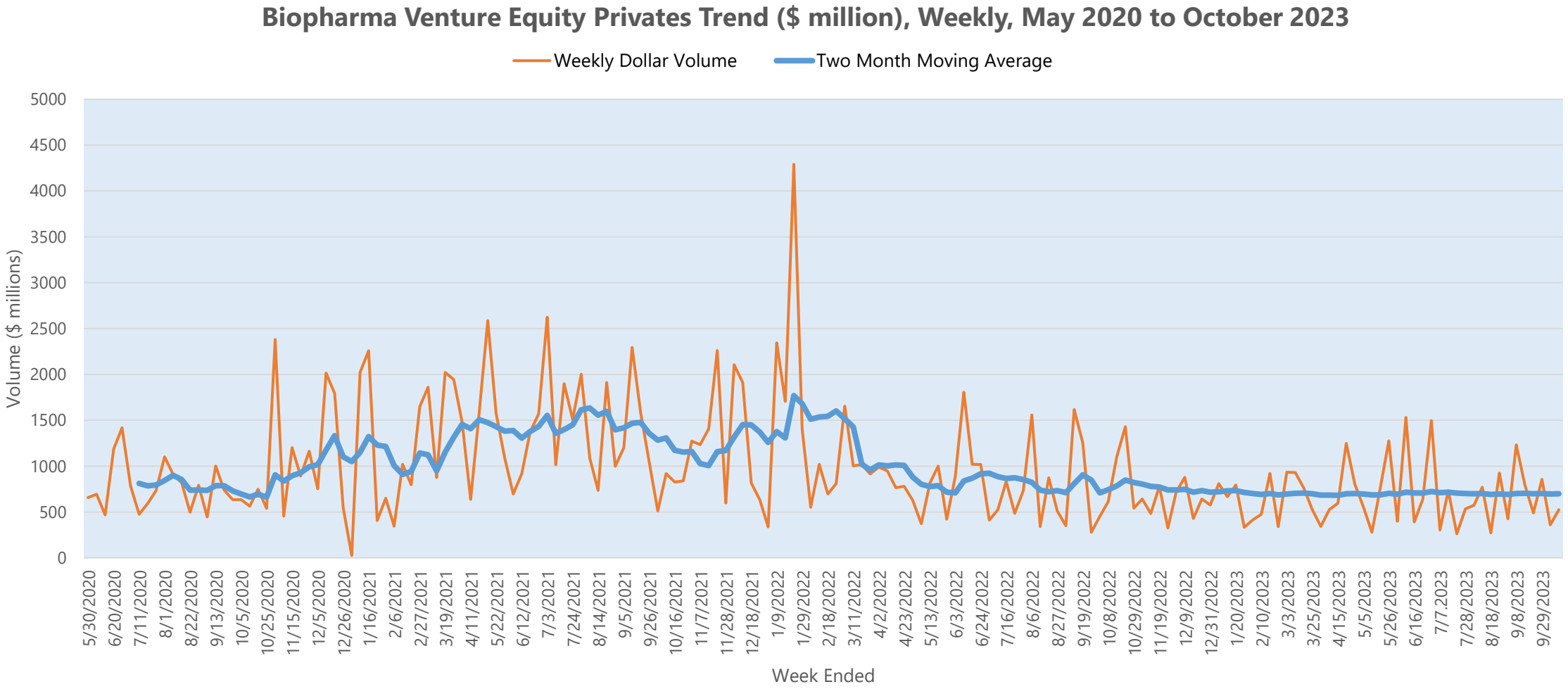
Joint Bookrunner

October 2023

Stifel was pleased to act as joint bookrunner on Cerevel's follow-on last week.

Venture Equity Market Quiet Last Week

Last week saw 30 companies raise $523 million in the venture equity market. The largest deal was a $100mm raise by Agromab Therapeutics.



Source: Data from CapitalIQ, Crunchbase.

Venture Slowdown Hits the Earliest Stages of Investing, Signaling Worsening Decline

Previously a haven, seed-stage investing is now losing steam along with later phases of investment. 'Everything is starting to clog up,' says one analyst.

By Marc Vartabedian **Wall Street Journal**

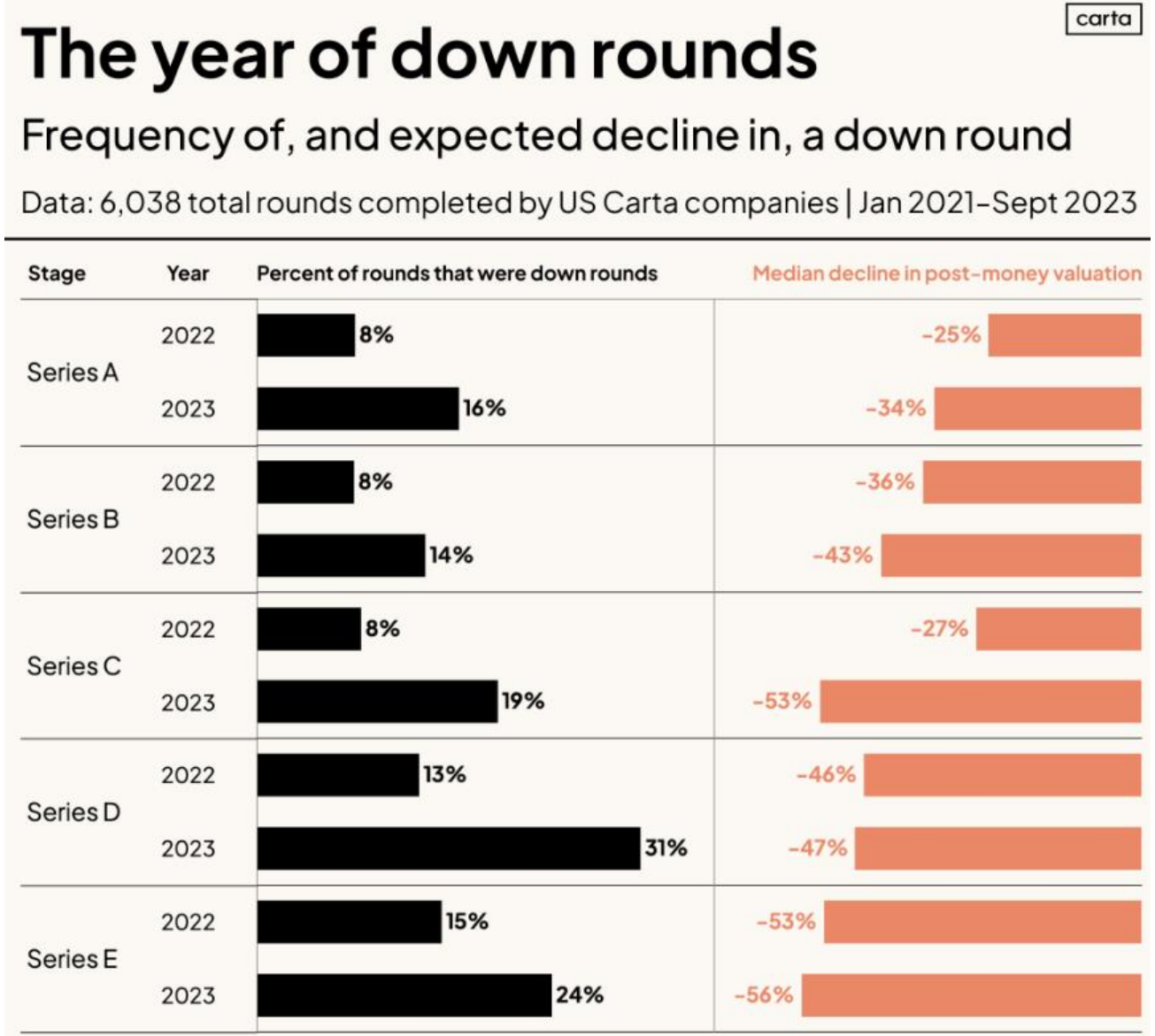
Oct. 12, 2023 6:42 pm ET | WSJ PRO

The slowdown afflicting the venture capital and startup sector has hit the worst point of the last 18 months, new third-quarter data shows. Financings at the seed stage—the earliest chapter of startup investing and one previously insulated from the choppy environment—are slowing, a sign that the downturn is deepening.

In the nine months leading up to this year's third quarter, the number of deals completed at the seed and pre-seed stage was mostly level, notching roughly 1,200 deals a quarter, according to the Venture Monitor report from analytics firm PitchBook Data and the National Venture Capital Association. In the third quarter, however, that fell to 820, the lowest number since at least 2013. While venture capitalists have curbed their investing broadly across various startup stages, they had still been willing to commit to seed-stage startups because the companies were five or more years away from reaching public markets—giving the market time to turn around. Seed-stage companies often have little or no revenue and usually raise funding rounds of under $5 million.

"Everything is starting to clog up," said Kyle Stanford, the lead U.S. venture capital research analyst at PitchBook. Investors are seeing portfolio companies have difficulty raising capital at the next stages, leading them to slow down investing at the previous stage, Stanford said. The slowdown in seed and pre-seed stages comes amid a broad venture downturn in which some startups are being forced to shutter as raising capital has become difficult across stages. Overall, venture investors completed 2,716 deals with U.S.-based startups in the third quarter, 31% fewer than in the same quarter of 2022, according to the report.

Source: https://www.wsj.com/articles/venture-slowdown-hits-the-earliest-stages-of-investing-signaling-worsening-decline-357fecb4



After pandemic sugar rush, a market 'hangover' opens biotech to funding approaches steeped in stigma

FierceBiotech, Oct 9, 2023

Cooley: More Down Rounds

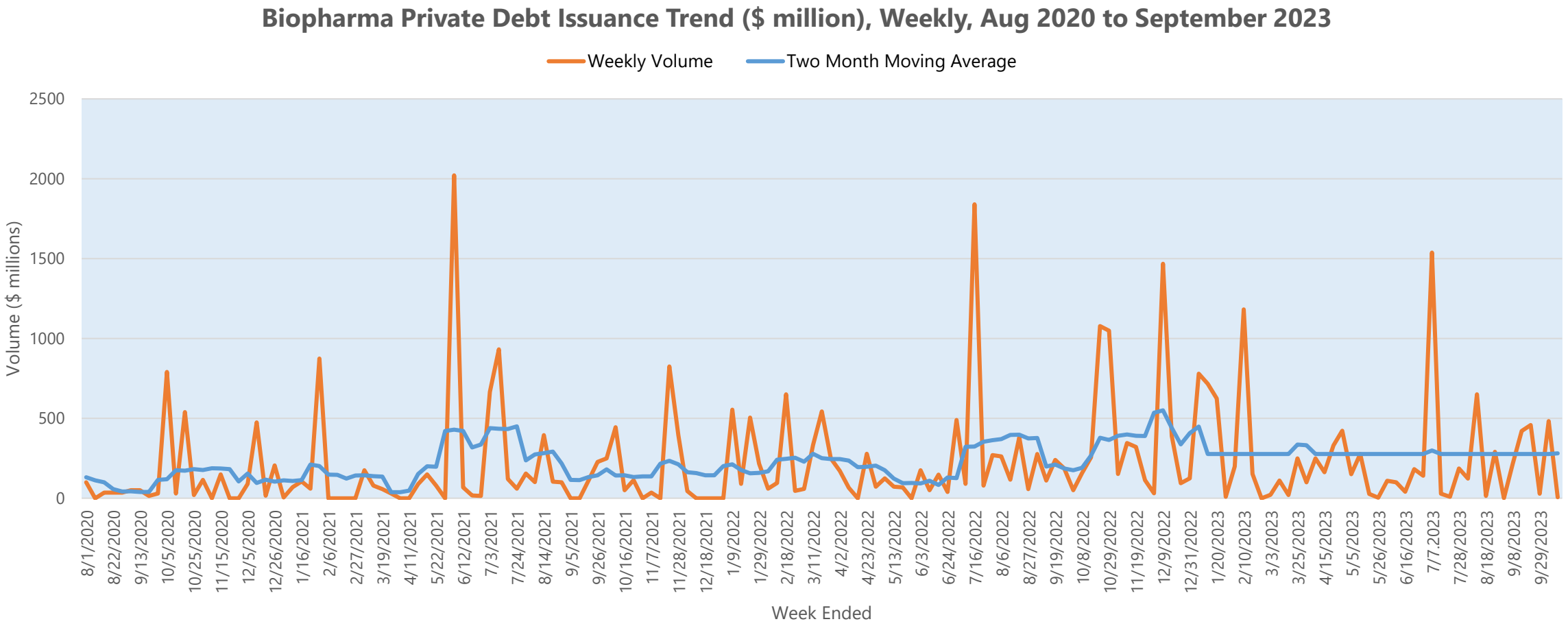
You're not going to hear a private biotech trumpeting a down round as they announce a new batch of funding, but industry experts say the broader market trend has seeped into the sector, while financings as a whole fell 24% last year.

In the second quarter of this year, the proportion of down private financing rounds across all sectors hit its highest peak in seven years, according to data collected by industry law firm Cooley. The firm reported that 21% of all the venture financing rounds it handled for the quarter were down, the most in any quarter since the second quarter of 2016. Meanwhile, flat rounds represented just 2% of deals during the quarter, down from 11% in the first quarter and aligning with numbers seen during 2021 and early 2022.

Sources: https://carta.com/data-desk/, https://www.fiercebiotech.com/biotech/market-hangover-why-down-rounds-are-rising-and-what-it-means

Weekly Global Biopharma Private Debt Placements

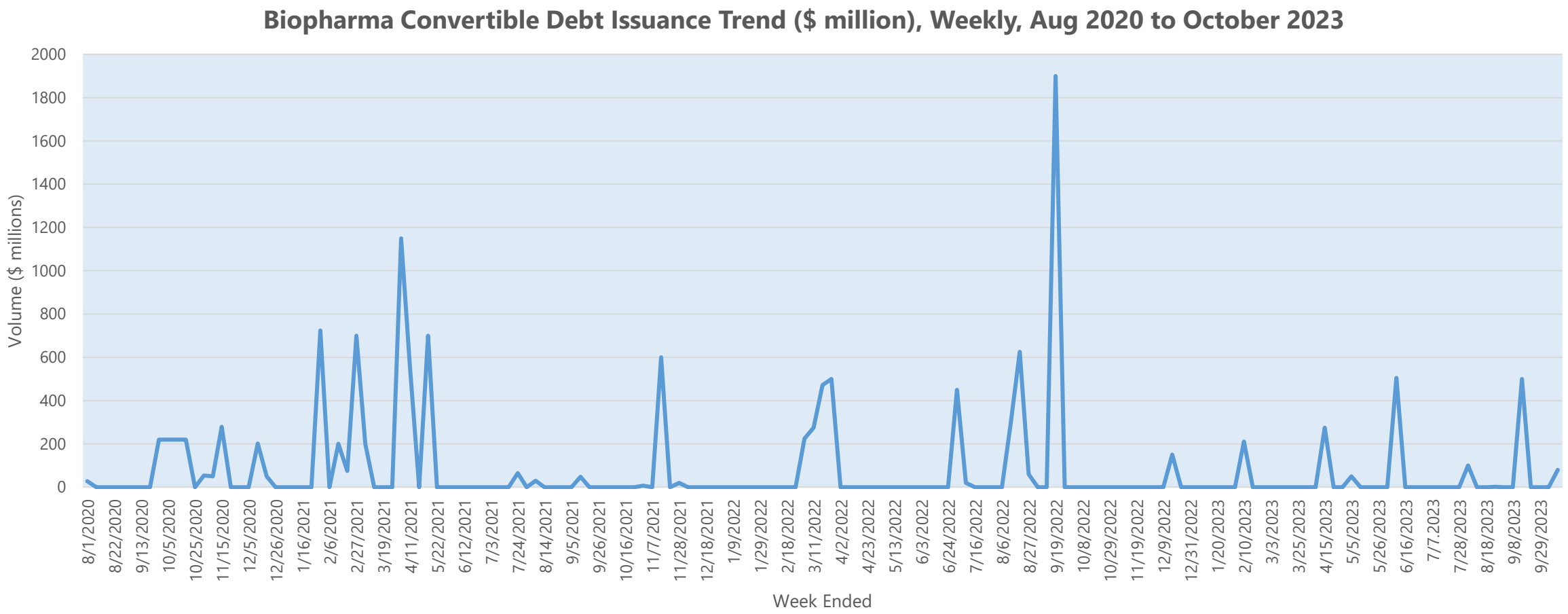
We saw one deal in the private debt market last week with $7mm raised. It was a quiet week on the debt front.



