Biopharmaceutical Sector

Weekly Update – September 25, 2023

STIFEL | Healthcare

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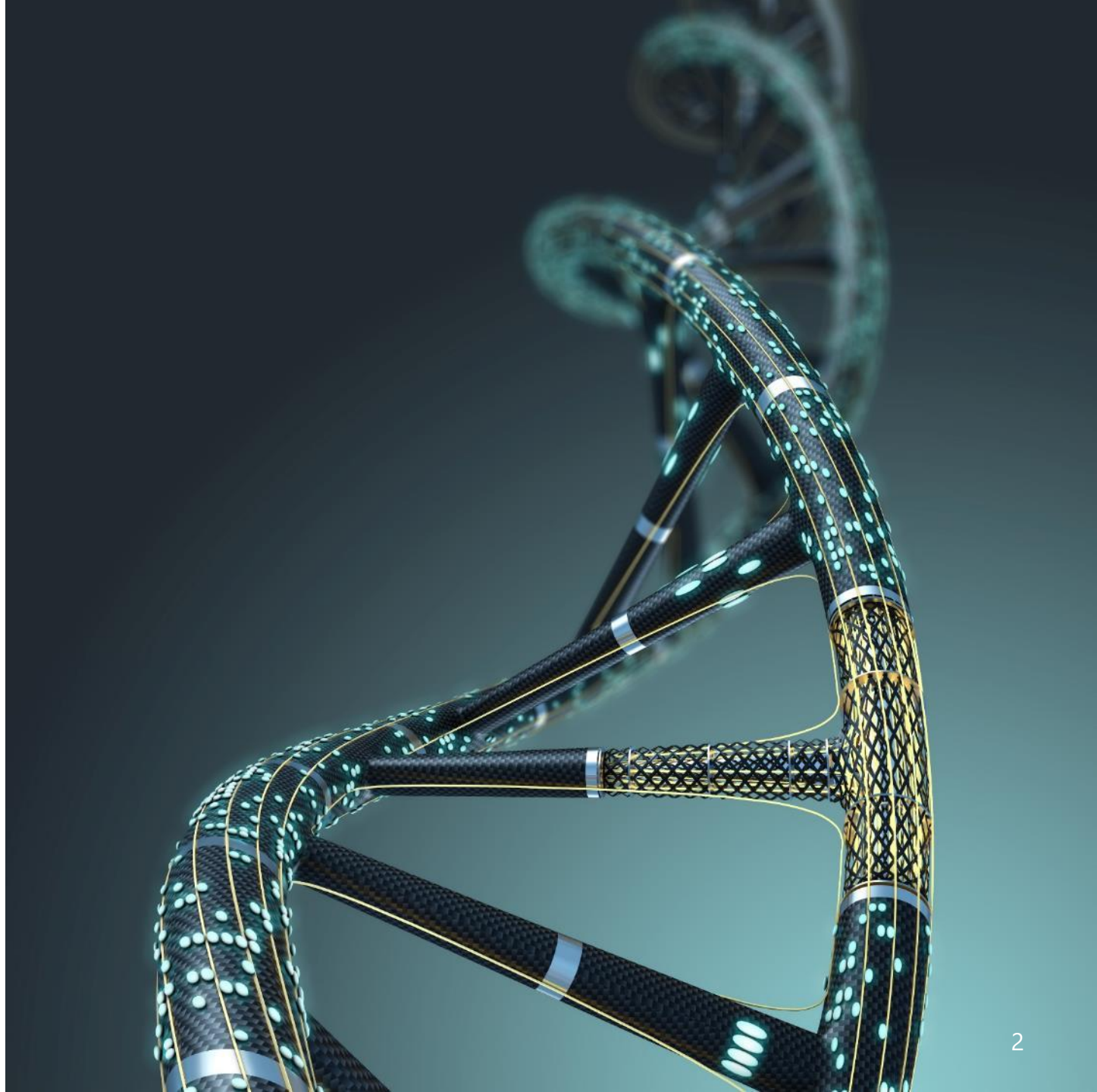

STIFEL | Healthcare

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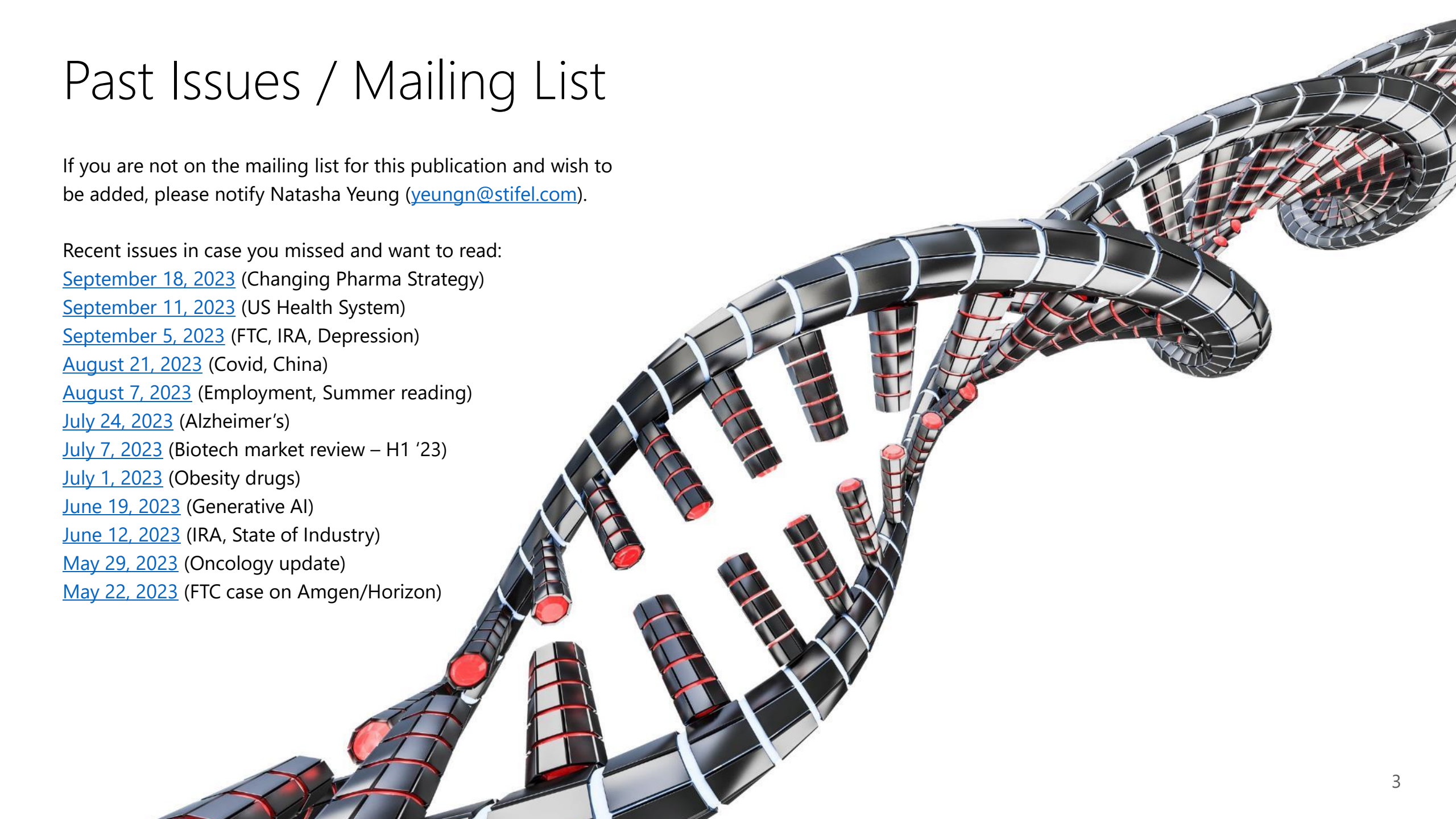
Recent issues in case you missed and want to read:
September 18, 2023 (Changing Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's)
July 7, 2023 (Biotech 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

1

Biotech Hangout held its latest event on September 22nd.

The next event will be on September 29, 2023.

Please join us.

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

2

bioFuture™

New York City | October 4-6, 2023

Innovators & Investors Come Together to Shape the Future of Healthcare

At this year's summit, BioFuture attendees will be exploring the exciting mashup between rapidly evolving fields including biopharma, digital medicine, big data, AI, healthcare systems, payors, and more. The coming decade will dramatically accelerate the transformation of the healthcare ecosystem. Be part of the discussions that will shape and transform the future of healthcare.

To Learn More
https://biofuture.com/

3

New Horizons for Biotech DealMaking in Europe

Zurich | October 4, 2023

STIFEL Baker McKenzie.

IQVIA™

Half Day Conference held at the Widder Hotel from 2-6pm.

To Learn More
please contact jade.atkinson@stifel.com

4

BIO-EUROPE®

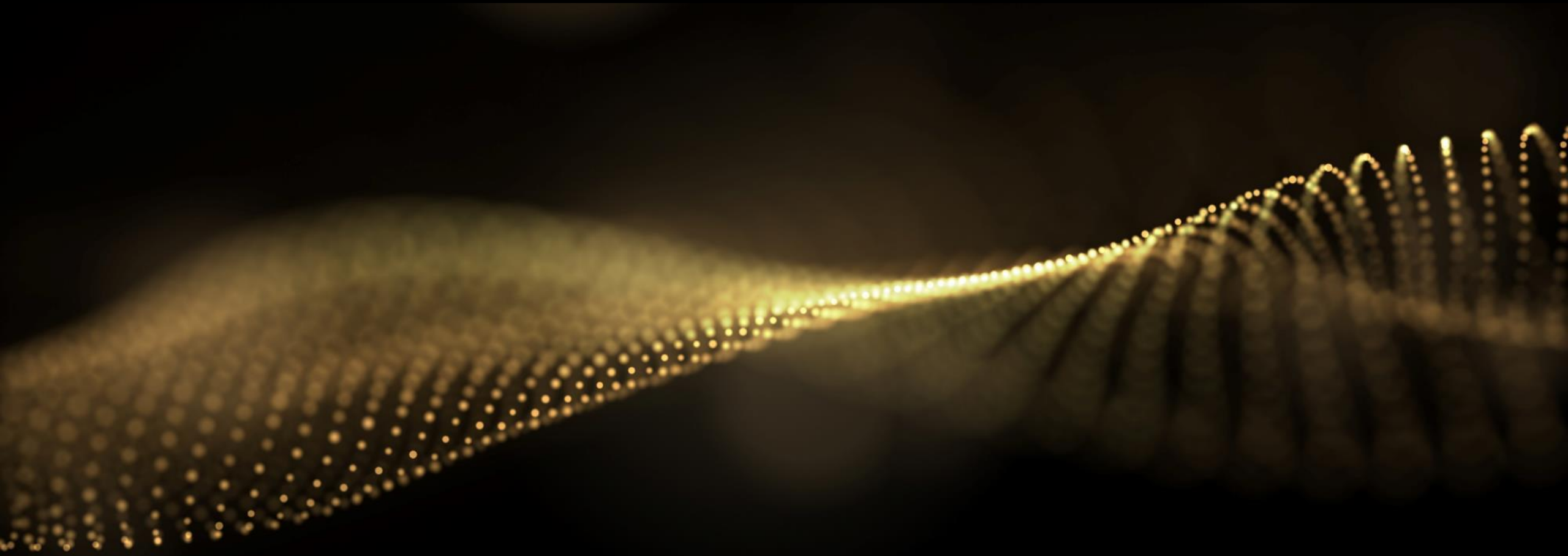
Munich | Nov 6-8, 2023

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: Interest Rates and Biotech



Board of Governors of the Federal Reserve System

The Federal Reserve, the central bank of the United States, provides the nation with a safe, flexible, and stable monetary and financial system.

September 20, 2023

Federal Reserve issues FOMC statement

The Committee seeks to achieve maximum employment and inflation at the rate of 2 percent over the longer run. In support of these goals, **the Committee decided to maintain the target range for the federal funds rate at 5-1/4 to 5-1/2 percent.** The Committee will continue to assess additional information and its implications for monetary policy. In determining the extent of additional policy firming that may be appropriate to return inflation to 2 percent over time, the Committee will take into account the cumulative tightening of monetary policy, the lags with which monetary policy affects economic activity and inflation, and economic and financial developments. In addition, the Committee will continue reducing its holdings of Treasury securities and agency debt and agency mortgage-backed securities, as described in its previously announced plans. The Committee is strongly committed to returning inflation to its 2 percent objective.

Source: https://www.federalreserve.gov/newsevents/pressreleases/monetary20230920a.htm

This was the second FOMC meeting in 14 meetings where the Fed chose to not raise rates.

In the post meeting press conference, Chairman Powell indicated that the Fed sees rates staying high throughout 2024. This is not good news for biotech.

The Fed Just Raised its Forecast for the Economy

Victoria Guida, *Politico*, Sep 20, 2023 (excerpt)

Federal Reserve officials on Wednesday gave the clearest signal yet that they expect to be able to beat inflation without causing a recession. But Chair Jerome Powell delivered a warning that new risks including surging oil prices — which he called "a significant thing" — and the autoworkers' strike could upend the forecasts.

The central bank held interest rates steady for just the second time this year as it assesses the extent to which the highest borrowing costs in more than two decades are already helping tame inflation.

Fed policymakers now expect the economy to grow 2.1 percent this year — a modest pace but still more than twice as fast as what they projected in June. They also see unemployment closing out the year at the current 3.8 percent rate, compared to their previous guess of 4.1 percent.

The Fed meeting comes amid growing optimism that the U.S. can see an end to high inflation without a big jump in joblessness or a painful recession. The labor market has stayed strong and consumers have continued spending, even as higher borrowing costs have begun to squeeze households and businesses.

Source: https://www.politico.com/news/2023/09/20/federal-reserve-inflation-bank-biden-00117140

Wall Street Closes Lower after Fed Warns of Higher for Longer

Reuters, Sep 20, 2023 (excerpt)

U.S. stocks slumped on Wednesday after the U.S. Federal Reserve held key interest rates unchanged as widely expected, and revised economic projections higher with warnings that the battle against inflation was far from over.

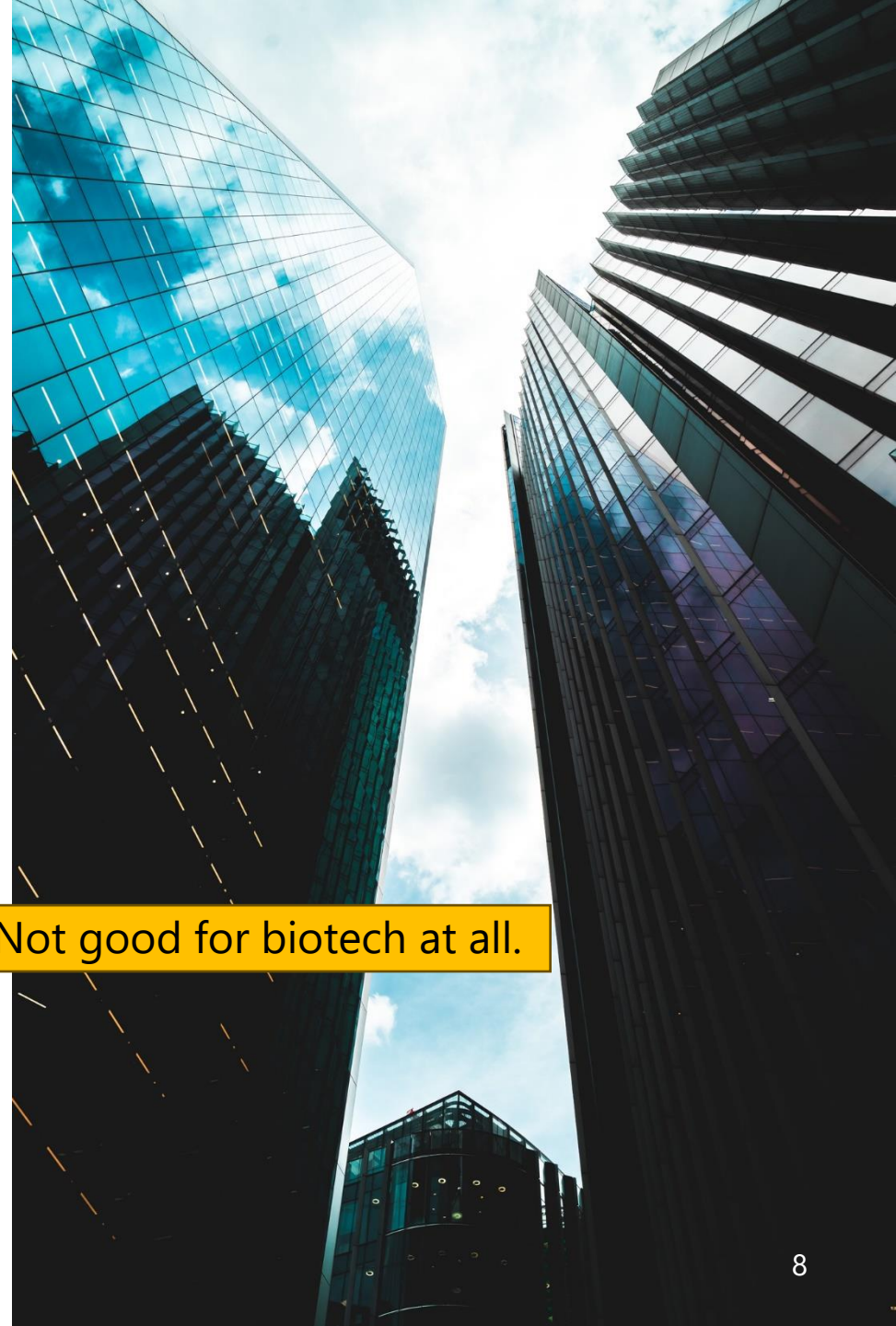
The Fed's announcement was accompanied by its Summary Economic Projections (SEP) and dot plot, which sees an additional 25 basis point rate hike this year, peaking in the 5.50%-5.75% range. The SEP projections also called for 50 basis points of rate cuts next year.

"It's your standard Fed day volatility," said Ryan Detrick, chief market strategist at Carson Group in Omaha, Nebraska. "Yet it wasn't really a curve-ball event, because markets took things in stride."