Source: Data from CapitalIQ, Crunchbase.

Convertible Market Open Last Week

Last week saw Bionano Genomics complete an $80.0 Million Registered Offering and Concurrent Private Placement of Senior Secured Convertible Notes and Warrants.



Source: Data from CapitalIQ, Crunchbase.

Bionano Prices $80 Million Registered Offering and Concurrent Private Placement of Senior Secured Convertible Notes and Warrants

SAN DIEGO, Oct. 11, 2023 (GLOBE NEWSWIRE) -- Bionano Genomics, Inc. (Nasdaq: BNGO) today announced the pricing of (i) $45.0 million aggregate principal amount of senior secured convertible notes due 2025 (the "Registered Notes") and warrants (the "Registered Warrants") to purchase 21,660,650 shares of its common stock in a registered offering, and (ii) $35.0 million aggregate principal amount of senior secured convertible notes due 2025 (the "Private Placement Notes" and together with the Registered Notes, the "Notes") in a concurrent private placement, in each case, to a certain accredited investor (the "Buyer"). Each Registered Warrant has an exercise price of $3.1855 per share and expires five years from the date of issuance. The gross proceeds from the registered offering and concurrent private placement to Bionano are expected to be approximately $80.0 million, before deducting placement agent fees and offering expenses payable by Bionano. The registered offering and the concurrent private placement are each contingent upon the other. The sale of the Notes and the Registered Warrants to the Buyer is expected to close on October 13, 2023, subject to customary closing conditions.

Bionano has also granted the Buyer an option to purchase up to an additional $25.0 million aggregate principal amount of senior secured convertible notes due 2025 (the "Additional Notes") and warrants to purchase up to 6,768,953 shares of common stock in a subsequent private placement on substantially the same terms as the Private Placement Notes and the Registered Warrants, respectively.

The Notes will not bear regular interest and will mature on September 1, 2025 (the "Maturity Date"), unless earlier repurchased, redeemed or converted. The Notes will be sold at an issue price of 100% of their principal amount, and when Bionano repays principal of the Notes at maturity pursuant to the terms of the Notes, it will be required to pay 115% of the principal amount repaid (the "Repayment Price"). Holders of the Notes will have the option to partially redeem a portion of the principal amount of the Notes on the first day of each month beginning on November 1, 2023 (a "Partial Redemption Date"), at the Repayment Price, plus any accrued and unpaid default interest thereon.

$80,000,000

bionano

Registered Offering and Private Placement of Convertible Notes

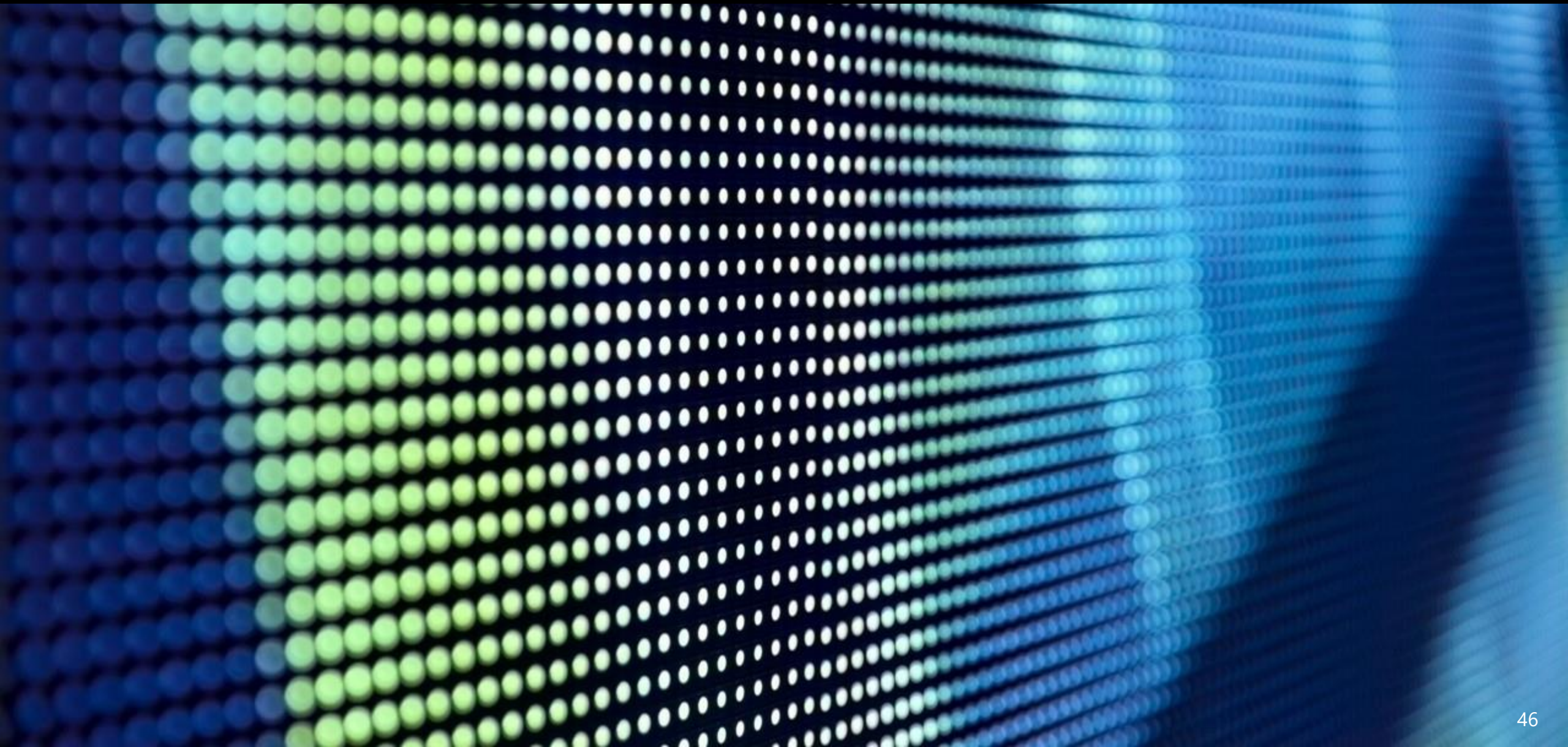
Co-Lead Placement Agent

October 2023

Stifel was pleased to act as co-lead placement on Bionano's registered offering and convertible last week.

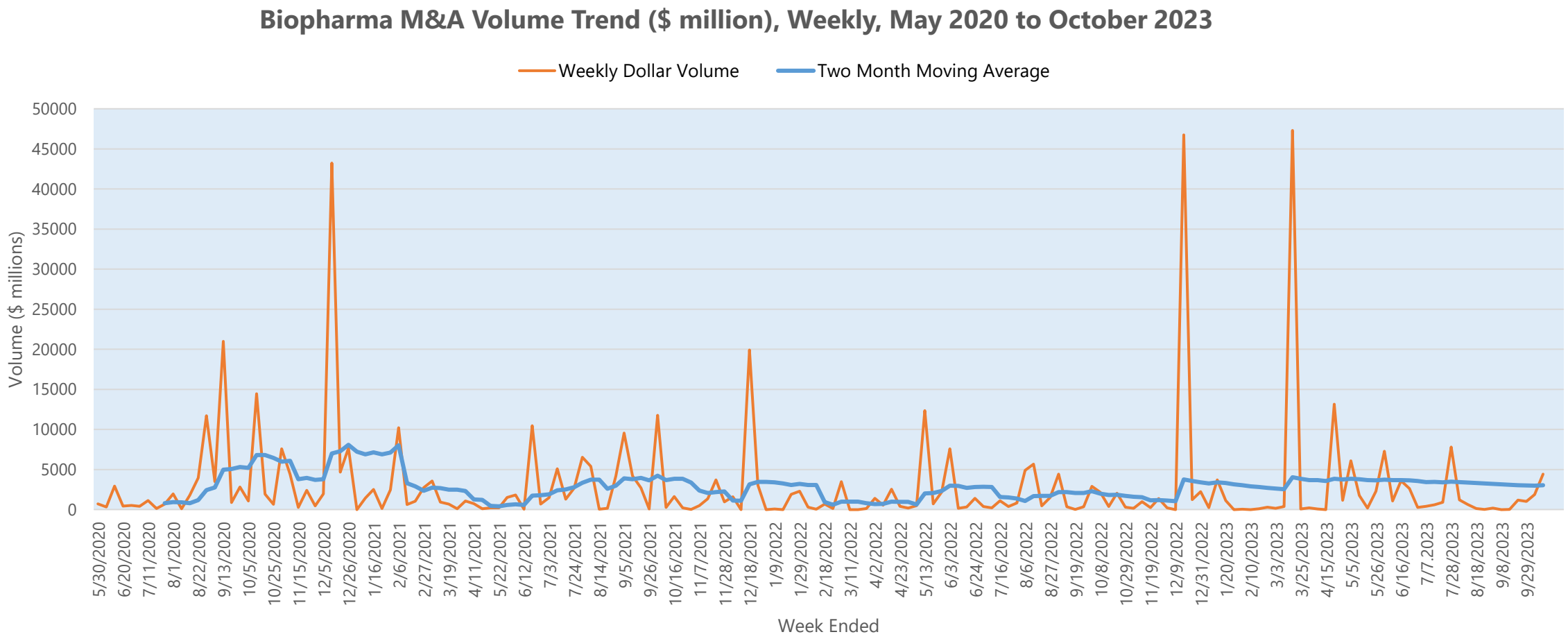
Source: https://ir.bionanogenomics.com/news-releases/news-release-details/bionano-announces-pricing-800-million-registered-offering-and

Biopharma Deals Environment



Major M&A Pick Up Last Week

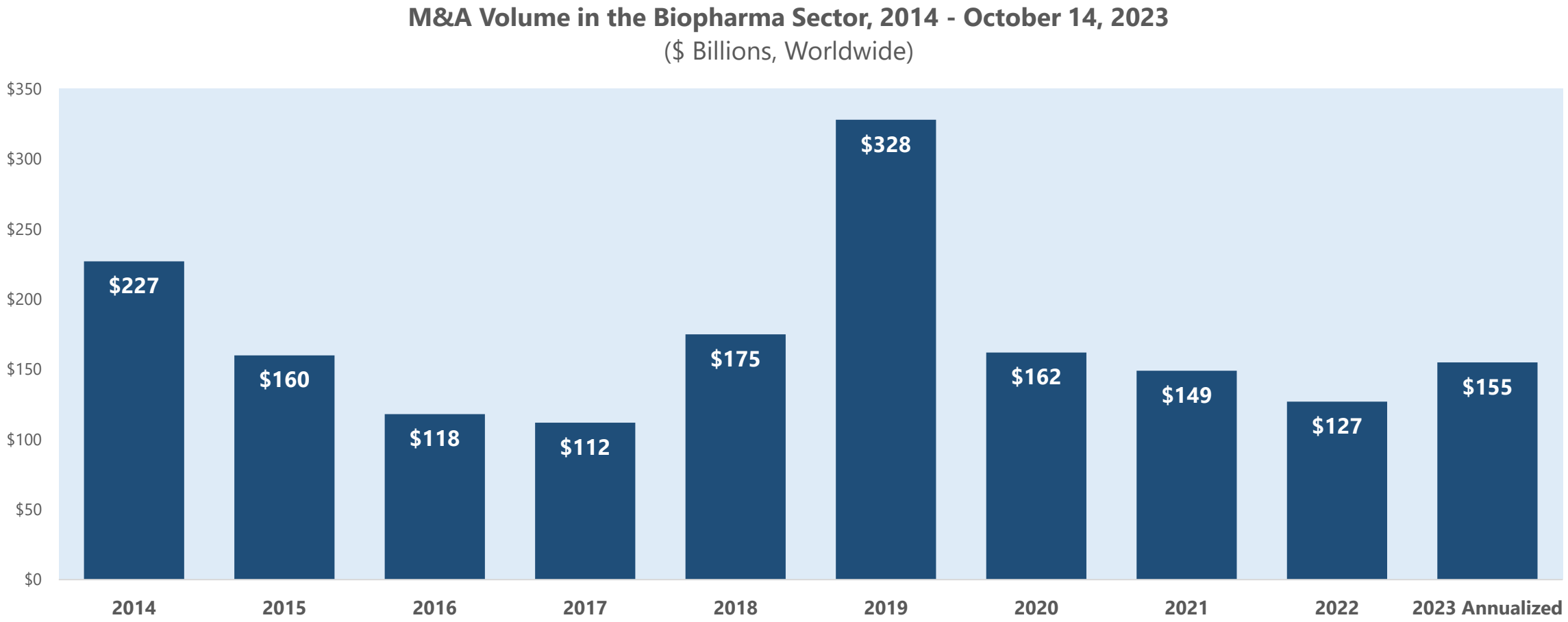
Last week saw $4.4 billion in M&A deals announce last week across four transactions. The largest transaction was the announcement that Bristol-Myers Squibb would acquire Mirati Therapeutics for $4.2 billion. Other transaction of note including a go private deal for Genetron in China ($151 million) and the purchase of Shanghai Chia Tai Tongyong Pharmaceutical for $40 million.



Source: S&P, CapitalIQ

Annualized 2023 M&A Volume Up 22% From 2022 and Up Slightly Over 2021.

We were on track for 2023 to be a typical M&A year compared to the last decade. Given the ongoing FTC regime and emergence of the IRA, this is quite a good performance.



Source: CapitalIQ and DealForma.

After summer slump, biotech M&A has a good week

A recent string of bigger-ticket acquisitions, including those of Mirati and Point, may serve as fodder to analysts who expect an uptick in biopharma deals.

Jacob Bell, *Biopharma Dive*, October 10, 2023 (excerpt)

This summer, large biotechnology deals took a vacation.

In the three-month stretch from July through September, just six acquisitions worth at least $50 million were announced, according to data compiled by BioPharma Dive. The tally is half of what was seen in the same period last year, and smaller than the 10 deals of that size unveiled between April and June.

Together, the half-dozen acquisitions in the third quarter carry a total consideration of more than $8.8 billion. Yet most of that sum comes from one deal: Biogen's proposed purchase of Reata Pharmaceuticals. Biogen's offer of $172.50 per share put a 59% premium on Reata, and valued the rare disease drugmaker at approximately $7.3 billion.

The dry spell of mergers and acquisitions could be coming to an end, though, if a recent string of buyouts is any indication.

The first weeks of October brought four deals collectively worth at least $6.7 billion. The list includes Eli Lilly's takeover of radiopharmaceuticals maker Point Biopharma; Kyowa Kirin's purchase of gene therapy developer Orchard Therapeutics; and Bristol Myers Squibb's acquisition of cancer-focused Mirati Therapeutics.

This activity may serve as fodder to some on Wall Street who've been forecasting an uptick in biopharma deals.