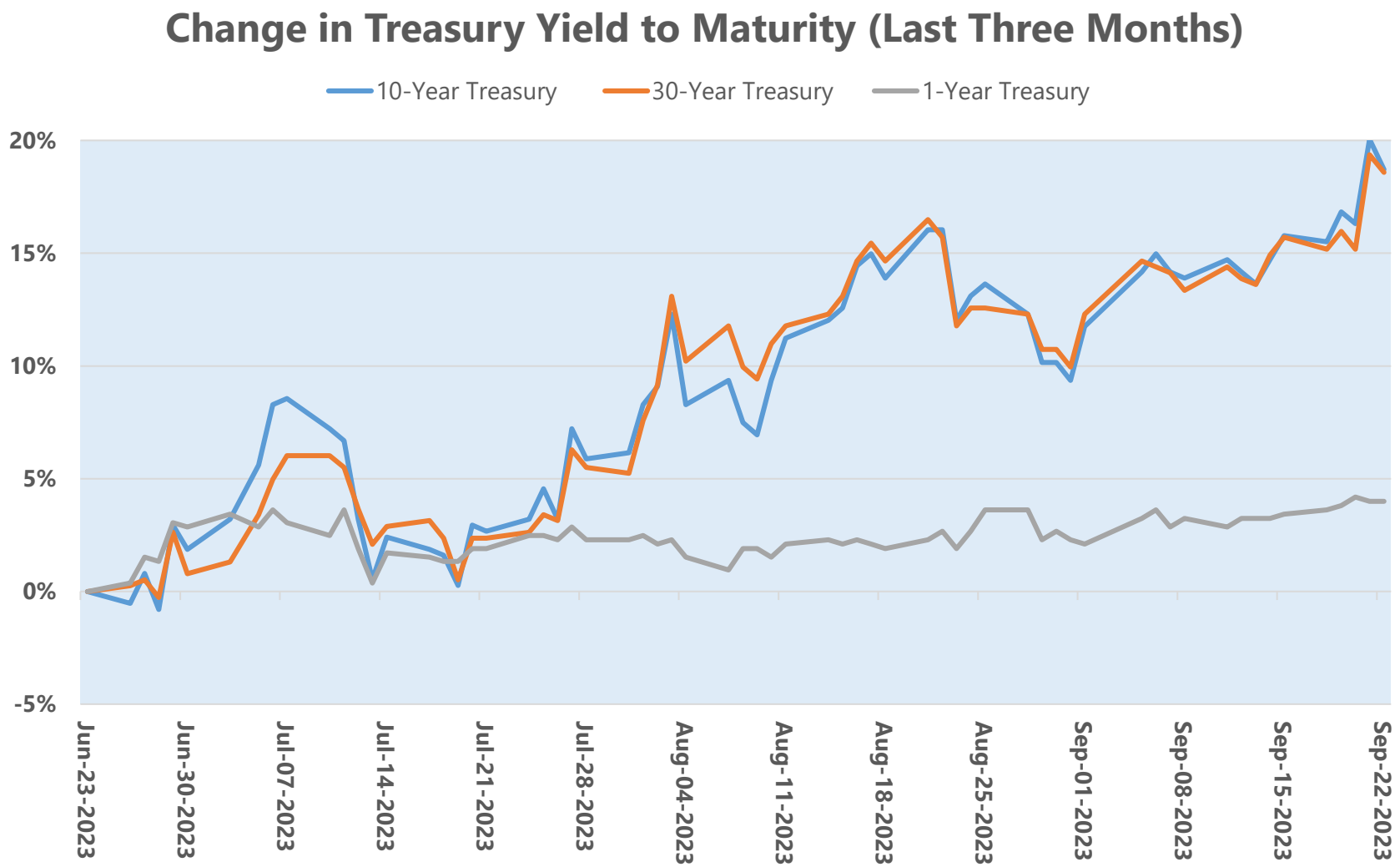
The updated projections see the Fed funds target rate edging down to 5.1% by the end of next year, and to 3.9% by the end of 2025.

Since the Fed began tightening in March, core inflation has cooled. But its slow descent toward the central bank's 2% target has been slow and uneven. The SEP forecasts inflation to drop to 3.3% by year-end, and to approach the central bank's average annual 2% target.

Source: https://www.reuters.com/markets/us/futures-inch-up-hopes-pause-fed-rate-hikes-2023-09-20/



Long Dated U.S. Treasury Bond Yields Up 20% in Last Three Months



It's one thing for short-term Treasury rates to rise. It's another when long-term yields rise by 20% in just a few months. This indicates that investors believe that the long-term cost of capital in the U.S. economy is going to be higher for a long-time to come.

Source: CapitalIQ

May 2050 U.S. Treasury Bonds Traded for Under 50 Cents on Dollar Last Week

Ye Xie, Bloomberg, Sep 18, 2023

(Bloomberg) -- Fifty cents on the dollar is a very low price in the world of bonds. In most cases, it signals that investors believe the seller of the debt is in such financial distress that it could default.

So when a US Treasury bond sank below that price Monday, it raised eyebrows. The security, due in May 2050, briefly touched as low as 49 29/32, marking the second time in the past two months it's fallen below the 50-cent level.

The US, of course, is not in danger of defaulting any time soon. Treasuries are generally considered to be the safest government debt in the world. What the price does illustrate in this case is the scope of pain inflicted on investors who piled into longer-term debt at rock-bottom interest rates during the pandemic, only to then be caught off-guard when the Federal Reserve carried out the the most aggressive monetary-policy tightening in decades.

The bond due in 2050 has been hit particularly hard, given that its interest rate — 1.25% — is the lowest ever on a 30-year Treasury

This is a crazy news story. A U.S. Treasury bond with a long maturity and low coupon is trading at less than 50 cents on the dollar.

It highlights the impact of changing long-term rates on the economy and is a bit of a metaphor for what's happened to biotech.

Source: https://finance.yahoo.com/news/sub-50-cent-price-treasury-190103366.html

Bill Ackman Explains Why He is Short Long-Treasury Bonds

Bill Ackman, CIO, Pershing Square Capital, Sep 22, 2023

I believe that long-term rates, e.g, 30-year rates, will rise further from here. As such, we remain short bonds through the ownership of swaptions.

The world is a structurally different place than it was. The peace dividend is no more. The long-term deflationary effects of outsourcing production to China are no more. Workers and unions' bargaining power continues to rise. Strikes abound, with more likely to come as successful walkouts achieve substantial wage gains. Energy prices are rising rapidly. Not refilling the SPR was a misguided and dangerous mistake. Our strategic assets should never be used to achieve short-term political objectives.

Now we must refill the SPR while OPEC and Russia cut production. The green energy transition is and will remain incalculably expensive. And higher gas prices will raise inflationary expectations. Just ask your average American. They see the prices at the pump and in the grocery store and don't believe inflation is moderating. Our national debt is $33 trillion and rising rapidly. There is no sign of fiscal discipline by either party or by the presumptive presidential nominees.

And each debt ceiling is an opportunity for our divided government and its most extreme actors to get media attention, and for our nation to threaten default. This is not a good way to recruit the many new buyers we need for our bonds. The government is selling hundreds of billions of bills, notes and bonds weekly.

China and other foreign nations, historically major buyers of our debt, are now selling. And the QT unwind experiment has barely begun. Imagine trying to do a massive IPO where the underwriter, insiders and short sellers are all selling at once, competing to hit every bid on the way down while the analysts downgrade their ratings to 'Sell.' Our economy is outperforming expectations. Major infrastructure spending is beginning to contribute to economic growth and the supply of additional debt. Recession predictions have been pushed out beyond 2024.

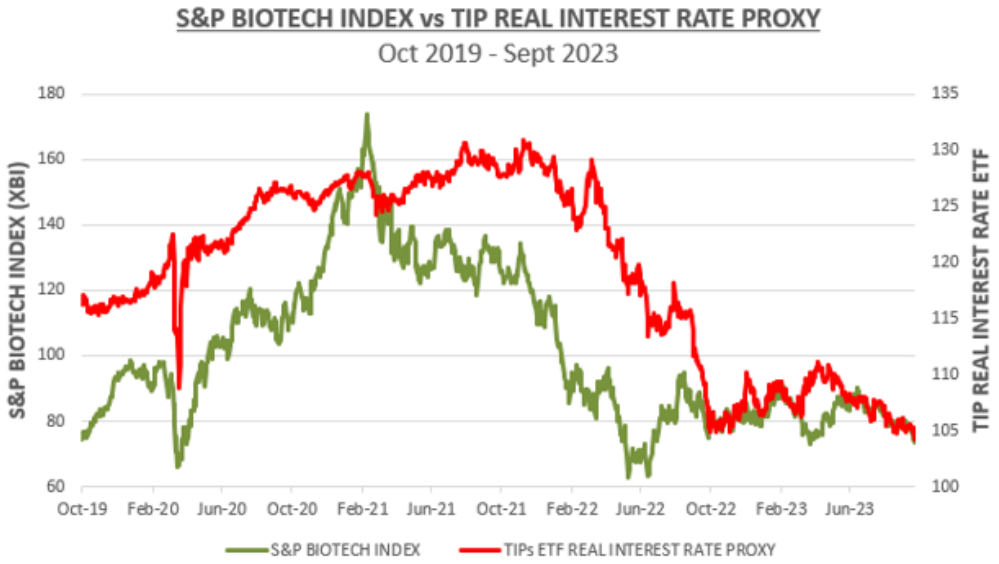
The long-term inflation rate is not going back to 2% no matter how many times Chairman Powell reiterates it as his target. It was arbitrarily set at 2% after the financial crisis in a world very different from the one we live in now. I bumped into the CIO of one of the world's largest fixed income asset managers the other night and asked him how it was going. He looked like he had had a tough day. He greeted me by saying: 'There are just too many bonds' — a veritable tsunami of new issuance each week. I asked him what he was going to do about it. He said: 'The only thing you can do is step away.' I have been surprised at how low long-term rates are. I think the best explanation is that bond investors thought of 4% as a high rate of interest because rates hadn't breached 4% for nearly 15 years. When investors saw the 'opportunity' to lock in 4% for 30 years, they grabbed it as a 'once-in-their-career opportunity,' but today's world is very different from the one they have experienced up until now. The long-term inflation rate plus the real rate of interest plus term premium suggests that 5.5% is an appropriate yield for 30-year Treasurys. And query whether 0.5% is a sufficient real long term rate in an increasingly risky world.