Source: https://www.biopharmadive.com/news/biotech-deals-acquisitions-third-quarter-2023/696068/

M&A Deal Size Up in 2023

Table 1: Aggregate, mean and median values of M&A deals, H1 2022 vs. H1 2023

ALL DEALS	H1 2022	H1 2023	CHANGE
AGGREGATE VALUE OF ALL M&A DEALS	US$54,380 M	US$100,541 M	+85%
MEAN DEAL VALUE	US$560 M	US$1,595 M	+185%
MEDIAN DEAL VALUE	US$125 M	US$97 M	-22%
ALL DEALS (EXCLUDING PFIZER/SEAGEN)	**H1 2022**	**H1 2023**	**CHANGE**
AGGREGATE VALUE OF ALL M&A DEALS	US$54,380 M	US$57,541 M	+6%
MEAN DEAL VALUE	US$560 M	US$928 M	+66%
MEDIAN DEAL VALUE	US$125 M	US$96 M	-23%

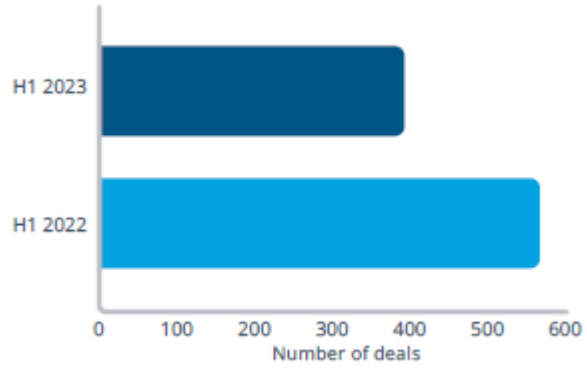
Source: IQVIA Pharma Deals.

The aggregate total value of all M&A deals signed in H1 2023 soared by 85% to US$100.5B and similarly, the mean total deal value increased 185% from US$560 M in H1 2022 to US$1,595 M in H1 2023. However, the dataset is skewed significantly by the inclusion of the announcement of the acquisition of Seagen by Pfizer in March for US$43 B. Excluding this mega-deal, the aggregate and mean total deal size is up less.

Source: https://www.iqvia.com/library/white-papers/half-year-review-of-2023

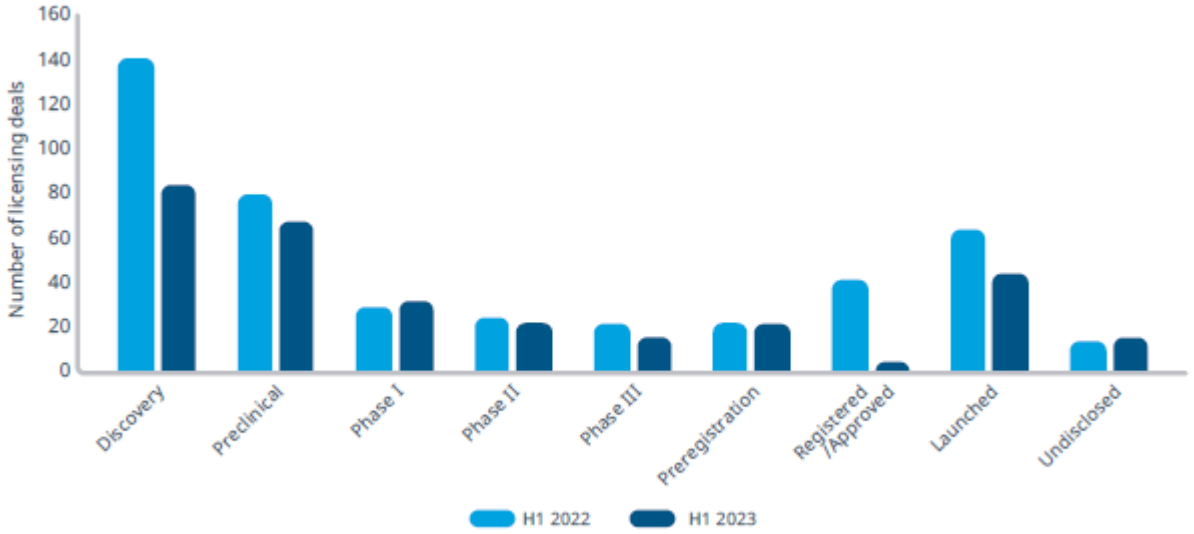
Big Drop in Discovery Stage Licensing Deals in 2023

Figure 3: Number of licensing deals, H1 2022 vs. H1 2023



Source: IQVIA Pharma Deals.

Figure 4: Therapeutic licensing deals by development stage, H1 2022 vs. H1 2023



Source: IQVIA Pharma Deals.

Source: https://www.iqvia.com/library/white-papers/half-year-review-of-2023

Industry News

Pfizer Updates Full-Year 2023 Guidance After Updating on U.S. Government Paxlovid and Comirnaty Status

October 13, 2023. NEW YORK--(BUSINESS WIRE)--Pfizer Inc. (NYSE:PFE) today announced that it has amended its supply agreement with the U.S. government for Paxlovid, the first oral antiviral pill approved by the U.S. Food and Drug Administration (FDA) and is updating its Full-Year 2023 Guidance.

At the end of 2023, Pfizer will accept a non-cash return of any remaining Emergency Use Authorized (EUA)-labeled U.S. government inventory, estimated to be 7.9 million treatment courses, and in the fourth quarter, will reverse the associated revenues currently estimated to be approximately $4.2 billion. The commercial transition will begin in November 2023, as the U.S. government begins to discontinue the distribution of EUA-labeled Paxlovid. Pfizer will ensure commercial readiness by providing NDA-labeled commercial supply to all channels by the end of 2023.

As previously announced, the European Union (EU) contract for Comirnaty supply was renegotiated with amended purchasing obligations through 2026. The U.S. market for Comirnaty transitioned to commercially available product in September 2023. Due to the recent commencement of the fall vaccination period, the outlook for year-end vaccination rates and market shares requires more time for more determinable estimates. In addition, in the fourth quarter of 2023, Pfizer announced that the company has launched a multi-year, enterprise-wide cost realignment program that will realign its costs with its longer-term revenue expectations. The program is expected to deliver targeted savings of at least $3.5 billion, of which $1.0 billion is expected to be realized in 2023 and an additional $2.5 billion is expected to be realized in 2024. The one-time costs to achieve the savings associated with the new cost realignment program are expected to be approximately $3.0 billion, of which the majority is expected to be cash. These costs will primarily include severance and implementation costs. Pfizer will continue to refine the estimated targeted savings and their associated costs over the remainder of the year and will incorporate them into its full-year guidance for 2024.

Pfizer also announced that it now anticipates full-year 2023 revenues to be in the range of $58.0 to $61.0 billion, versus its previous guidance range of $67.0 to $70.0 billion solely due to its COVID products. Full-year 2023 revenues for Paxlovid and Comirnaty are expected to be approximately $12.5 billion, a decline of $9.0 billion versus original expectations. The company is also reducing its full-year 2023 revenue expectations for Comirnaty by approximately $2.0 billion due to lower-than-expected vaccination rates.

	2023 Previous Guidance[1] *(August 1, 2023)*	One-Time Items[a]	All Other Adjustments[b]	2023 Revised Guidance[1]
Revenues*	$67.0 to $70.0 billion	-$(4.2) billion	~$(4.8) billion	$58.0 to $61.0 billion
***Non-cash* Inventory Write-offs[a]**		$5.5 billion		
Adjusted[2] Diluted EPS*	$3.25 to $3.45	$(1.46)	$(0.34)	$1.45 to $1.65

Source: https://www.businesswire.com/news/home/20231013643494/en

Pfizer Stock Takes Hit in After-Hours Trading After Updating 2023 Earnings Guidance

While Pfizer stock took a hit in after hours trading on Friday evening, it wasn't that big.

The reason is that Pfizer shares have been down all year as investors have anticipated the news that Covid product sales will be well less than guided.

However, Pfizer is transitioning to commercial pricing for Covid products which could be a major positive for earnings.

Further, Pfizer's announcement of $2.5 bn in annualized cost reductions is likely, on balance, to be a further major positive for future earnings.

The timing of this release on Friday after hours was odd but we at Stifel don't see it all as bad news, on balance.

Pfizer had a pretty good week last week with FDA approval of its UC drug from Arena and continues to show a strong pipeline of launches. The shares seem quite depressed as the market has been waiting for the Covid shoe to finally drop.

Source: Google Finance

Bayer: Cell Therapy is a Promising Prescription

***Financial Times*, October 10, 2023 (excerpt)**

Bayer has lost a lot of ground since its disastrous 2018 acquisition of Monsanto. Bill Anderson, who became chief executive in June, describes it as bogged down in litigation, bureaucracy and debt.

Yet the German conglomerate is making rapid moves in its pharma division. On Tuesday, it underlined its commitment to cell therapy by investing $250mn in a new production plant in Berkeley, California. Bayer's first potential drug is bemdaneprocel, designed to replace the dopamine-producing neurons that are lost in Parkinson's disease. The results of an early stage trial were promising. A Phase 2 trial is due to begin next year.

There is as yet no cure for Parkinson's, which leads to a progressive loss of motor function. A one-time treatment would be a valuable asset. But investors cannot ascribe much value to that yet. They are pinning their hopes on Asundexian, a blood thinner that can prevent strokes. This is in advanced clinical trials. It could fill some of the looming gap caused by the expiry of patents for anti-clotting medication Xarelto and eye medicine Eylea.

These patent expiries, declining farm incomes and a battery of legal claims — estimated at €9bn by Berenberg's Sebastian Bray — weigh on Bayer shares. There is a case for a break-up. Crop science is the largest part of the business and would work as a standalone. There is also a case for splitting off pharma, which would be worth about €33bn. The consumer health division has a value roughly half that.

That would raise questions about the independence of a business that is small by industry standards. However, as an incoming boss, Anderson has a licence to think the unthinkable.

Source: https://www.ft.com/content/466716f3-8085-4fd0-8dd4-03a05cf4fab8

DRUGS ALONE ARE NOT ENOUGH TO SOLVE THE OBESITY EPIDEMIC

Dr. Oliver Eitelwein, Rolf Fricker, Dr. Clemens Freytag, and Harsh Baid

Oct 13, 2023

5 min read

The sudden and meteoric rise in use of new weight-loss drugs put a spotlight on obesity prevention. But decades before Wegovy and Ozempic took the market by storm, public health agencies ranging from the US Centers for Disease Control and Prevention to the World Health Organization had deemed obesity an epidemic. The crisis shows no sign of abating — the World Obesity Federation reported that more than half of the world's population will be obese by 2035.

A set of interconnected challenges face patient segments, including lack of awareness around health risks, pervasive stigma, inadequate treatment coverage, and limited long-term monitoring options. Recognizing the urgent need for action, key stakeholders — patients, healthcare professionals, payers, and drug manufacturers — need to re-evaluate their roles for treating the disease and find new ways to collaborate to alleviate the burden of obesity on individuals and society.

Source: https://www.oliverwyman.com/our-expertise/perspectives/health/2023/oct/drugs-alone-are-not-enough-to-solve-the-obesity-epidemic.html

Ultragenyx and Mereo BioPharma Announce Interim Phase 2 Data from Phase 2/3 Orbit Study Demonstrating Setrusumab (UX143) Significantly Reduced Fracture Rates in Patients with Osteogenesis Imperfecta (OI)

NOVATO, Calif., VANCOUVER, British Columbia and LONDON, Oct. 14, 2023 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) and Mereo BioPharma Group plc (NASDAQ: MREO) today announced interim data from the Phase 2 portion of the Phase 2/3 Orbit study demonstrating that treatment with setrusumab (UX143) significantly reduced incidence of fractures in patients with OI with at least 6 months of follow-up and continues to demonstrate ongoing and meaningful improvements in lumbar spine bone mineral density (BMD). The data were presented in a late-breaker presentation at the American Society for Bone and Mineral Research 2023 Annual Meeting (ASBMR).

As of the cut-off date and following at least 6 months of treatment with setrusumab, the annualized fracture rate across all 24 patients in the Phase 2 portion of the study was reduced by 67%. In the 2 years prior to treatment with setrusumab all patients experienced at least 1 fracture. The median annualized fracture rate of 0.72 in the 2 years prior to treatment was reduced to 0.00 (n=24, p=0.042) during the mean treatment duration period of 9 months. Following initiation of treatment with setrusumab, 20 patients experienced no radiographic-confirmed fractures, and 4 patients experienced 7 radiographic-confirmed fractures in 5 separate events. These fractures exclude fractures of the fingers, toes, skull, and face consistent with the Phase 3 study design.

“I have not yet encountered a patient with a fragility fracture while on setrusumab, and this may result from setrusumab’s effects on the skeleton, improving the rate of new bone formation and bone quality,” said Gary Gottesman, M.D., Professor of Pediatrics and Medicine, Washington University School of Medicine. “Some of the kids feel well enough they are participating in activities that they might normally avoid and have suffered some relatively minor fractures.”

Source: https://ir.ultragenyx.com/news-releases/news-release-details/ultragenyx-and-mereo-biopharma-announce-interim-phase-2-data

A Tempestuous Ride

Angel Adegbesan, Fortune, Oct 13, 2023

An under-the-radar biotech firm called Tempest Therapeutics Inc. is set to notch its best week on record after results from a liver cancer trial sent the stock surging 3,973% — and tumbling the next day.

Wall Street cheered as the stock shot up to $9.77 on Wednesday when the drug developer said its experimental cancer therapy in a cocktail with two Roche Holding AG drugs worked better than the pair of drugs by themselves. The surge after the Roche-run study helped push Tempest's market value to $130 million from a mere $3 million as of the previous day's close.

Shares of Tempest have come off that high in the two latest trading sessions as investor enthusiasm moderated and a broader market selloff in risky assets batters the high-risk biotechnology sector. The firm's current market value of $54 million remains more than 16-fold of what it was, before the jump.

Tempest was "coming from an almost unfathomably low valuation going into this data readout," as investors were skeptical following earlier study results, according to William Blair analyst Matt Phipps. "The company is still clearly undervalued for the blockbuster opportunity" of its cancer drug, he wrote in a note dated Wednesday.

Analysts tracked by Bloomberg that cover the company are universally bullish, with all four rating Tempest the equivalent of a buy. The average of three price targets suggests the stock could more than quadruple from its current $4 a share level.

Source: https://fortune.com/2023/10/13/tempest-therapeutics-shares-surge-after-roche-led-cancer-treatment-trial/

Updated Cancer Immunity Cycle Chart From Ira Mellman and Shannon Turley

Mellman I, Chen DS, Powles T, Turley SJ. The cancer-immunity cycle: Indication, genotype, and immunotype. Immunity. 2023 Oct 10;56(10):2188-2205.

The cancer-immunity cycle provides a framework to understand the series of events that generate anticancer immune responses. It emphasizes the iterative nature of the response where the killing of tumor cells by T cells initiates subsequent rounds of antigen presentation and T cell stimulation, maintaining active immunity and adapting it to tumor evolution. Any step of the cycle can become rate-limiting, rendering the immune system unable to control tumor growth. Here, we update the cancer-immunity cycle based on the remarkable progress of the past decade. Understanding the mechanism of checkpoint inhibition has evolved, as has our view of dendritic cells in sustaining anti-tumor immunity. We additionally account for the role of the tumor microenvironment in facilitating, not just suppressing, the anti-cancer response, and discuss the importance of considering a tumor's immunological phenotype, the "immunotype". While these new insights add some complexity to the cycle, they also provide new targets for research and therapeutic intervention.

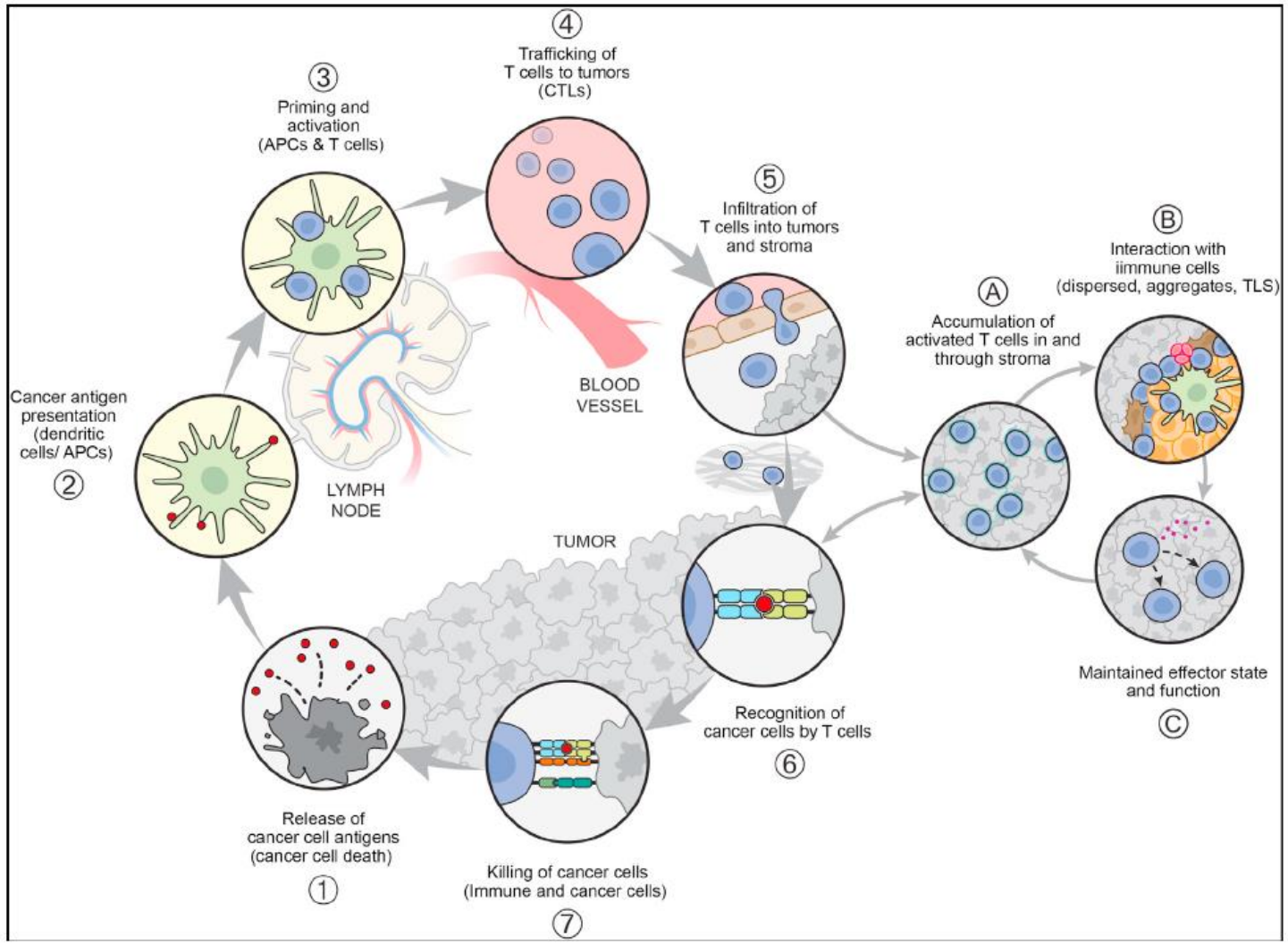


Figure 3. The cancer-immunity cycle and the tumor microenvironment cancer-immunity subcycle
Progress in the field of cancer immunity since 2013 has highlighted the importance T cell migration through tumor stroma, interaction with intratumoral immune cells, persistence, and function within the tumor microenvironment. T cells within the TME can respond in a series of steps that are a microcosm of what occurs systemically beyond the tumor. These subcycle steps represent an immunologic eddy in the TME, which we refer to as the cancer-immunity subcycle. When cancer immunity is active, stimulation, proliferation, and functional killing of cancer cells is possible. However, inhibitory immune cells and stroma, metabolic derangements, and loss of T cell function can occur within the TME, halting the cancer-immunity cycle.
APCs, antigen-presenting cells; CTLs, cytotoxic T lymphocytes; TLS, tertiary lymph node structure.

Source: https://pubmed.ncbi.nlm.nih.gov/37820582/

Amgen PRMT5 Inhibitor Shows Promise

AACR Newsroom, October 13, 2023

BOSTON – AMG 193, a second-generation protein arginine methyltransferase 5 (PRMT5) inhibitor, was safe and demonstrated preliminary antitumor activity in patients with solid tumors with methylthioadenosine phosphorylase (MTAP) deficiency, according to results from a phase I clinical trial presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held October 11-15 in Boston.

"Loss of MTAP is the consequence of a genetic alteration present in 10-15% of a long list of tumor types, including lung cancer, bile duct cancer, pancreatic cancer, melanoma, mesothelioma, and others, affecting a significant number of patients," explained presenter Jordi Rodon, MD, PhD, associate professor in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center.

Loss of MTAP results in accumulation of a metabolite that inhibits the activity of PRMT5, an enzyme involved in essential cellular functions. This renders the tumor cells vulnerable to additional PRMT5 inhibition. "The first generation of PRMT5 inhibitors, however, were not tumor-specific and were, therefore, associated with high toxicity," added Rodon.

AMG 193 belongs to a class of compounds called MTA-cooperative PRMT5 inhibitors. These second-generation PRMT5 inhibitors are designed to suppress PRMT5 function specifically in MTAP-null cells while sparing it in healthy cells, thus selectively killing the tumor cells, Rodon explained. Rodon and colleagues tested AMG 193 in a first-in-human phase I clinical trial that involved 47 patients with MTAP-null solid tumors, including 10 patients with pancreatic ductal adenocarcinoma, six patients with non-small cell lung cancer, five patients with cholangiocarcinoma (bile duct cancer), three patients with mesothelioma, and 23 patients with other cancer types. Study participants were enrolled in seven dose-escalating cohorts to identify the recommended phase II dose.

AMG 193 was safe and did not result in bone marrow toxicity, which was an issue with first-generation PRMT5 inhibitors. "We demonstrated that AMG 193 did not cause significant neutropenia and thrombocytopenia and had a wide therapeutic window that allowed it to target PRMT5 at low doses," said Rodon.

The most common adverse events were gastrointestinal toxicities associated with higher dose levels. "We suspect this might be related to the number of pills that patients had to take to achieve the higher dosage, and we are working to develop an improved formulation to address this issue," said Rodon.

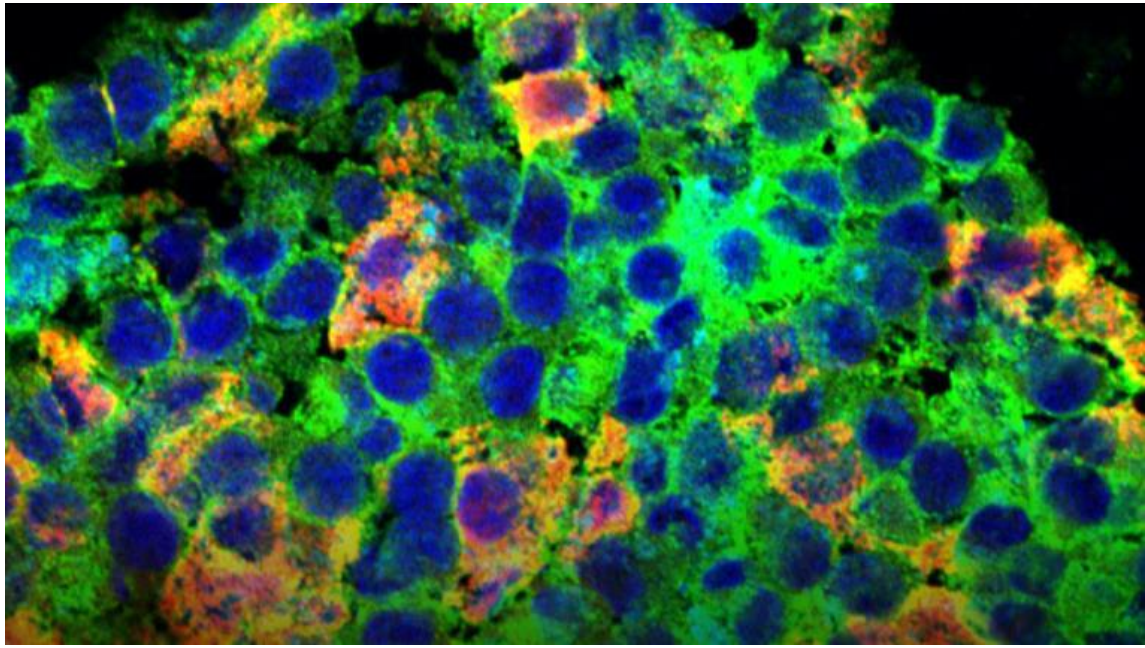
Among 31 patients who received at least one scan after starting therapy, five patients with different tumor types experienced a partial response (PR), 14 patients had stable disease (SD), and 12 patients had disease progression. Notably, the PRs were durable and were ongoing at the time of data analysis, when patients had been on treatment for 140–275 days.

Source: https://www.aacr.org/about-the-aacr/newsroom/news-releases/new-investigational-targeted-therapy-shows-early-promise-in-patients-with-solid-tumors/

A Metabolic Role for CD47 in Pancreatic β Cell Insulin Secretion and Islet Transplant Outcomes

Ghimire K, Kale A, Li J, Julovi SM, O'Connell P, Grey ST, Hawthorne WJ, Gunton JE, Rogers NM. A metabolic role for CD47 in pancreatic β cell insulin secretion and islet transplant outcomes. *Sci Transl Med.* 2023 Oct 11

The cell surface glycoprotein CD47 is commonly understood as an immune-evasive "don't eat me" signal. Ghimire *et al*. now report that CD47 also limits insulin secretion by human and mouse pancreatic beta cells. Reducing CD47 improved glucose homeostasis and insulin sensitivity in an in vivo model of streptozotocin-induced diabetes and delayed disease onset and reduced disease severity in a model of autoimmune diabetes. Blocking islet CD47 with an antibody before syngeneic transplantation also improved graft survival and function, illustrating potential therapeutic relevance for type 1 diabetes.



Source: https://www.science.org/doi/10.1126/scitranslmed.add2387

Visualization of ADC Research Field

Bioconjugate Chemistry
Sep 27, 2023
Open Access
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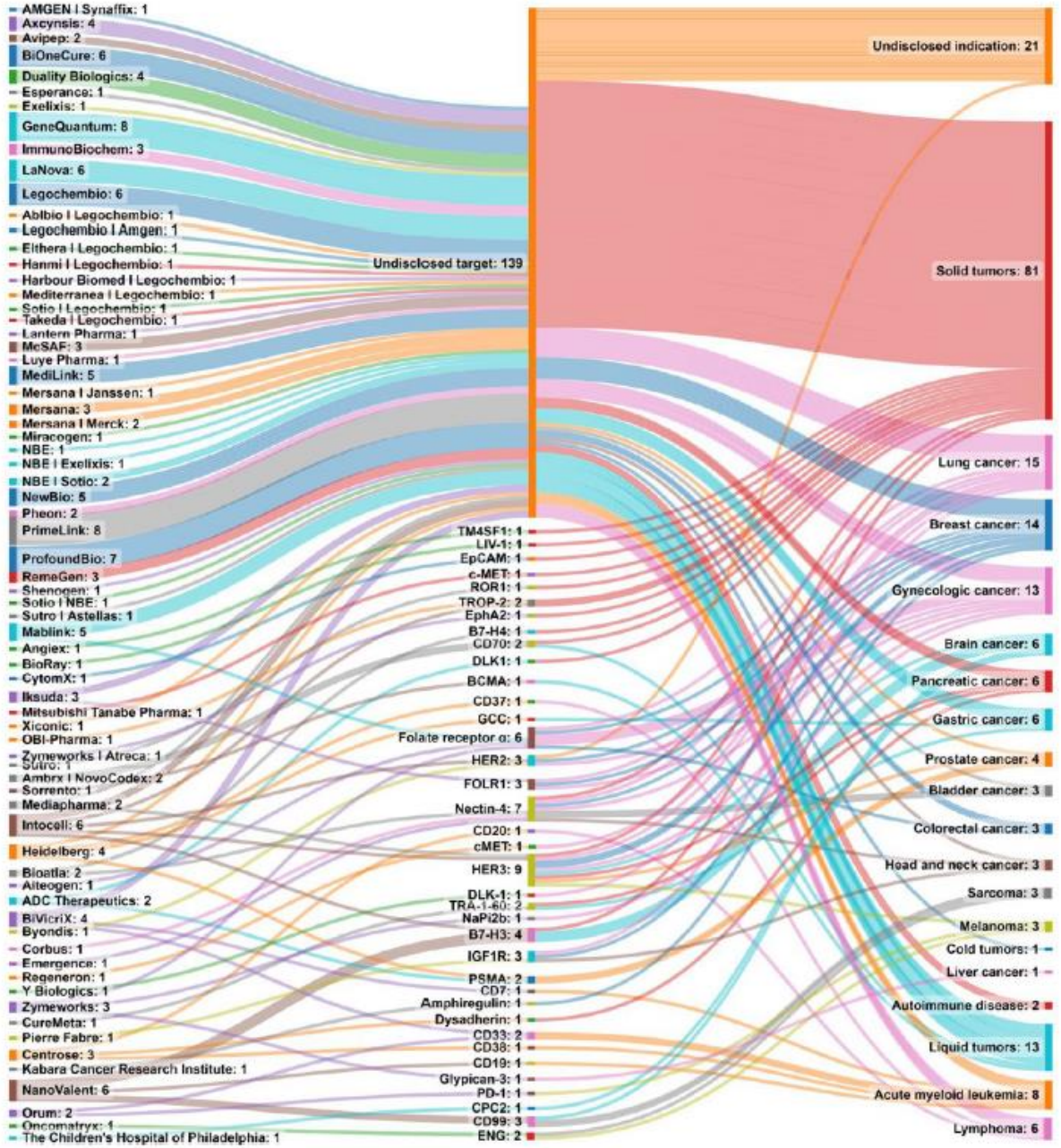
pubs.acs.org/bc
Review

The Evolving Landscape of Antibody–Drug Conjugates: In Depth Analysis of Recent Research Progress