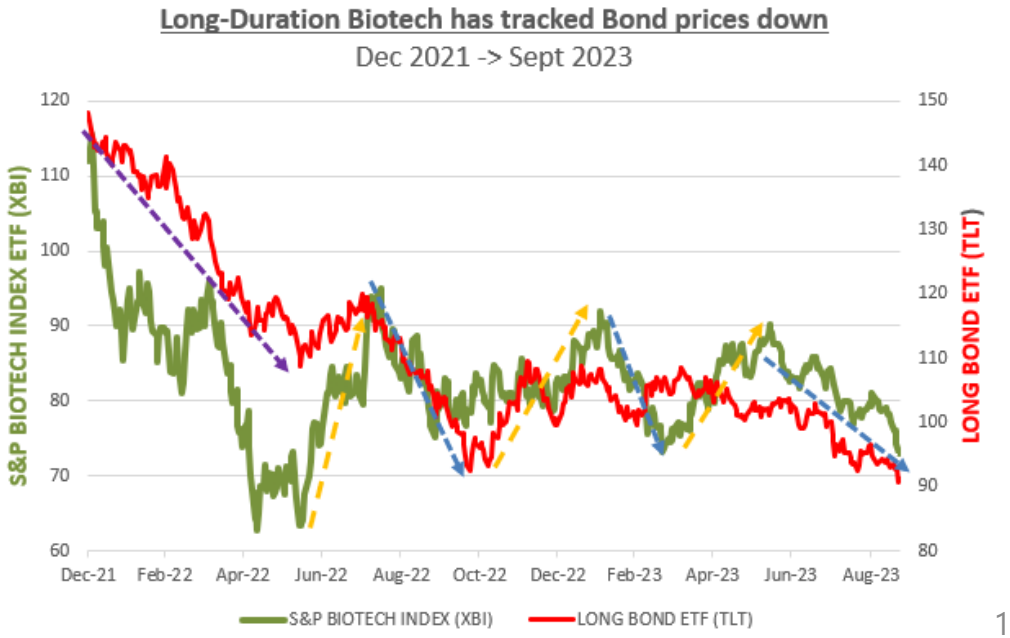
Source: https://twitter.com/BillAckman/status/1705056634072863102

Eden Rahim Comment on Biotech and Rates on Sep 23

Eden Rahim is a biotech investor at Next Edge Capital and industry commentator.

As the ultimate Long-duration asset (heavy capital demands now for promise of risky distant future cash-flows) biotech continues to by hypersensitive to hurdle of changing Real Rates, and track the path of long bonds, TLT step-for-step.



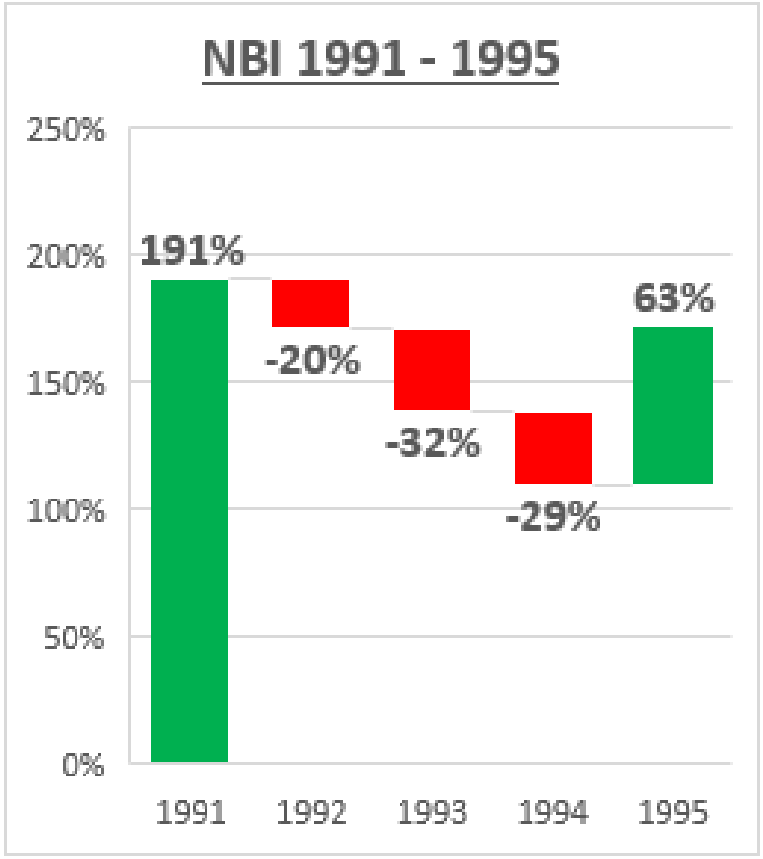


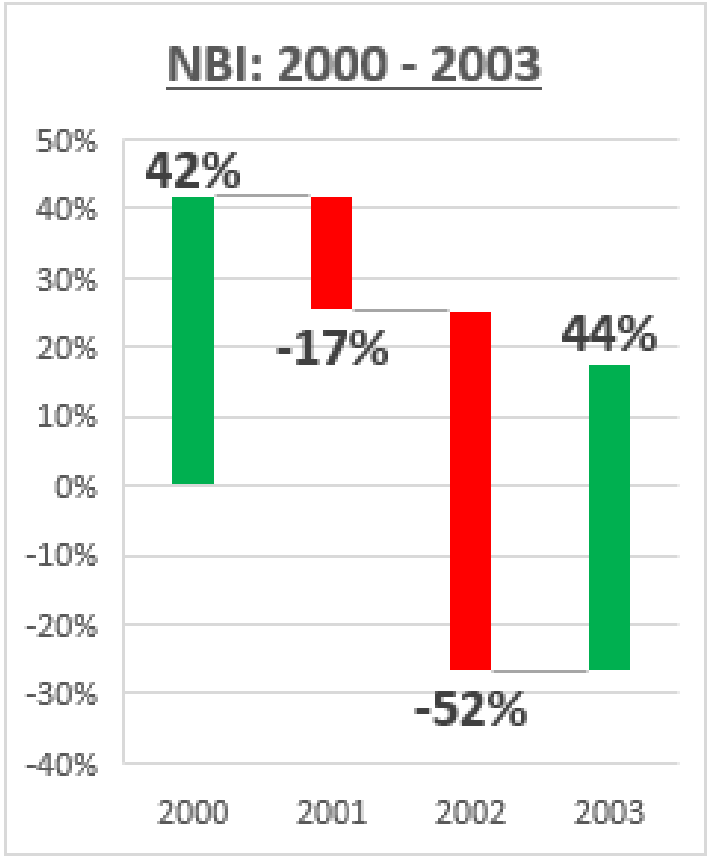
Source: https://twitter.com/EdenRahim

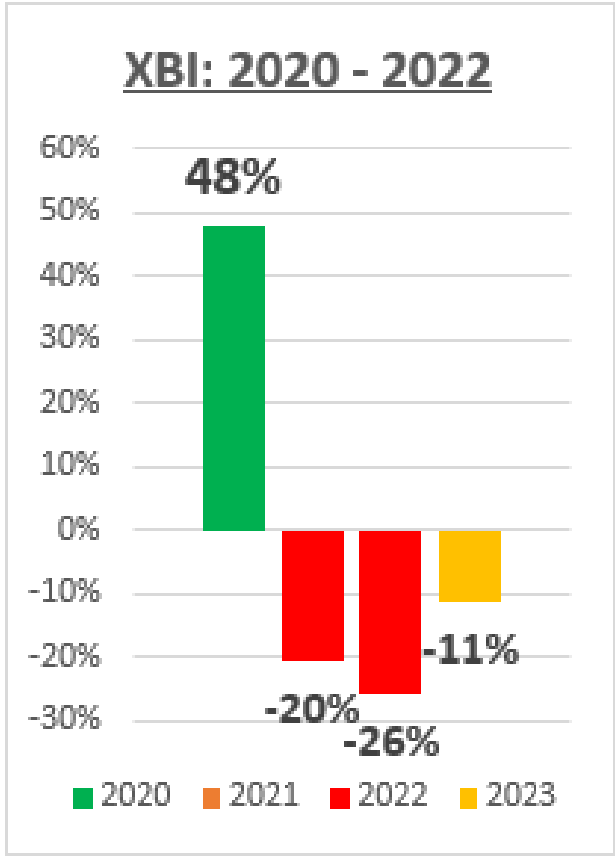
Eden Rahim Comment on Biotech and Rates

Eden Rahim is a biotech investor at Next Edge Capital and industry commentator. This is a Twitter comment on Sep 23, 2023.

You have to go back 30 years to the relentless -75% Jan 1992-mid 1995 biotech bear market to find the only other time in 42 years Bios have declined 3-years in a row. Big difference between now vs then is the 1992 & 2000 bears were correcting prior +500% & +1,000% multiyear bull markets.







Source: https://twitter.com/EdenRahim

U.S. Economy Could Withstand One Shock, but Four at Once?

Wall Street Journal , Sep 24, 2023 (excerpt)

"A year of surprisingly strong growth is about to be tested by a strike, the possibility of a government shutdown, student loans and oil prices

The U.S. economy has sailed through some rough currents this year but now faces a convergence of hazards that threaten to create more turbulence.

Among the possible challenges this fall: a broader auto workers strike, a lengthy government shutdown, the resumption of student loan payments and rising oil prices.

Each on its own wouldn't do too much harm. Together, they could be more damaging, particularly when the economy is already cooling due to high interest rates.

"It's that quadruple threat of all elements that could disrupt economic activity," said Gregory Daco, chief economist at EY-Parthenon."

Source: https://www.wsj.com/economy/u-s-economy-could-withstand-one-shock-but-four-at-once-8312ba51

Biopharma Market Update

Biotech Stocks Down Last Week

The XBI was down last week by 5.4% and is now down 12.1% for the year. With the XBI below 73 now, we are getting ever closer to the post-Pandemic low of 63.3 hit on June 16, 2022. Only three of the last fourteen weeks have been up for the XBI.