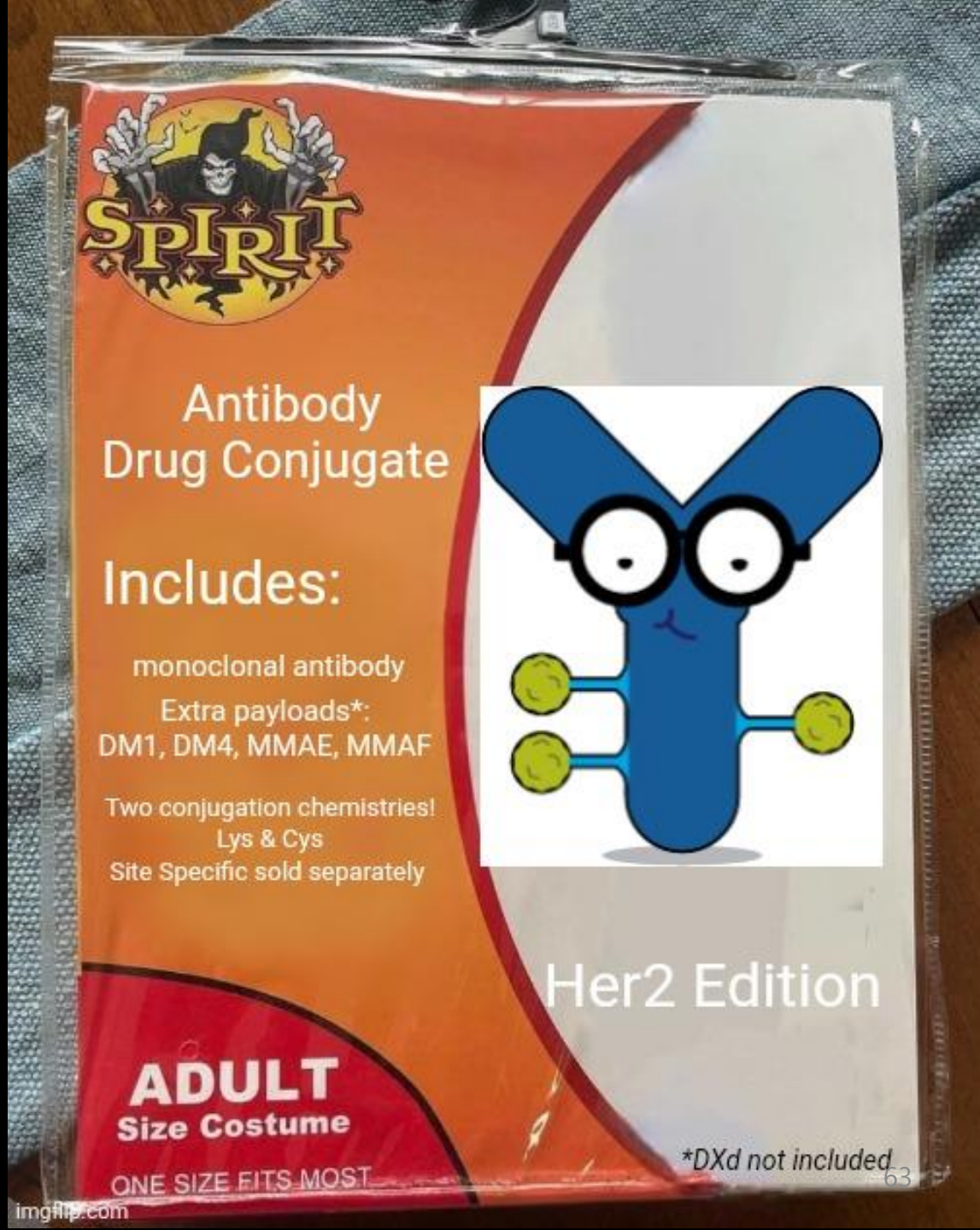
Janet M. Sasso,[§] Rumiana Tenchov,[§] Robert Bird, Kavita A. Iyer, Krittika Ralhan, Yacidzohara Rodriguez, and Qiongqiong Angela Zhou*

Examination of preclinical ADC development reveals that over 50 worldwide organizations, mainly from the United States, Europe, and Asia, are currently conducting research on over 160 ADC preclinical candidates. The figure at reveals organizations conducting preclinical ADC research, their ADC drug candidates, and target antigens, along with target indications. A few of these companies have disclosed the target antigens for their ADC. Antigens HER3, Nectin-4, Folate receptor α, B7H3, CD99, and IGF1R are leading the way with the most ADC drug candidates utilizing these targets for disease treatment.

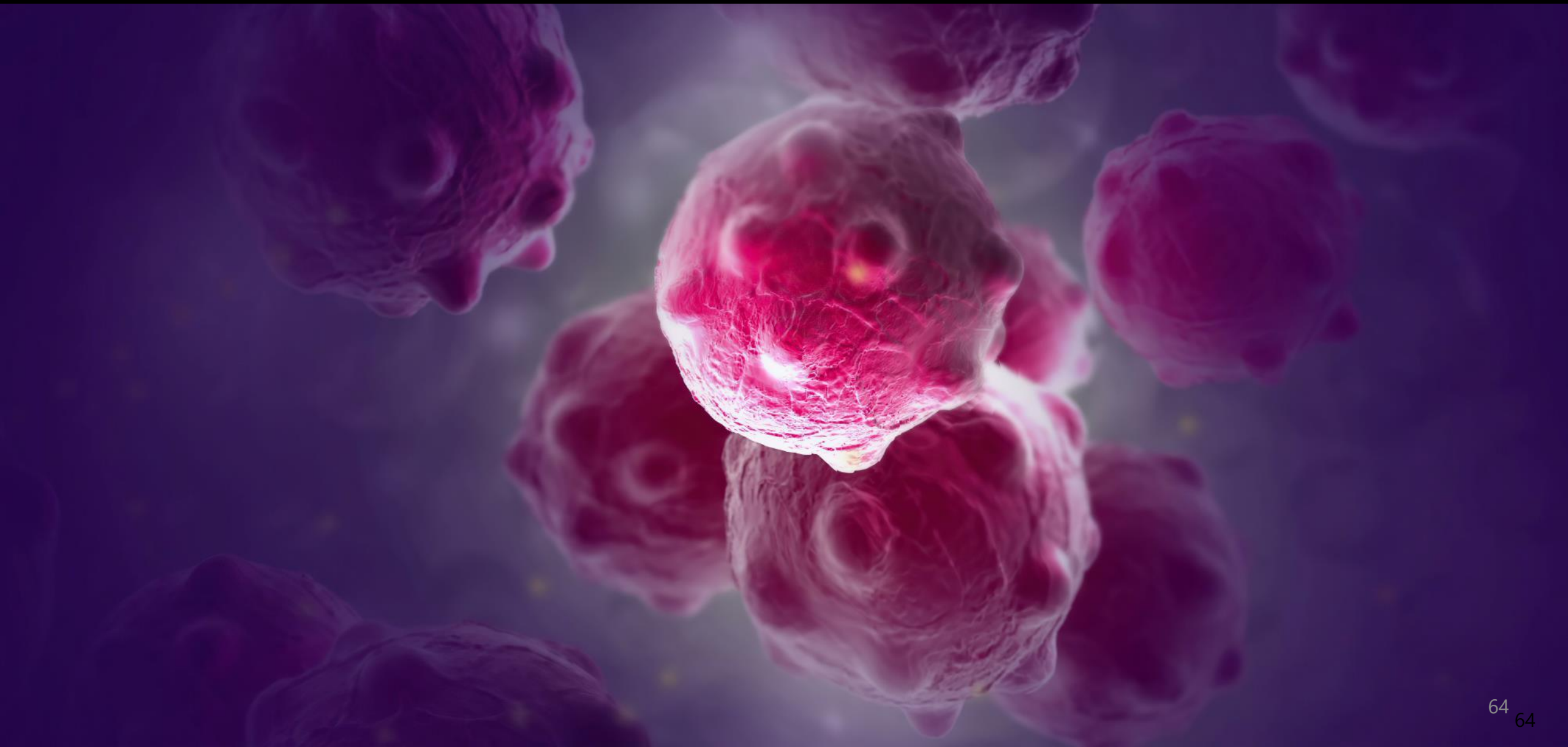


Source: https://pubs.acs.org/doi/epdf/10.1021/acs.bioconjchem.3c00374

Suggestion for This Season's Halloween Costume



Pan Cancer Screening Progress



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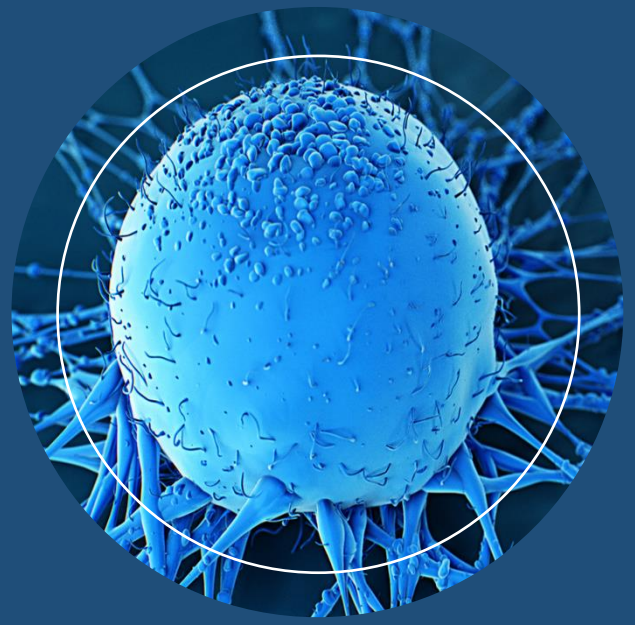


Cancer

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Tumors may form from these abnormally grown cells which are lumps of tissue. Tumors can be cancerous or not cancerous (benign). Tumors have the potential to spread cells throughout the body (metastatic). Cancer is the leading cause of death worldwide and lung cancer is the number one cause of death from cancer in the United States.

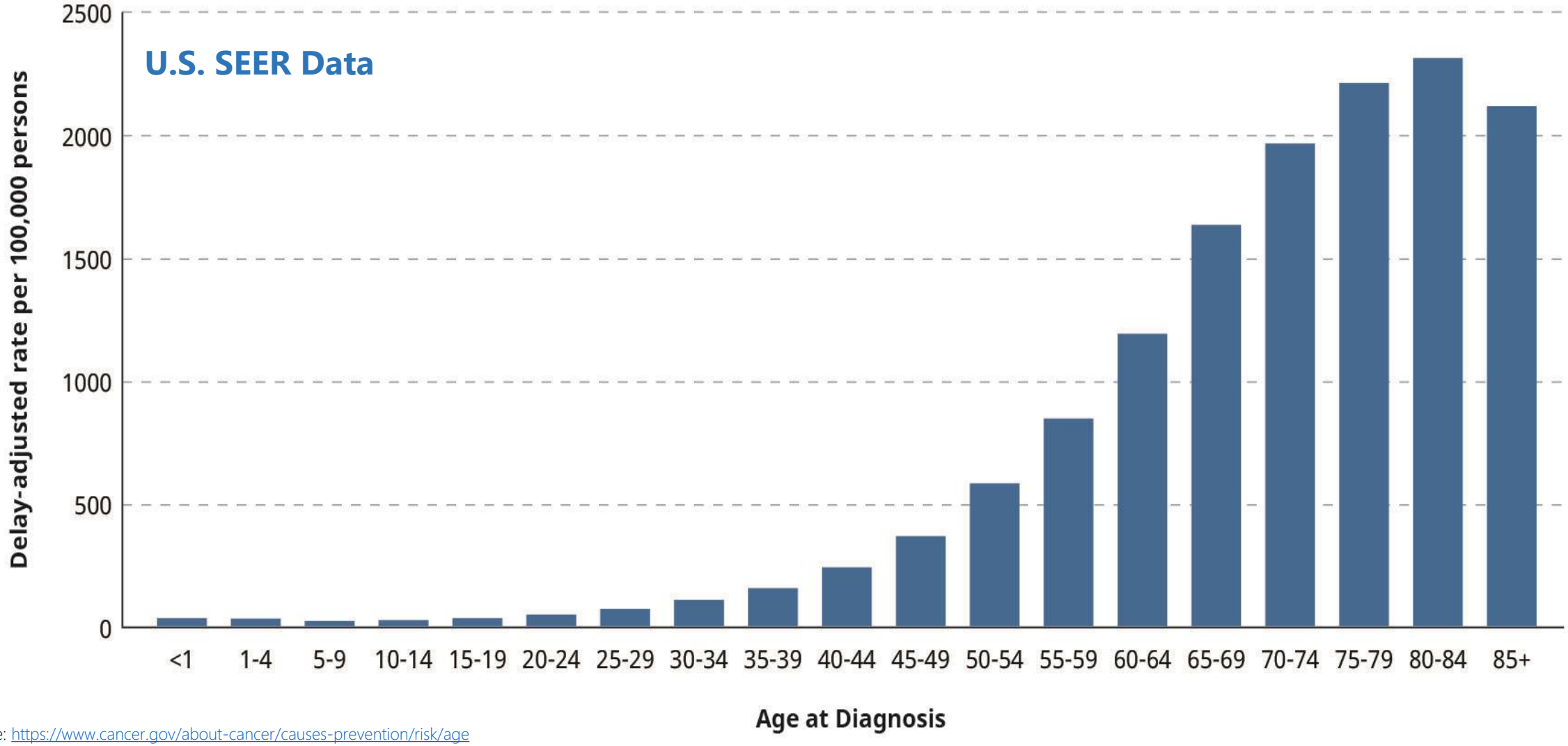
Key Points

1. Medicare reimburses cancer in five major groups: lymphomas, serious solid tumors (lung, ovarian, pancreatic) and less life threatening solid tumors (breast, prostate). There is also a colorectal and bladder cancer.

2. Certain cancers including ovarian cancer, lung cancer and pancreatic cancer are often detected late when survival rates are low. A key research priority has been to accelerate early detection of cancers of all kinds.

3. There has been intense interest in early cancer detection and, in the recent years, both GRAIL and Thrive have introduced early pan-cancer detection tests. GRAIL relies on DNA methylation analysis while Thrive uses proteomics and CTC analysis.

Cancer is a Disease of Old Age



Source: https://www.cancer.gov/about-cancer/causes-prevention/risk/age

Good Market Opportunity for a Low-Cost Pan-Cancer Detection Test in Medicare

1. Because Medicare serves the 65+ population in the U.S. it is the perfect place in which to institute pan-cancer screening.
2. No pan-cancer screening test in the Medicare guidelines today.
3. Medicare does recommend and pay for breast, colorectal, cervical and prostate cancer screening.
4. For past or current heavy smokers, Medicare does cover the cost of low-dose CT screens for lung cancer.
5. Other countries have not been able to implement pan-cancer screening.
6. Screening services in older populations in the U.S. like Optum HouseCalls and Signify do not screen for cancer
7. Strong societal interest in low cost screening for cancer.
8. Economic value of pan-cancer detection tests high:
    a) **Exact Sciences Acquisition of Thrive**: Paid over $1bn upfront with potential payments of $2.15 billion. Test had been through its first field trial.
    b) **Illumina Acquisition of Grail**: Paid $8 billion for a test that had yet to become commercially successful.
9. Lucas deBreed, American Cancer Society: “We are very interested in a low-cost pan-cancer screening test.”

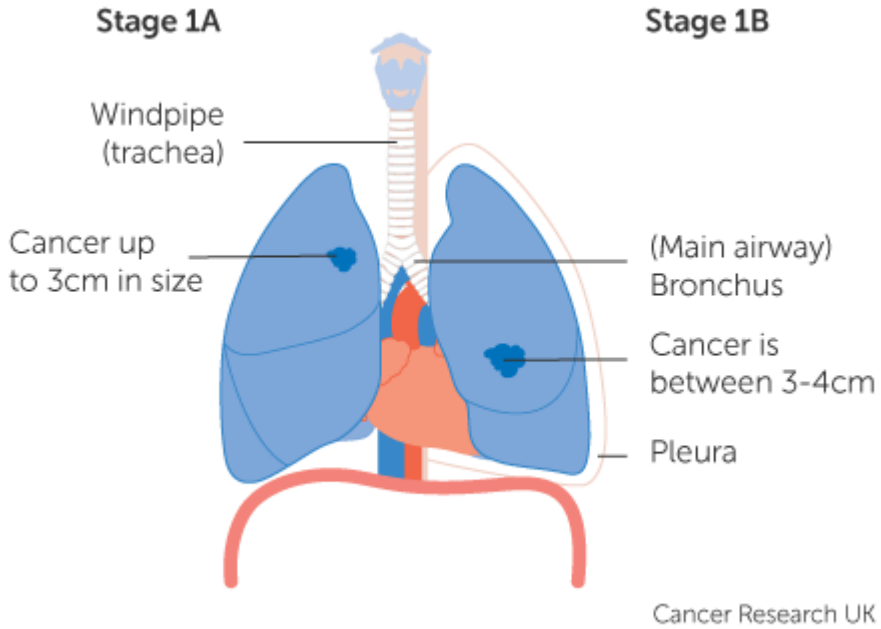
Designing a Medicare Screening Test: What is and isn't Cancer in Medicare

Medicare coding requires an analysis of the histology of a suspected tumor, a treatment plan and location. Suspected disease is not codeable.