Biotech Stocks Down Last Week

Return: Sep 16 to Sep 22, 2023

Nasdaq Biotech Index: -2.8%
Arca XBI ETF: -5.4%
Stifel Global Biotech (EV): -7.4%*
S&P 500: -2.9%

Return: Jan 1 to Sep 22, 2023

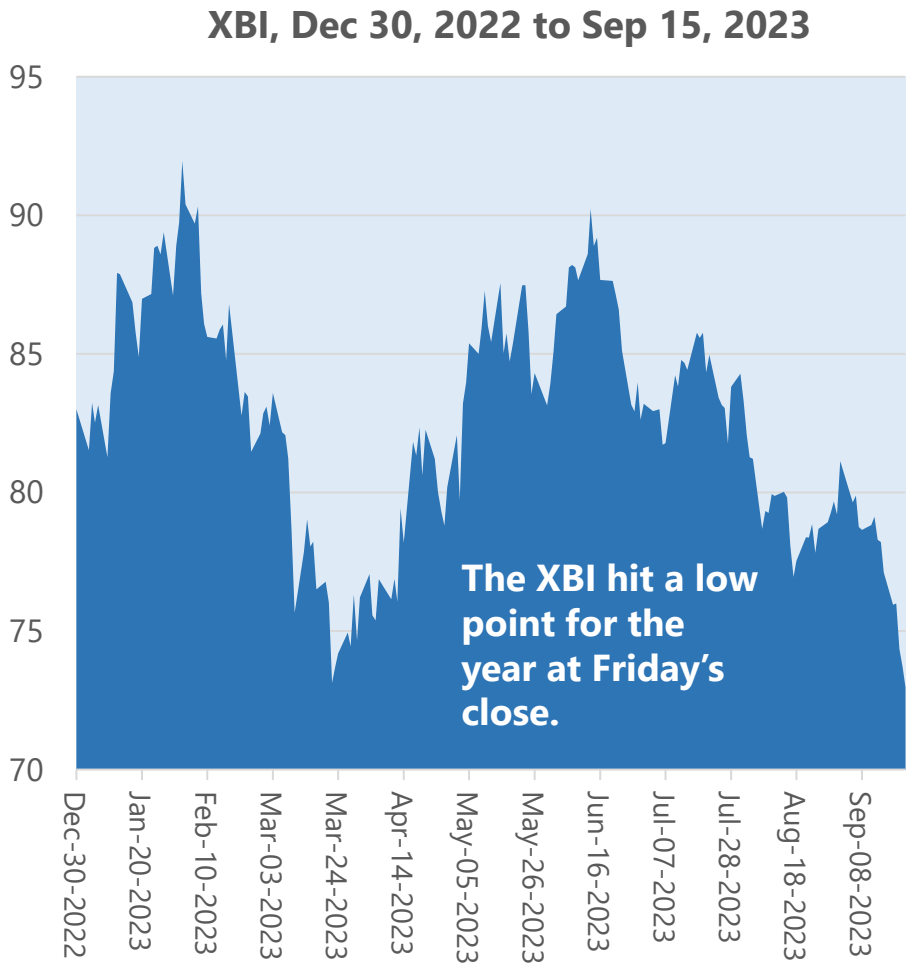
Nasdaq Biotech Index: -6.4%
Arca XBI ETF: -12.1%
Stifel Global Biotech: -15.0%*
Stifel Global Biotech (adjusted): -9.1%*
S&P 500: +12.9%

VIX Up

Oct 21: 29.7%
Jan 20: 19.9%
Mar 17: 24.6%
May 26: 18.0%
July 21: 13.6%
Sep 8: 13.8%
Sep 15: 13.8%
Sep 23: 17.2%

10-Year Treasury Yield Up

Oct 21: 4.2%
Jan 20: 3.48%
Mar 17: 3.39%
May 26: 3.8%
July 21: 3.84%
Sep 8: 4.26%
Sep 15: 4.33%
Sep 23: 4.44%

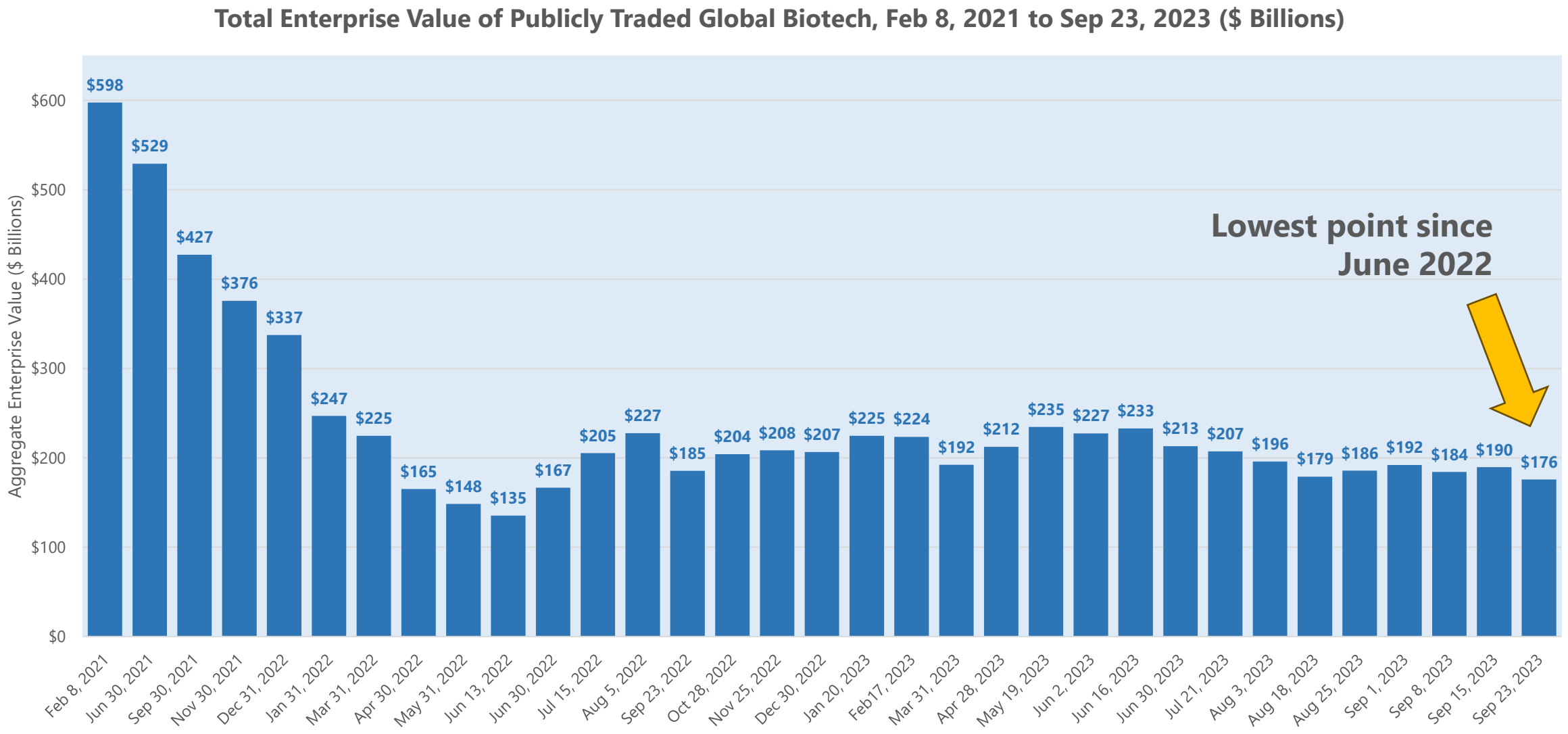


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Down Big Last Week

The total value of the global biotech sector dropped 7.3% last week. Biotech is down 70% since peak in 2021.

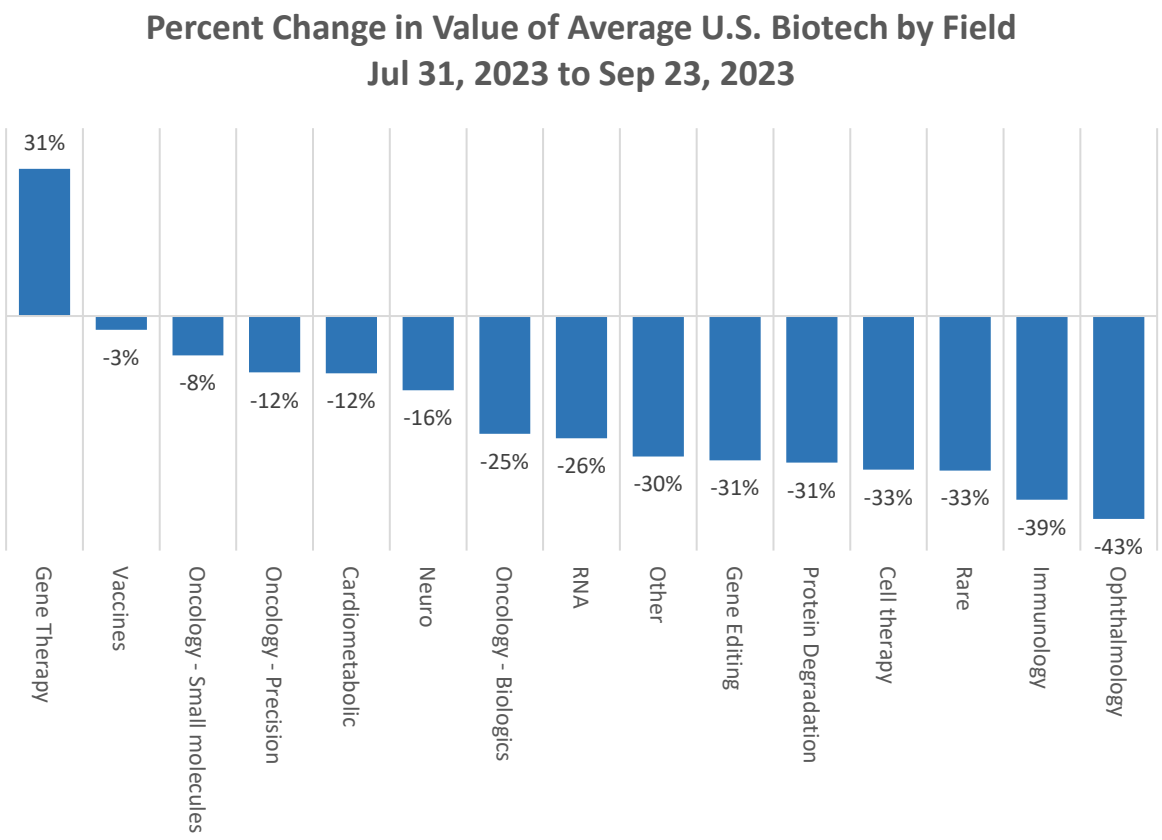


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

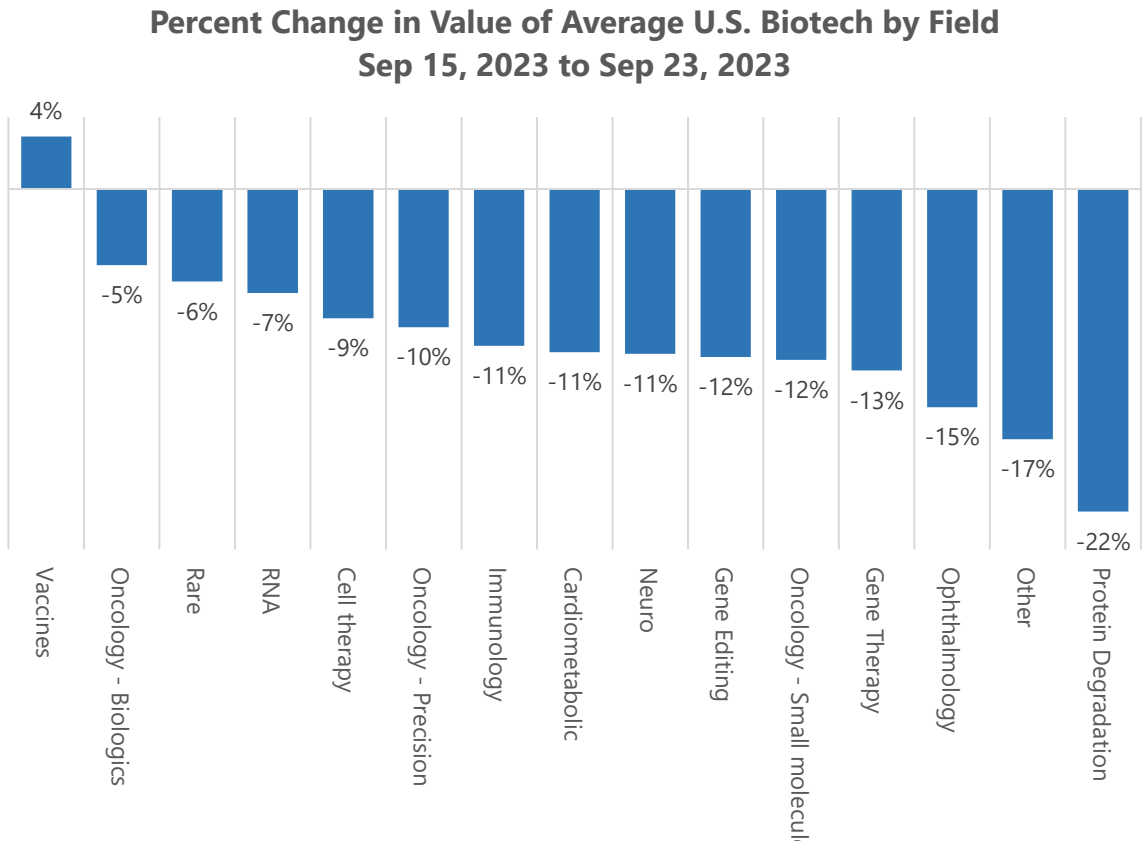
Average Percent Change in Enterprise Value by Field

The last seven weeks have seen significant weakness in ophthalmology stocks, immunology stocks, rare disease stocks and cell therapy stocks. Gene therapy stocks have performed well. The last week has seen the most weakness in protein degradation therapeutics stocks, ophthalmology stocks, gene therapy stocks and small molecule oncology players. Vaccine stocks rose last week.