Stage IA or IB Lung cancer is codeable. For example, a tumor in the lung that is less than 3cm in size can be coded (see figure at right). However, the attending physician would need to biopsy that tumor and classify its histology as malignant (e.g., squamous cell, large cell, non-small cell). Many lung nodules that are seen with CT scans turn out not to demonstrate a cancerous histology upon examination by a pathologist.

An important factor is CHIP (clonal hematopoesis of indeterminate potential). This could be thought of a precursor to liquid tumors.

The presence of somatic mutations in hematopoietic stem cells in an individual without a detectable hematologic cancer. The definition of CHIP requires that mutations are present with a variant allele frequency of 2% or higher and they are located in genes described to be affected in hematologic cancers. This condition is more common in older individuals and in those who have received treatment for other cancers. It is associated with both an increased risk of developing cardiovascular disease and hematologic cancers. CHIP is not codeable in Medicare.



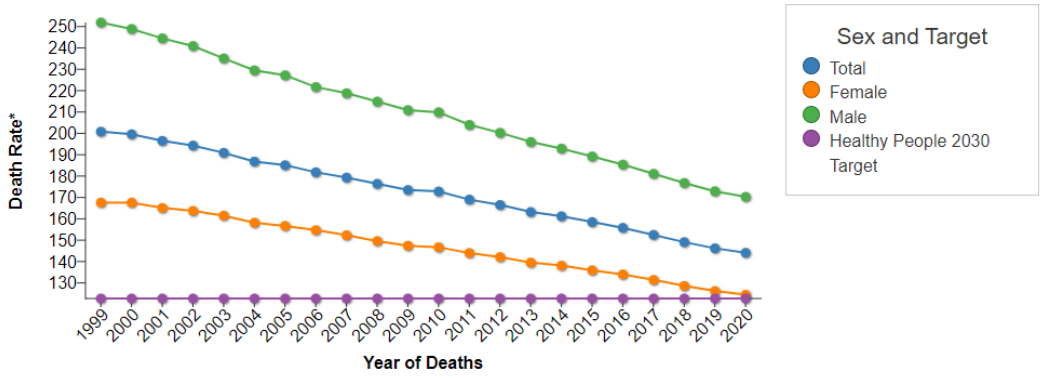
Cancer Statistics

CDC: In the United States in 2018, 1,708,921 new cancer cases were reported and 599,265 people died of cancer. For every 100,000 people, 436 new cancer cases were reported and 149 people died of cancer.

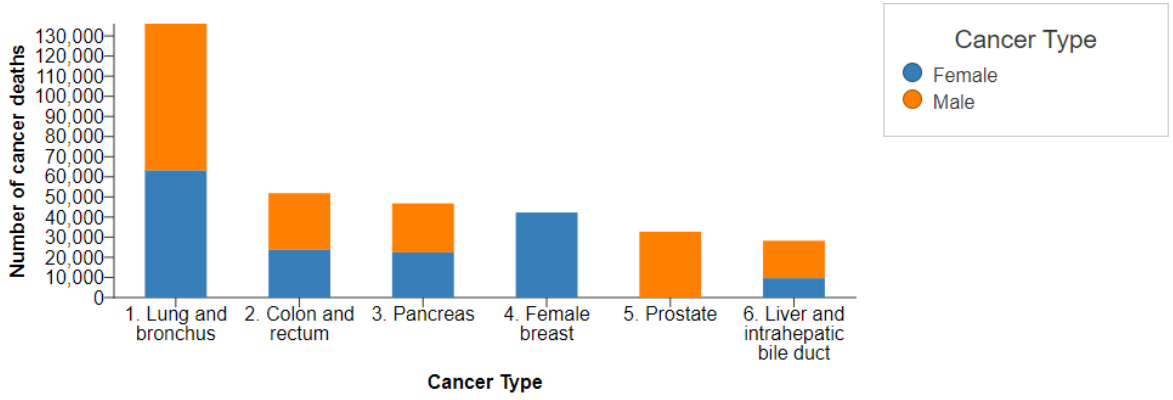
Cancer was the second leading cause of death, after heart disease, in the United States in 2019. In 2019, there were 599,601 cancer deaths; 283,725 were among females and 315,876 among males.

From 1999 to 2019, cancer death rates went down 27%, from 200.8 to 146.2 deaths per 100,000 population. Healthy People 2030 set a target of 122.7 cancer deaths per 100,00 population.

Age-adjusted cancer death rates, by sex, United States, 1999–2020



Deaths by Tumor Type, 2020



Source: https://www.cdc.gov/cancer/dcpc/research/update-on-cancer-deaths/index.htm

The Importance of Early Cancer Detection

Screening

American Society for Clinical Oncology 2021

Screening in both healthy and high-risk populations offers the opportunity to detect cancer early and with an increased opportunity for treatment and curative intent. Currently, a defined role for screening exists in some cancer types, but each screening test has limitations, and improved screening methods are urgently needed.

For screening to be efficacious, a number of conditions are necessary. The cancer should be an important cause of morbidity and mortality. A proven, safe, and acceptable test should exist to detect early-stage disease. The natural history of the cancer should be understood. The cancer should have a recognizable latent or early asymptomatic stage. In the absence of intervention, all or most cases in a preclinical phase should progress to a clinical phase.

Cancer Screening

American Society for Clinical Oncology 2021

"Screening" is the use of a test to detect cancer sooner (secondary prevention) or prevent its complications (tertiary prevention) among individuals at high risk for cancer. When screening is offered for patients already diagnosed with cancer, the term "surveillance" should be used instead.

Tumor markers, such as prostate-specific antigen, carcinoembryonic antigen, CA-15.3, and CA-27.29, have not demonstrated accuracy and efficacy in neither diagnosing prostate cancer nor detecting breast cancer relapse sooner than other screening tools.

Mammography in women age 50 to 70 (even possibly starting at age 40) and colonoscopy in the healthy population over age 50 play an important role in the early detection of cancer and are part of recommended guidelines for cancer screening.

Current Screening Options Quite Limited

National Geographic, 2021.

The goal of these new blood tests is to save lives by catching cancers earlier, especially those that don't currently have reliable screening tests. In the United States, there are now ways to screen people at high risk for five types of cancer: breast, colon, prostate, cervical, and lung—by blood or other types of tests, like mammograms.

But of the roughly 600,000 cancer deaths that occur in the U.S. each year, more than two-thirds are caused by cancers that have no good screening options, studies show. They are usually not discovered until they have metastasized.

Sources: https://ascopubs.org/doi/10.14694/EdBook_AM.2015.35.57, https://www.nationalgeographic.com/science/article/innovative-new-blood-tests-could-detect-cancers-early-when-will-they-be-ready

Early vs. Late Detection Across Cancers

Five-year Relative Survival Rates* (%) by Stage at Diagnosis, US, 2004-2010

	All Stages	Local	Regional	Distant		All Stages	Local	Regional	Distant
Breast (female)	89	99	85	25	Ovary	45	92	72	27
Colon & rectum	65	90	71	13	Pancreas	7	26	10	2
Esophagus	18	40	21	4	Prostate	99	>99	>99	28
Kidney†	72	92	65	12	Stomach	28	64	29	4
Larynx	60	75	43	35	Testis	95	99	96	73
Liver‡	17	30	11	3	Thyroid	98	>99	98	55
Lung & bronchus	17	54	27	4	Urinary bladder§	77	69	34	6
Melanoma of the skin	91	98	63	16	Uterine cervix	68	91	57	16
Oral cavity & pharynx	63	83	61	37	Uterine corpus	82	95	68	18

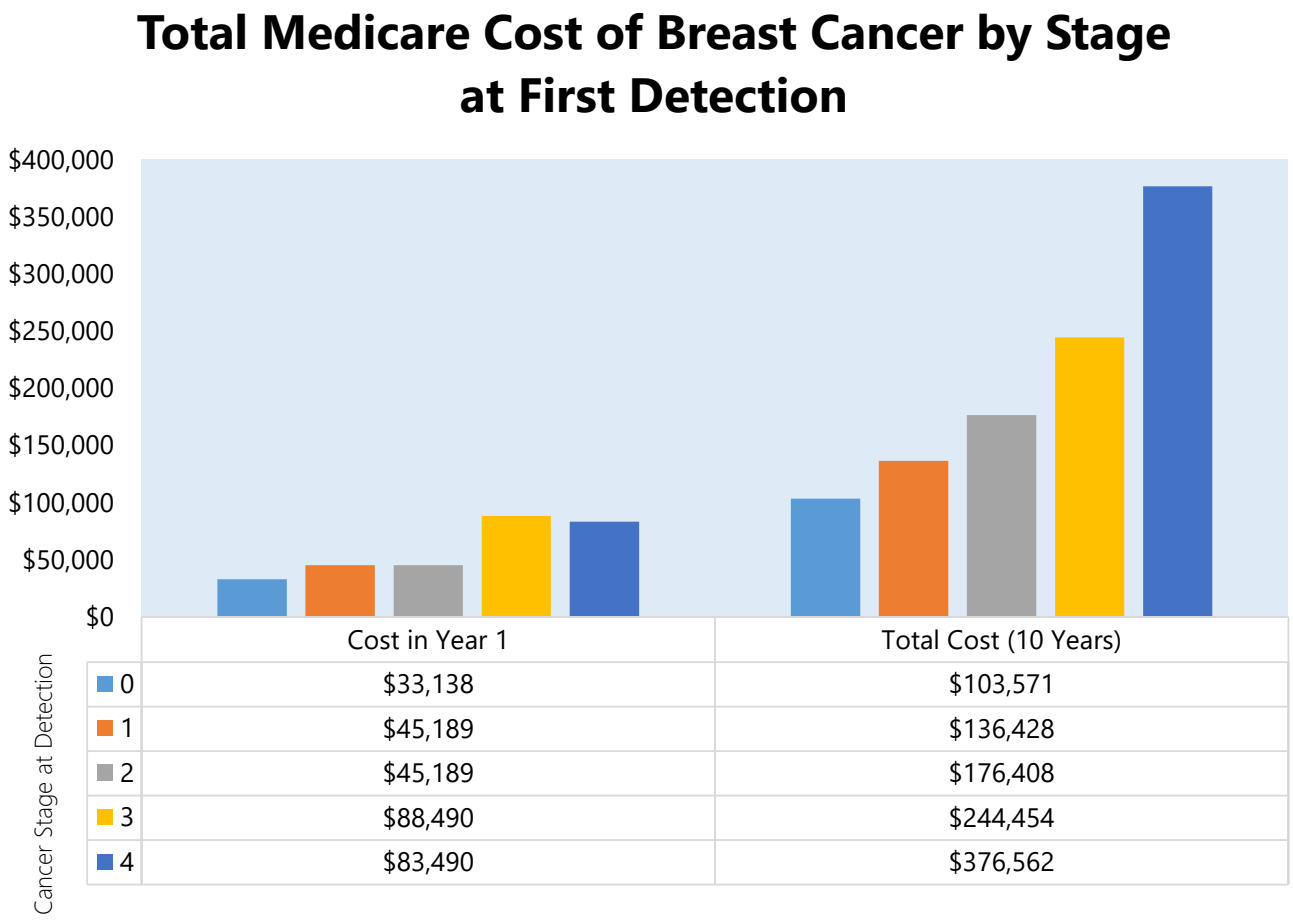
*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2004-2010, all followed through 2011. †Includes renal pelvis. ‡Includes intrahepatic bile duct. §Rate for in situ cases is 96%.

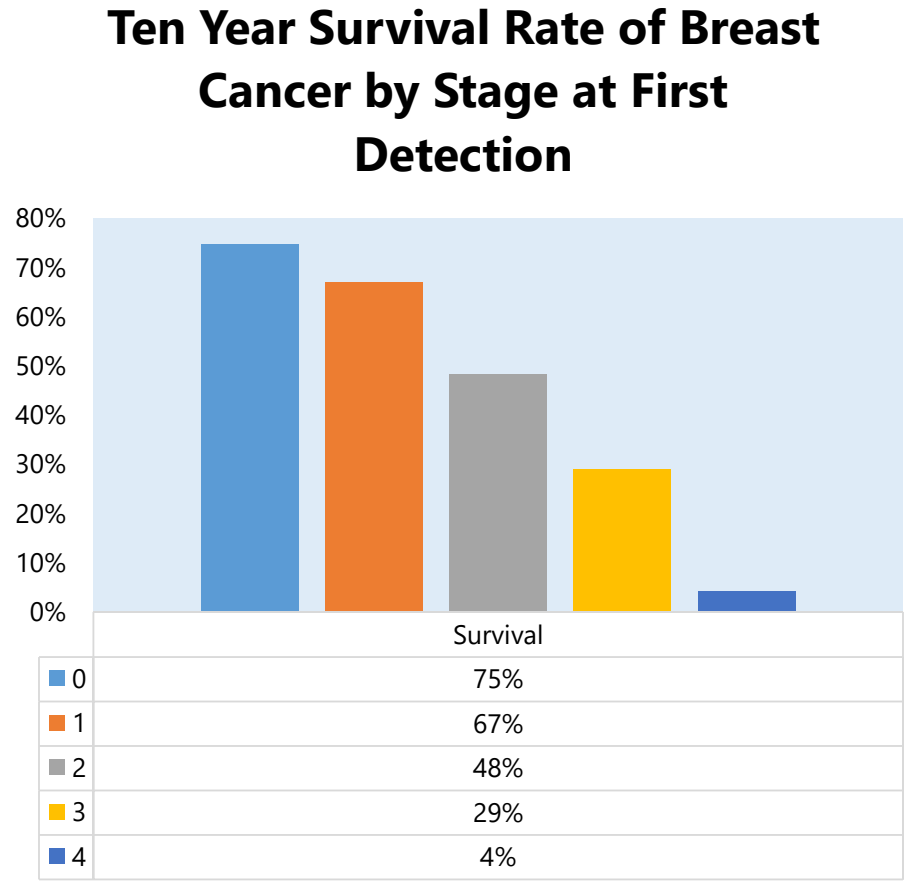
Local: an invasive malignant cancer confined entirely to the organ of origin. **Regional:** a malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** a malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

Source: Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission.

American Cancer Society, Inc., Surveillance Research, 2015

Early vs. Late Detection: Breast Cancer





Source: https://pubmed.ncbi.nlm.nih.gov/34008086/

Business Models for Early Cancer Detection in the U.S.

Almost universally, companies developing early cancer screening tests are focused on achieving FDA approval. This is not necessarily the best path to market.

	Insurer Savings / Cost Neutral	LDT Test With a Positive Net Cost	FDA / USPTF Approved Test
Description	An LDT test is made available whose use saves insurers money by preventing costly spend on cancer with a modest implementation cost.	Suitable for application with sophisticated clients including health insurers, governments, pharma partners and health systems.	The FDA approves diagnostic tests under device regulations and requires substantial evidence of clinical utility. USPTF will recommend if the test is broadly cost effective.
How it would be paid for	Medicare Advantage insurers would generally welcome a screening test that saves them money. Obviously, a body of evidence would be required to show patient and insurer benefit. FDA approval is generally not required to achieve reimbursement.	Some clients could cover cost directly including Medicare Advantage companies and selected providers. Eligible for payment from private insurers and CMS. Generally, reimbursement coverage discussions would begin with MolDx (Palmetto).	Reimbursement for an ECD test would be mandatory for commercial insurers under Obamacare and in Medicare with a strong USPTF recommendation following FDA approval. MolDx will influence broad availability of reimbursement from insurers and CMS.