Last Seven Weeks

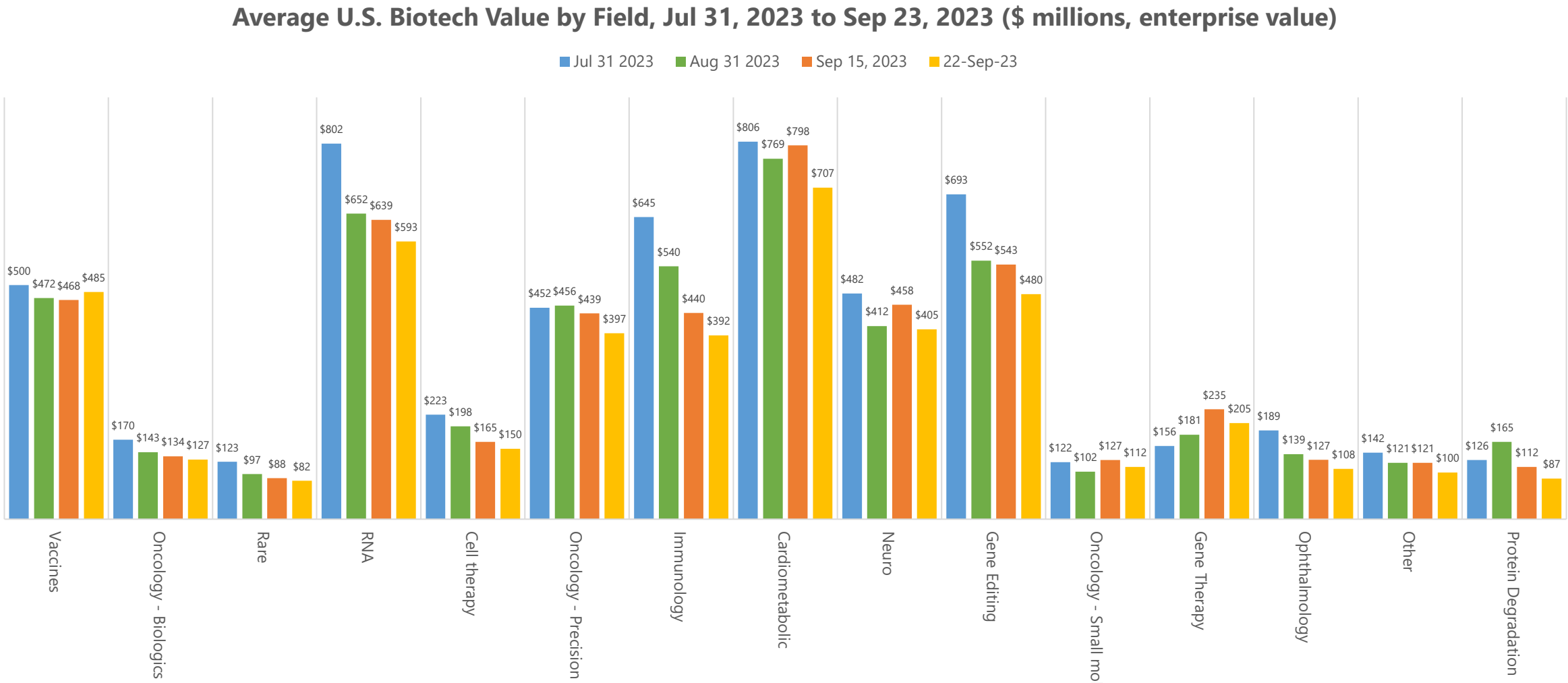


Last Week



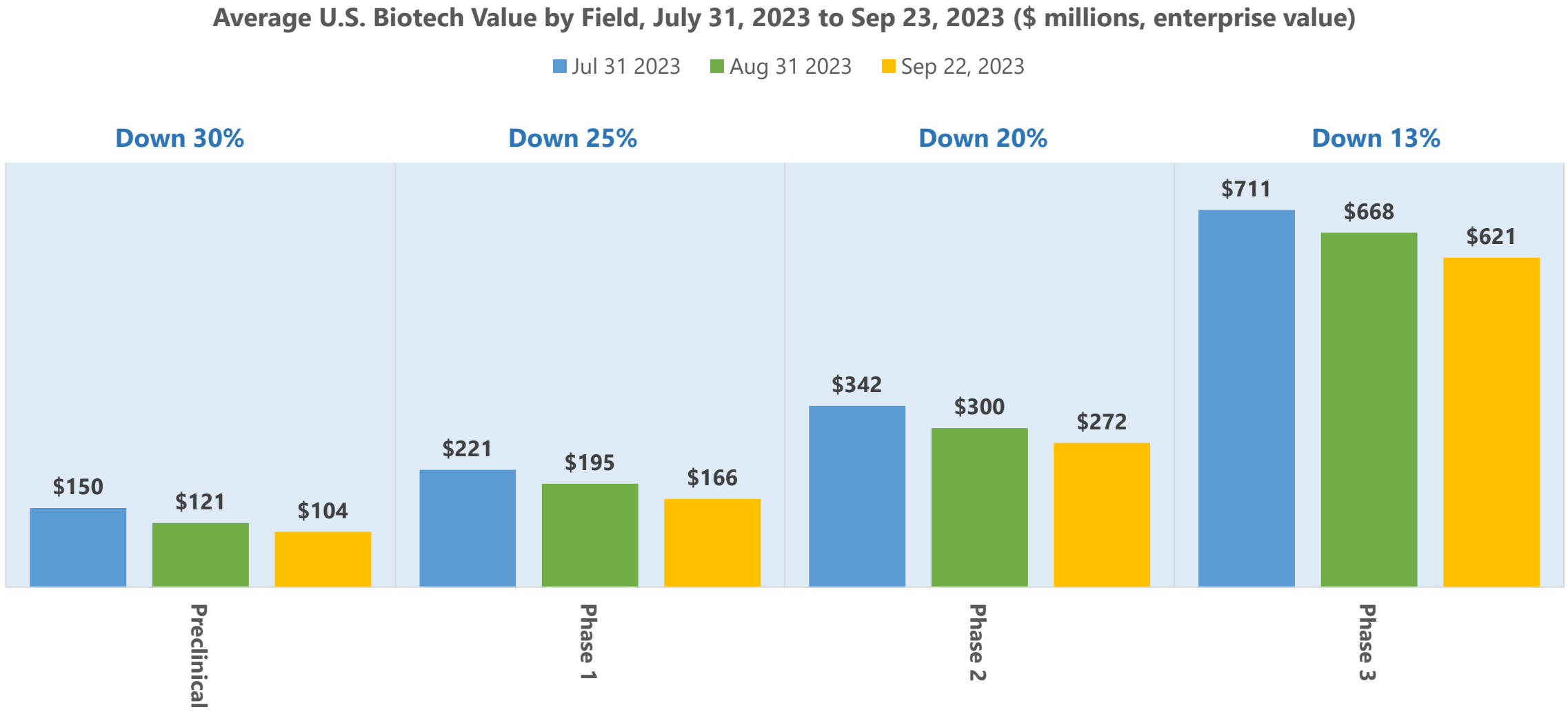
Source: CapitalIQ and Stifel analysis.

Evolution of Value Structure by Field, Last Seven Weeks, U.S. Public Biotechs



Source: CapitalIQ and Stifel analysis.

Early-Stage U.S. Biotechs Down the Most Over the Last Seven Weeks

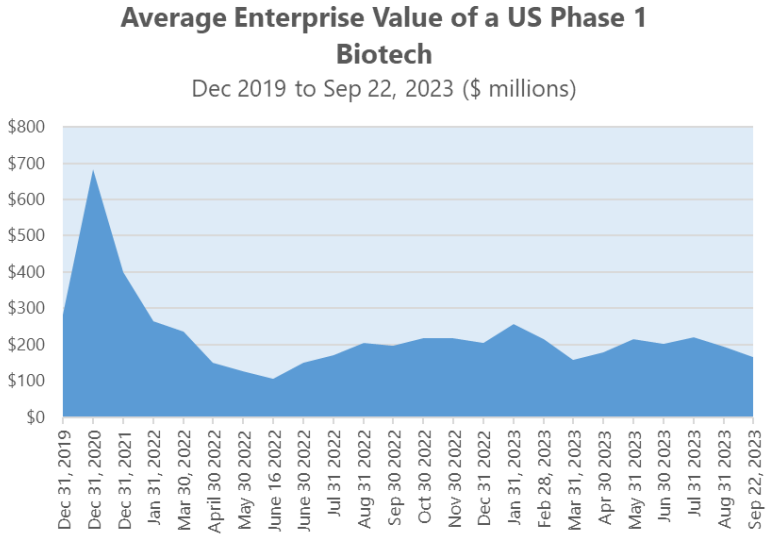


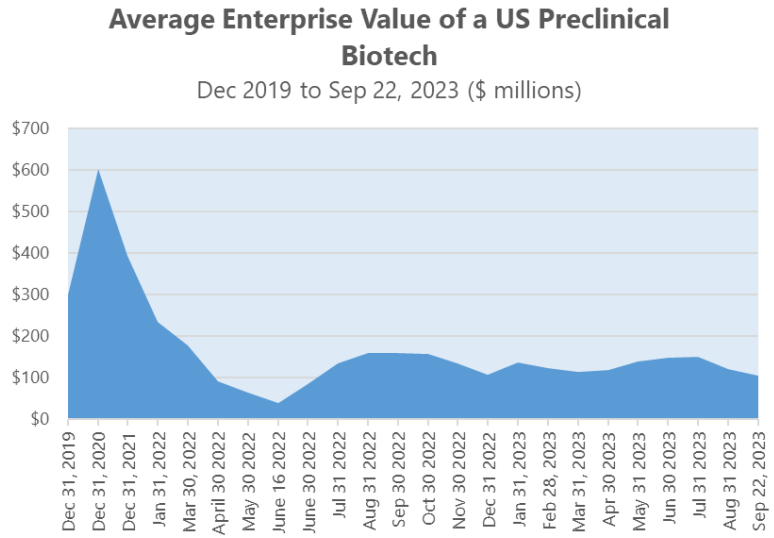
Source: CapitalIQ and Stifel analysis. Stage of development is defined by the last completed stage rather than the stage that is ongoing now.

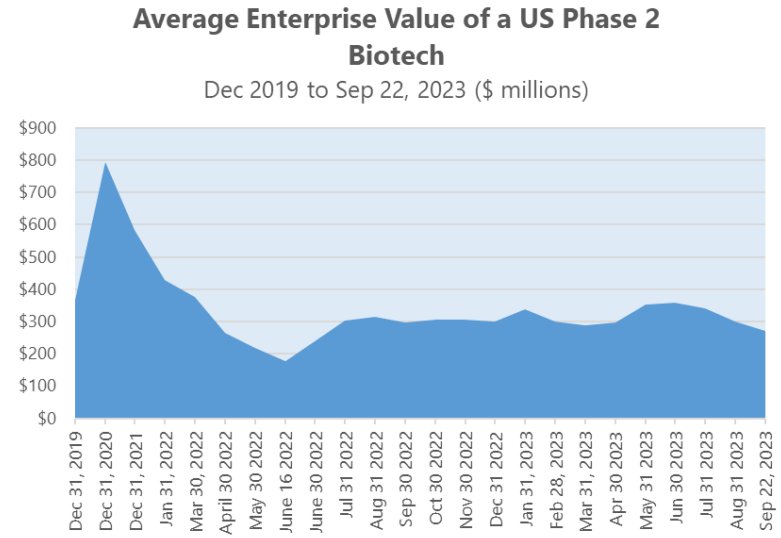
Average Biotech Valuation by Stage of Development, 2019 to Present

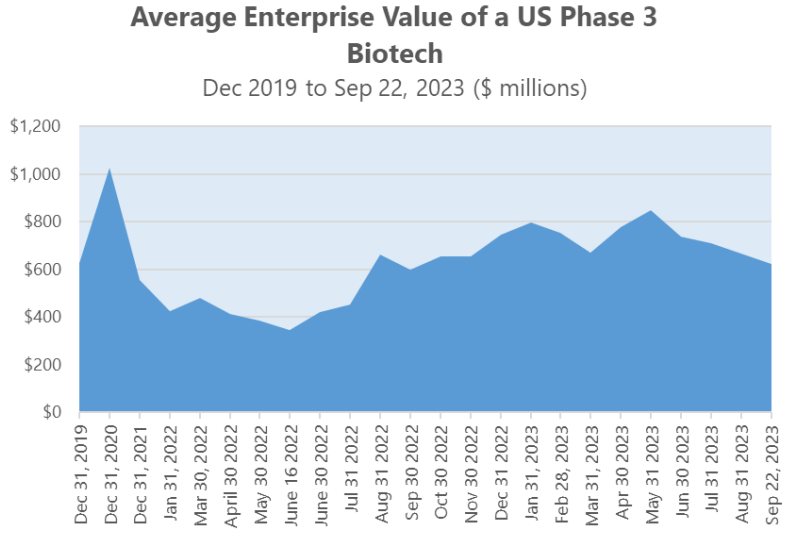
Late-stage biotechs have held up much better than Phase 1 and preclinical biotechs since 2020.

This is consistent with the effect of a rising rate environment.