We are aware of only one molecular diagnostics company that has achieved USPTF support for a screening test in the last decade. This was for the Exact Sciences Cologuard® test. Medicare and commercial insurers do cover the cost of the test to great benefit of Exact Sciences. However, the cost and risk of following this approval pathway is great. In the meantime, there have been many dozens of smaller cancer screening companies that have not been successful given the high hurdles. We simply wish to note that there are other ways to get a good screening test on the market than an FDA approval route.

Emerging Tests for Pan-Cancer Detection

GRAIL

Grail has developed a pan-cancer test based on DNA methylation analysis. The test is commercially available.

Grail has published clinical data showing that its test can detect cancer early.

The Grail test costs $949.

GUARDANT

Guardant360 CDx liquid biopsy is FDA-approved for genomic profiling across all solid tumors. This test is based on detection and analysis of CTCs and is indicated for analysis of advanced tumors.

Guardant has published data supporting its intended use.

This test costs $6,800.

SINGLERA Genomics

Singlera Genomics Inc., a company focusing on non-invasive genetic diagnosis, was co-founded in July 2014 in San Diego, California. Singlera's pan-cancer test looks at patterns of DNA methylation to detect cancer early.

Singlera has published data supporting its intended use.

The test is not commercially available.

STAGE ZERO LIFE SCIENCES

Stage Zero Life Sciences Aristotle® test is a multi-cancer test panel that uses mRNA technology to detect multiple cancer signatures from a single sample of blood. The test can detect nine cancer types but lung cancer and pancreatic cancers are not included.

At a 99% specificity the test exhibited an average sensitivity of 75% across 11 tumor types.

This test costs $1,500.

Thrive.
AN EXACT SCIENCES COMPANY

Thrive has developed a pan-cancer test based on CTC burden and proteins. This company was acquired by Exact Sciences and is preparing to introduce its test to the market.

Thrive has published clinical data showing that its test can detect cancer early.

The test is not commercially available.

Comparative Performance of Emerging Tests

The best combination of sensitivity and specificity seen is from Singlera's Pan-Seer test. This test is based on DNA methylation. However, it has been tested on a limited tumor set to date.

Ability to Identify Any Tumor from Not

Company	Technology	Name	In Sample Correct Positives Sensitivity	In Sample Correct Negative Specificity	In Sample AUC	FDA Approved?	On Market?	Price
Thrive	ctDNA + Proteins	CancerSeek	58%	99.0%	0.93	No	No	NA
StageZero	RNA transcriptomics	Aristotle	75%	99.0%	0.95	No	Yes	$1500
Grail	DNA methylation	Galleri	76%	99.3%	0.845	No	Yes	$950
Singlera	DNA methylation	PanSeer	89%	93%	0.97	No	No	NA

Ability to Identify Any Stage 1 / Early Tumor from Not

Company	Technology	Technology	In Sample Correct Positives Sensitivity	In Sample Correct Negative Sensitivity
Thrive	CRC + Proteins	CancerSeek	42%	99.0%
UniversalDX	DNA methylation	Signal-X	75%	NA
Singlera	DNA methylation	Panseer	74%	92.6%
Grail	DNA methylation	Galleri	27%	99.0%

Other Emerging Tests

There are quite a few companies working on novel approaches to pan-cancer detection.

OneTest (20/20 GeneSystems, Gaithersburg, MD) measures different tumor antigens: alpha fetoprotein (AFP), carciembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19–9), cytokeratin 19 fragment (CYFRA21–1), and prostate-specific antigen for males and AFP, CEA, CA19–9, CYFRA21–1, cancer antigen 125 (CA125), and cancer antigen 15-3 (CA15–3) for females.

OneTest targets several malignancies including colon, ovarian, and lung. Coupled with artificial intelligence algorithms, the reported specificity is~80%; sensitivity for any cancer in males is~82% and in females is ~62% (39). OneTest is currently available as a companion test to age-appropriate cancer screening and requires an order from a health practitioner. OneTest costs $189.00, making it one of the lower-cost MCEDs.

Analyzes RNA signatures of cancer but unlike other companies focused on nucleic acid analysis, Datar argues that circulating tumor cells are best found by eliminating non-cancerous cells from a sample rather than fishing out the cancerous cells.

This process results in a lower cost nucleic acid test than is required with other approaches as less sample amplification is required.

The company has good supportive data for a number of assays including a breast cancer detection assay and an assay to detect glioma. Datar has received FDA Breakthrough designation for its breast cancer assay.

Analyzes glycosaminoglycans (GAGs) in the metabolome to detect early cancer.

The underlying theory is that certain glycosaminoglycans are highly dysregulated due to cancer metabolism.

Company measures changes in sulfation patterns in specific GAGs in both blood and urine using mass spec.

Sensivity to Stage I cancers is 36% in a retrospective study with 99% specificity. However, these results required both urine and blood and involved an unconventional nested control design.

Sensitive to tumors with low cfDNA shedding.

Analyzes Phagocyte biology

The SNEP methodology subtracts the gene expression signals of the non-phagocytic CD2+ cells from those of the phagocytic CD14+ cells by taking the log ratio of CD14/CD2 signals

Four tumor types: 100% sensitivity / 95% specificity.

This test requires whole transcriptome sequencing and is likely quite expensive.

We think their model is likely to be have been overfit. Very few cases. No prospective study done.

Analyzes microbiome in the quest to find cancer early. While they can do pan-cancer tests, Micronoma has been focused on an assay for lung cancer detection called the Oncobiota Lung test®. Micronoma has found strong diagnostic performance of cell-free metagenomes when evaluating an age-, sex-, and risk-matched and treatment-naive cohort of more than 1,000 patients with lung cancer, benign lung diseases, and no disease (healthy). In addition, the research demonstrated the possibility and utility of performing metagenome assembly on more than 5,000 blood and tumor tissue samples, producing a proprietary metagenomic database with superior diagnostic power for nodule malignancy status compared to publicly available reference metagenomes.

commentaries

Multicancer Screening: One Size Does Not Fit All

Girish Putcha, MD, PhD[1]; Alberto Gutierrez, PhD[2]; and Steven Skates, PhD[3]

Cancer is the second leading cause of death in the United States,[1] and early detection represents one of the best hopes for reducing cancer-associated morbidity and mortality. However, current screening strategies are limited by suboptimal adherence, low sensitivity for early-stage disease, high false positive rates, and varied cost-effectiveness. Blood-based multicancer screening tests offer an appealing means of streamlining the screening process to improve adherence and cost-effectiveness. Recent studies evaluated two such tests,[2,3] yet substantial barriers remain for test development, validation, and implementation. For example, both tests demonstrate low sensitivity for early-stage cancer (with no characterization of performance for precancerous lesions) and unclear risk-benefit. Furthermore, these tests will require significant changes to clinical workflows. In an effort to realize the promise of a multicancer test, we discuss notable challenges and potential solutions for implementation in a clinically responsible manner.

DIFFERENT INTENDED USES REQUIRE DIFFERENT TEST PERFORMANCE CHARACTERISTICS

Cancer sounds like one disease but is actually many: there are more than 100 different cancers, each with multiple subtypes reflecting different underlying molecular pathophysiologies. Cancers are caused by dysregulation of diverse biological pathways, evolve at varying rates, have distinct diagnostic workups, and can have vastly different clinical outcomes.[4] Indeed, this heterogeneity affects screening, diagnosis, and treatment of each cancer.[4,5] Just as the benefits of an effective cancer screening test are clear (ie, reducing cancer-related morbidity and mortality), so too are the harms (ie, adverse effects resulting from false positives and false negatives). It is precisely because the invasiveness and therapeutic effectiveness of diagnosis and treatment—and therefore the consequences for the patient of inaccurate results—differ significantly for each cancer that there is no one-size-fits-all performance requirement for a multicancer screening test. For example, the impact to the patient of a false positive screen for colorectal cancer (CRC) resulting in an unnecessary colonoscopy is meaningfully different from the unnecessary major abdominal surgery that results from a false positive screen for pancreatic or ovarian cancer. Performance requirements are cancer-specific and depend on how and where in the care pathway the test is used (Fig 1). For a first-line test, some cancers may require greater sensitivity at a clinically acceptable specificity, whereas others may require very high specificity at a clinically acceptable sensitivity because of the benefits and risks of the subsequent diagnostic workup. Furthermore, performance characteristics depend on whether the test precedes, complements, or follows an accepted method of screening, or represents a new frontline screen for an otherwise unscreened cancer, either in an asymptomatic, average-risk, or symptomatic, high-risk individual.

CLINICAL UTILITY OF MULTICANCER SCREENING HAS NOT BEEN DEMONSTRATED IN THE SAME POPULATION

Clinical utility for any test requires that the results change patient management and improve health outcomes. A cancer screening test must accurately identify the cancer at a time when clinical intervention is beneficial to the patient without causing undue harm. These considerations underpin cancer screening recommendations from guideline bodies, such as the US Preventive Services Task Force (USPSTF). Following thorough risk-benefit assessments, the USPSTF recommends screening for only four cancers (cervical, colorectal, breast, and lung) and even goes so far as to recommend against screening for three cancers (ovarian, pancreatic, and thyroid), noting that there is no net benefit of screening or that the harms outweigh the benefits.[6] Even among the four cancers recommended for population screening, the populations recommended are not identical, which begs the question: What population should be screened with a multicancer screening test and is there clinical utility in that population?

PATH TO IMPLEMENTATION OF MULTICANCER SCREENING TESTS IN REAL-WORLD CLINICAL PRACTICE IS UNCLEAR

Integration into patient care pathways is another important consideration. For example, will the test replace, be a gatekeeper to, or supplement existing cancer screening tests? Any new cancer screening paradigm faces educational and behavioral barriers from patients, providers, and payers, but multicancer screening tests will face unique challenges. Since the diagnostic and therapeutic odyssey following a positive result depends on anatomically localizing the cancer, identification of the tissue of origin is required for any such test. Without localization, patients will

Author affiliations and support information (if applicable) appear at the end of this article.

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Freenome's Perspective on Pan-Cancer Detection

Freenome is an incredibly well funded cancer detection company, having last raised a $300mm Series D round in December 2021. The company's view is that cancer is too heterogenous to allow a pan-cancer test to work. Their view is that one can't get sensitivities high enough on early tumors to matter across enough tumor types. As a result, they argue for creating a series of cancer specific screens. We would suggest that the emerging sensitivities of both the Singlera and UniversalDx early pan-cancer screeners are likely good enough for broad use. In contrast, the Grail test is not there yet while the Thrive test has potential to get there. We acknowledge Freenome's point, however, that one might be able to do better, perhaps a lot better, by optimizing test performance for a specific type of early tumor. Freenome is also running multi-cancer tests presently with their Vallania and Sanderson studies.

Final Results of Grail's PATHFINDER Study Published Last Week in Lancet

Between Dec 12, 2019, and Dec 4, 2020, we recruited 6662 participants. 4204 (63·5%) of 6621 participants with analysable results were women, 2417 (36·5%) were men, and 6071 (91·7%) were White. A cancer signal was detected in 92 (1·4%) of 6621 participants with analysable results. 35 (38%) participants were diagnosed with cancer (true positives) and 57 (62%) had no cancer diagnosis (false positives). Excluding two participants whose diagnostic assessments began before MCED test results were reported, median time to diagnostic resolution was 79 days (IQR 37–219): 57 days (33–143) in true-positive and 162 days (44–248) in false-positive participants. Most participants had both laboratory tests (26 [79%] of 33 with true-positive results and 50 [88%] of 57 with false-positive results) and imaging (30 [91%] of 33 with true-positive results and 53 [93%] of 57 with false-positive results). Fewer procedures were done in participants with false-positive results (17 [30%] of 57) than true-positive results (27 [82%] of 33) and few had surgery (one with a false-positive result and three with a true-positive result).

Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01700-2

European Commission Orders Illumina to Divest Grail

Alex Philippidis, *GenEng News*, Oct 12, 2023 (excerpt)

The European Commission (EC) has formally ordered Illumina to divest itself of Grail, more than two years after the sequencing giant angered the regulator by completing the $7.1 billion deal for the cancer blood test developer before receiving EC approval.

The divestment order was all but expected since July, when the EC fined Illumina and Grail approximately €432 million ($456.4 million), amounting to 10% of Illumina's revenue—the largest fine ever imposed by the Commission. The EC also fined Grail a symbolic €1000 ($1,056) in connection with the merger, which has drawn the ire of antitrust regulators in Europe and the U.S.

The fine followed the EC's ruling last year that Illumina's purchase of Grail violated antitrust regulations. The EC then blocked the acquisition, asserting that the deal would stifle innovation and reduce choice in the emerging market for blood-based early cancer detection tests.

Illumina has maintained that there's no legal basis to order a divestiture and that the EC does not have jurisdiction over the Grail acquisition since Grail only operates in the U.S. and the U.K., not in any EU member states. Illumina is appealing the jurisdiction of the EC over Grail to the European Court of Justice (ECJ).

Source: https://www.genengnews.com/news/industry-news/european-commission-orders-illumina-to-divest-of-grail/

Pan-Cancer Screening with GRAIL's Test

GRAIL's Galleri™, a multi-cancer early detection test that can detect over 50 types of cancers — over 45 of which lack recommended screening today — with a low false positive rate, through a single blood draw.

Galleri®

The pitch take this test and find cancer early.

The test is available today from GRAIL's CLIA lab on an LDT basis. The potential was exciting enough to convince Illumina to acquire GRAIL for $7.1 billion.

The Math on GRAIL's Galleri® is Challenging

GRAIL needed to screen over 500 people to find one case of early cancer. With a thousand dollar test it's very hard to justify population health management with Galleri®.

GRAIL's PATHFINDER interim data were published in June 2021. The study analyzed 6,629 individuals aged 50 years or older, an age group at elevated risk for cancer, but with no suspicion of active cancer.

In the interim analysis, Galleri accurately detected 23 new cancers across 13 types.

Of the new cancers detected, nearly 40% (9/23) were localized (stage I-II), and more than half (13/23) were detected before distant metastases (stage I-III).

The positive predictive value (PPV), or the likelihood that a person has cancer when a positive test result is returned, was 44.6%.

The test costs $949. This works out to $273,518 to detect any cancer or $483,917 to detect an early case of cancer.

Ignoring humanitarian considerations, an insurer can save approximately $40,000 from catching a cancer early. Given the cost of finding the cancer, the benefits of screening with the GRAIL Galleri test appear difficult to justify.

The main problem is that while common over one's lifetime, the odds that any one person has cancer in a large population is low.

Obviously, the math on an equally expensive test for a single type of cancer (e.g., lung or breast) would be even more challenging.

Source: https://grail.com/press-releases/grail-presents-interventional-pathfinder-study-data-at-2021-asco-annual-meeting-and-introduces-galleri-a-groundbreaking-multi-cancer-early-detection-blood-test/

Similar Math with Exact Sciences CANCERSeek Test

Source: Guerra CE, Sharma PV, Castillo BS. Multi-Cancer Early Detection: The New Frontier in Cancer Early Detection. Annu Rev Med. 2023 Sep 20.

The DETECT-A study (Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing) combined the blood test with whole-body positron emission tomography (PET) imaging to evaluate an early version of CancerSEEK, one without the machine learning methods developed to increase the test's sensitivity and specificity (50). In this prospective interventional study, the investigators screened 10,006 female patients (aged 65–75 years) without a history of cancer using an initial blood draw of both ctDNA (prespecified panel of 61 known oncogenic mutations) and cancer-associated proteins (e.g., cancer antigen 19–9, carcinoembryonic antigen, alpha fetoprotein). Positivity for ctDNA or elevated protein levels led to a second blood draw to confirm the first, and if this too was positive, patients were evaluated by a multidisciplinary review committee regarding the need for a PET–computed tomography (CT) scan, to confirm and precisely localize the site and extent of disease. The diagnostic PET-CT was therefore integrated into the screening strategy. A total of 96 (1%) cancer diagnoses were made during the 12-month study period. Of these, 26 were initially detected by blood testing. The specificity was 98.9%. PPV and NPV of blood testing alone were 19.4% and 99.3%, respectively, and combined with PET-CT, the specificity and PPV increased to 99.6% and 28.3%, respectively. A total of 65% of cancers were detected at an early stage, and sensitivity varied with tumor type. **The blood test first detected 14 of 45 cancers (31%) in seven organs for which no standard-of-care screening test is available. The number-needed-to-screen to detect one cancer was 661.**

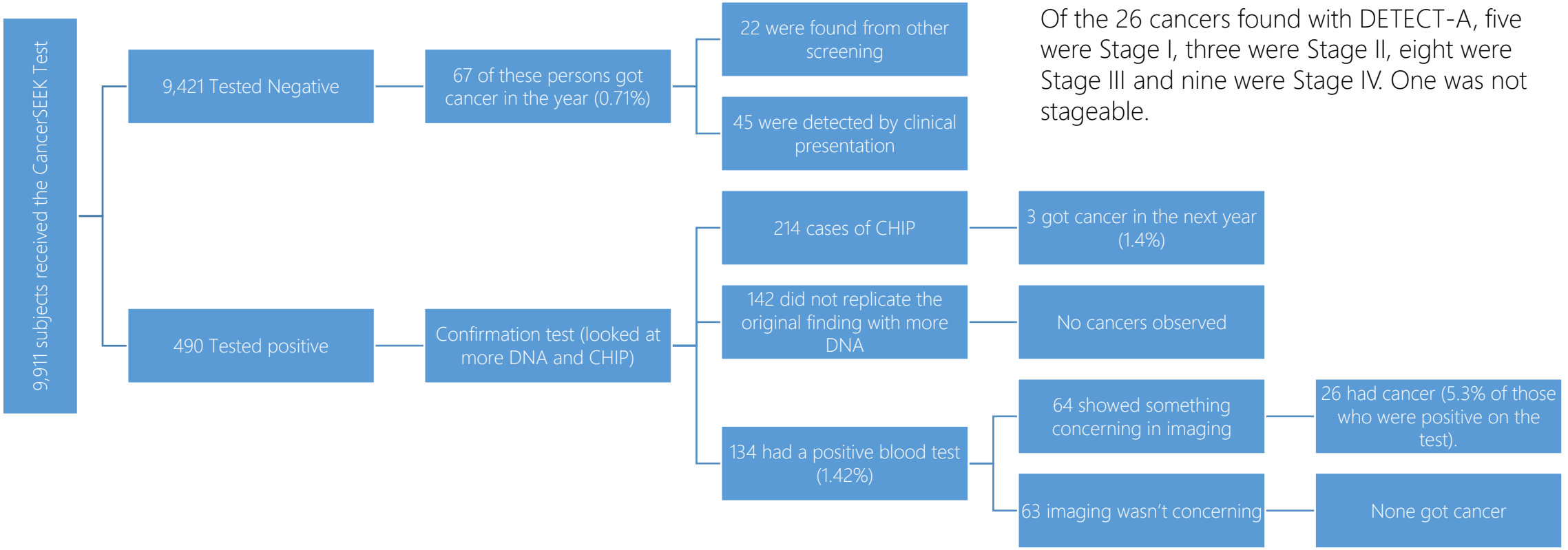
EXACT SCIENCES

Thrive.

Source: https://pubmed.ncbi.nlm.nih.gov/37729031/

What Happened in the Thrive DETECT-A Study

The screening test was positive 4.9% of the time. Of these persons, 5.3% had confirmed cancer. When the test was negative subjects got cancer 0.71% of the time in the next year. The sensitivity was 16% and specificity was 99.6%. The positive predictive value was 28%. Overall, these results are not great, and the economics of the test aren't great. Assuming that the cost of the test plus doctor time was $1,500 per case and the reflex test $1500 and the CT (with doctor time) was $10,000 it works out to $650,000 per cancer found. Almost all of the cost is for the original test rather than the reflex tests.



Of the 26 cancers found with DETECT-A, five were Stage I, three were Stage II, eight were Stage III and nine were Stage IV. One was not stageable.

Illustrative Medicare Budget Impact of a Thousand Dollar Pan-Cancer Screening Test

Adoption of a pan-cancer screening test at a cost of $1,000 per member would cost the U.S. government $57 billion a year. This strikes us as highly unlikely to occur given current budget pressures.

$829 Billion

Medicare Budget in 2023

57 Million

Members in 2023

7%

Total Medicare Budget in 2023
For a $1,000 Pan-Cancer Screening Test if Used on All Members

Increasing interest in risk-based cancer screening as a tool to reduce inefficiency of current screening approaches.

The Mypebs trial aims to enroll 85,000 women 40–70 years of age and randomly assign them to either the standard screening program or a personalized screening on the basis of their individual risks.

CLINICAL TRIALS ASSESS A PRECISION-MEDICINE APPROACH TO CANCER SCREENING

Risk-based screening approaches can reduce over-detection, while self-testing and new diagnostics find early disease. **By Sofia Moutinho**

In 2020, after a routine mammogram at her local clinic in the United Kingdom, 60-year-old Sally was invited to participate in a study on breast-cancer screening. She did not think twice before enrolling, remembering her best friend, who died from the disease at 30 years of age. "I would do anything I could to pick up any size of breast cancer earlier," she says. The study, called 'My Personal Breast Screening' (MyPebs), is a large-scale randomized trial enrolling 85,000 women 40–70 years of age in six countries – Belgium, France, Israel, Italy, the United Kingdom and Spain – to evaluate the benefits of risk-based screening compared with the current screening strategy in each country. As a first step, the researchers analyzed Sally's family history and hormonal status and ran a saliva-based DNA test to identify genetic variations known to be linked to breast cancer.

CREDIT: TOMMY / DIGITALVISION VECTORS / GETTY

nature medicine

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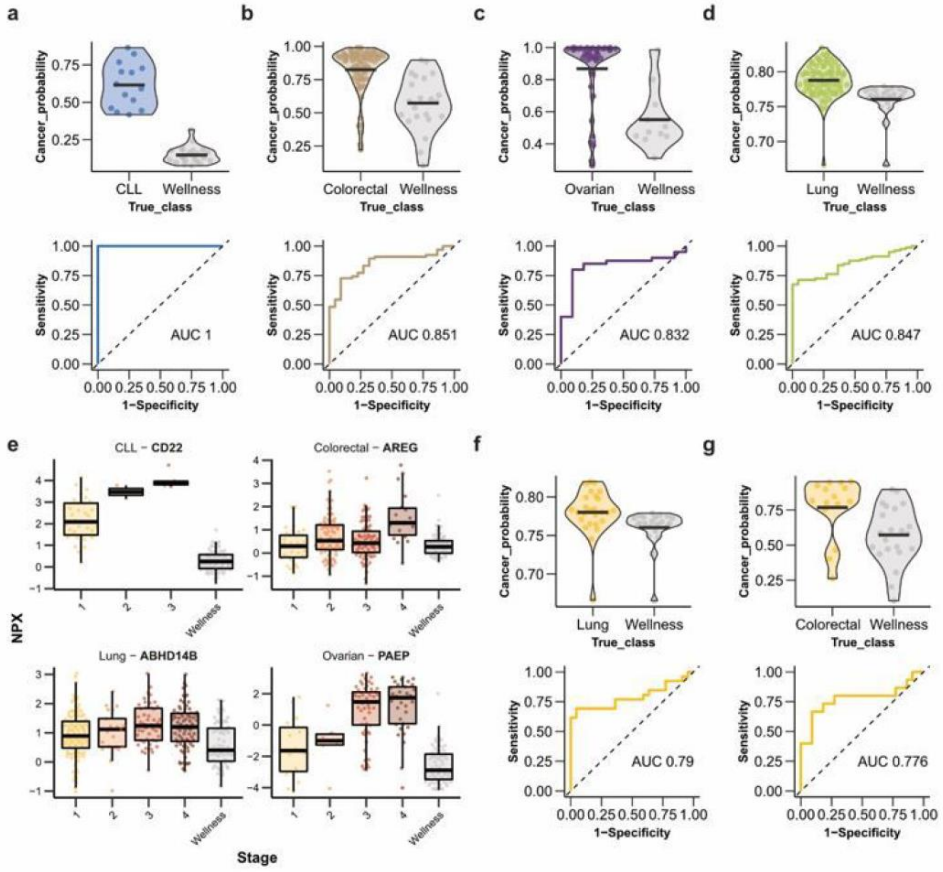
Recent Paper by Uhlen Lab at the Royal Institute of Technology (KTH) in Sweden

There has been only one large scale proteomics effort to detect cancer using blood samples. This was done by SEER. But this was confined to lung cancer only.

1. In late 2022 the lab of Mathias Uhlen published results from cancer classifiers that used a broad set of protein Amarkers measured using the OLINK system.
2. ll of the results and analytes have been placed in the public domain.
3. The results demonstrated extraordinary power to tell one type of cancer from another. AUC's were in the high 90s.
4. AUCs for detecting cancer from normal were less strong and typically ran in the low to mid-80s (fig at right).
5. The important contribution of this paper is to identify a much broader set of candidate proteins for use in development of pan-cancer detection algorithms.



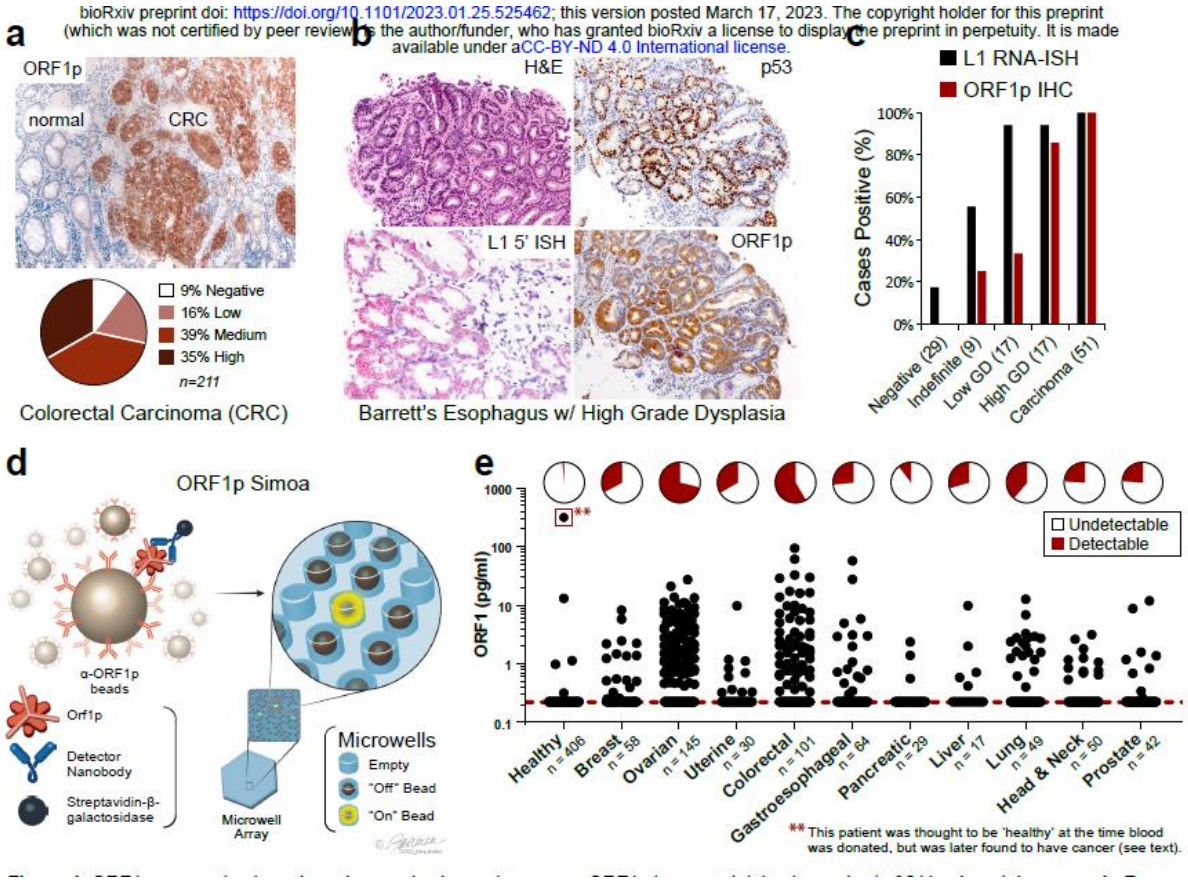
Uhlen et.al., "Next generation pan-cancer blood proteome profiling using proximity extension assay," Preprint, November 2022.

Ultrasensitive Detection of Circulating LINE-1 ORF1p as a Specific Multi-cancer Biomarker

Taylor MS, et.al. Ultrasensitive detection of circulating LINE-1 ORF1p as a specific multi-cancer biomarker. *Cancer Discov.* 2023 Sep 12.

Improved biomarkers are needed for early cancer detection, risk stratification, treatment selection, and monitoring treatment response. While proteins can be useful blood-based biomarkers, many have limited sensitivity or specificity for these applications. Long Interspersed Element-1 (LINE-1) open reading frame 1 protein (ORF1p) is a transposable element protein overexpressed in carcinomas and high-risk precursors during carcinogenesis with negligible expression in normal tissues, suggesting ORF1p could be a highly specific cancer biomarker.

To explore ORF1p as a blood-based biomarker, we engineered ultrasensitive digital immunoassays that detect mid-attomolar (10_{-17} M) ORF1p concentrations in plasma across multiple cancers with high specificity. Plasma ORF1p shows promise for early detection of ovarian cancer, improves diagnostic performance in a multi-analyte panel, provides early therapeutic response monitoring in gastroesophageal cancers, and is prognostic for overall survival in gastroesophageal and colorectal cancers. Together, these observations nominate ORF1p as a multi-cancer biomarker with potential utility for disease detection and monitoring.



Source: https://pubmed.ncbi.nlm.nih.gov/37698949/

NCI Planning a Massive Study of MCEDs

Source: Guerra CE, Sharma PV, Castillo BS. Multi-Cancer Early Detection: The New Frontier in Cancer Early Detection. Annu Rev Med. 2023 Sep 20.

National Cancer Institute Vanguard Study

In June 2022, the National Cancer Institute (NCI) board of scientific advisers endorsed the funding for a 4-year pilot study, the Vanguard study, that will enroll at least 24,000 individuals at average risk for cancer. The study is expected to launch in 2023–2024, after the NCI validates the cancer early detection tests it plans to study. The Vanguard study will be a feasibility and acceptability study to inform the NCI on issues including participant acceptance of randomization and adherence to testing and diagnostic evaluations. It will be a multi-arm randomized controlled trial comparing different cancer early detection tests to a control arm. All individuals will be offered standard-of-care cancer screenings. The Vanguard study will inform the NCI on the design and protocol of a longer-term clinical trial with as many as 225,000–300,000 volunteers aged 45–70 to ultimately learn whether MCEDs impact cancer-related and all-cause mortality. If launched, the trial would be the largest cancer prevention study in US history and is expected to run for approximately 7–8 years.

Source: https://pubmed.ncbi.nlm.nih.gov/37729031/

Disclosure

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