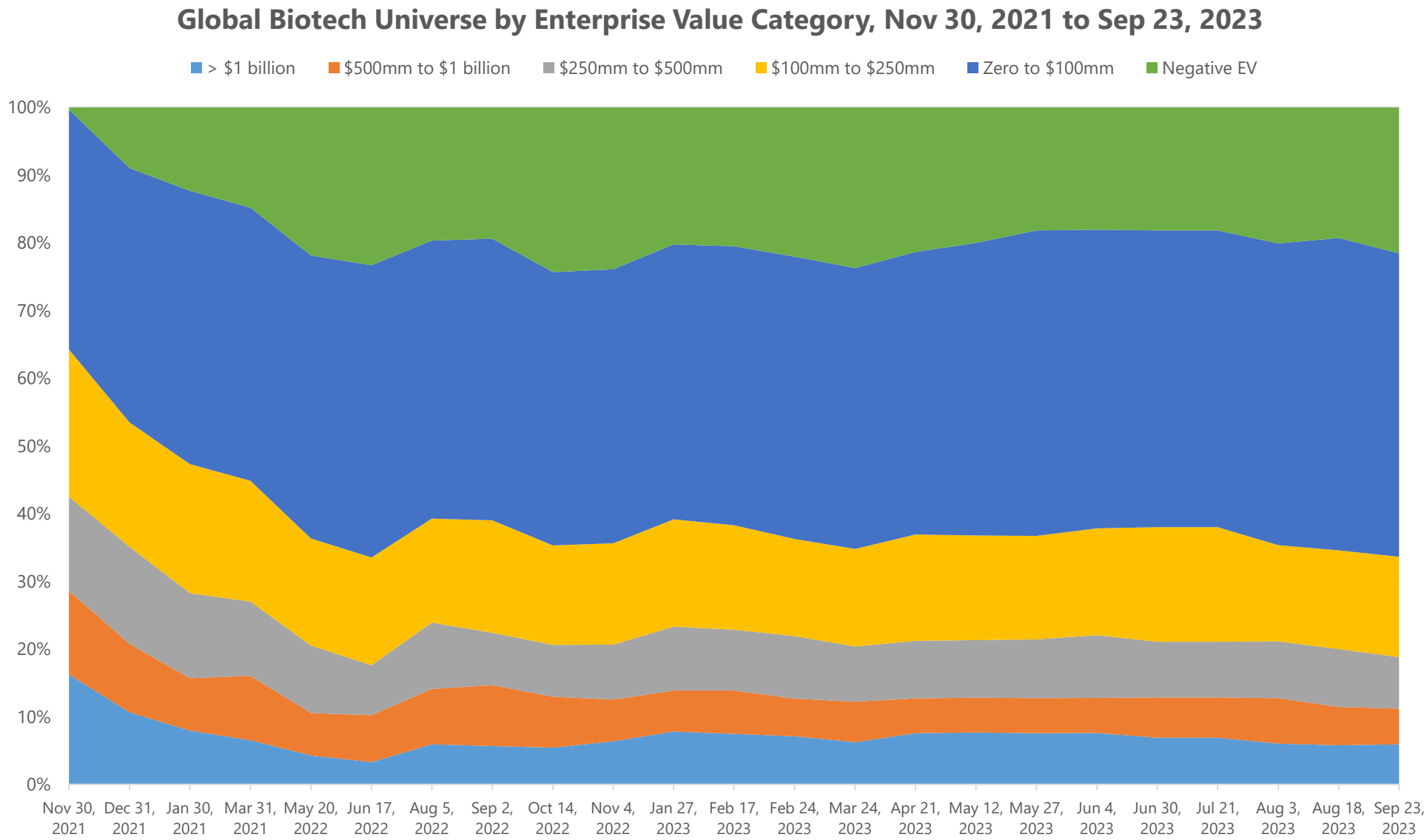






Source: CapitalIQ and Stifel analysis.

How's The Global Biotech Neighborhood Doing?



Even though the XBI was lower in mid-June 2022, the number of companies with an EV under $100mm (the dark blue and green regions in the chart) is higher today.

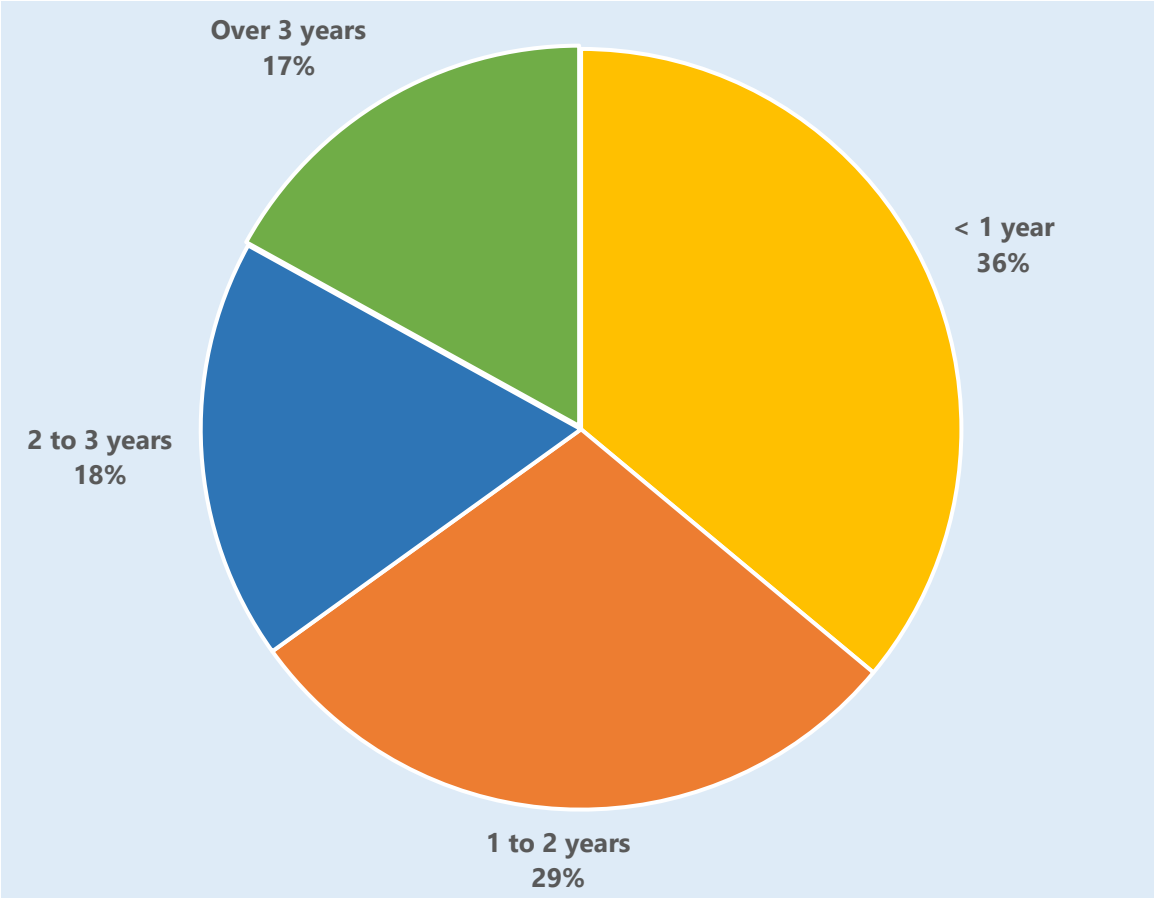
The biotech market is more bifurcated than ever. Only 11% of companies enjoy an EV over $500mm today. This is down from 29% in November 2021.

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

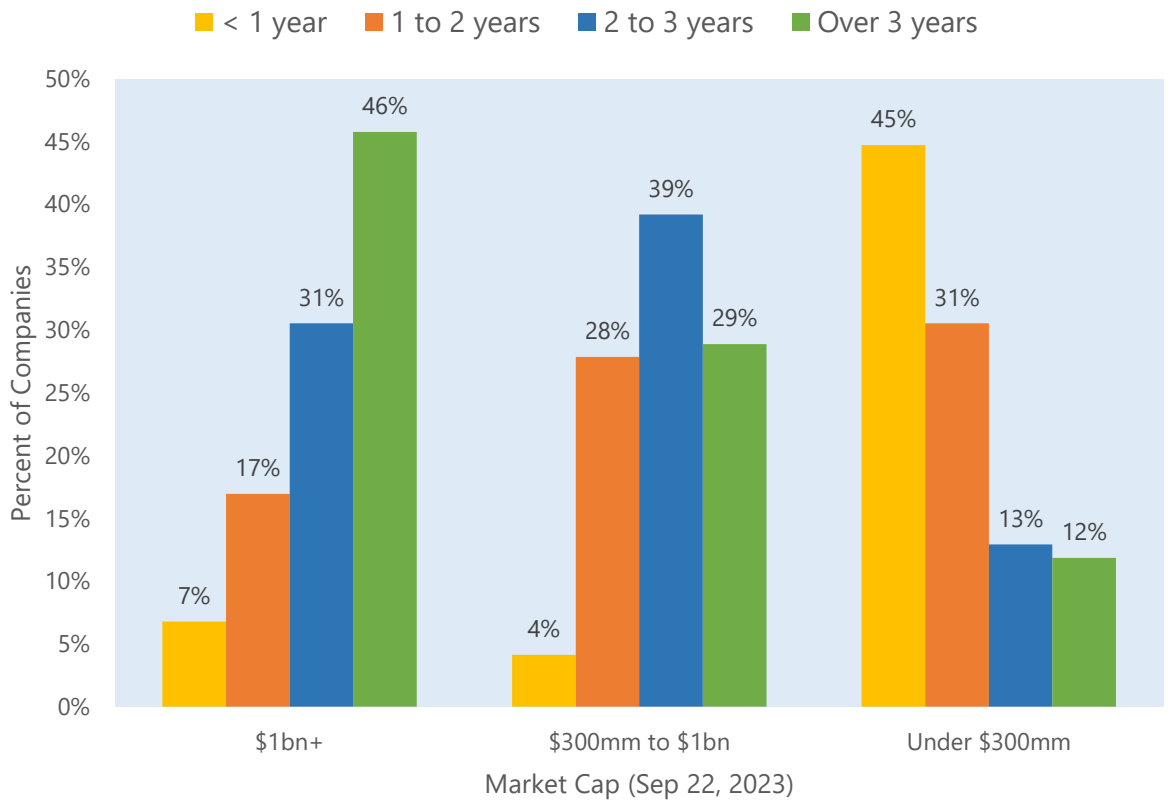
Over a Third of Global Biotech Cohort Has Less Than a Year of Cash - But High Cap Companies in Good Shape

If one looks at all 830 public biotech companies worldwide, there is a substantial fraction that have less than a year of cash. However, Only 7% of companies with market caps over $1bn are in this situation.

Years of Burn, Public Biotech Sector, Sep 22, 2023

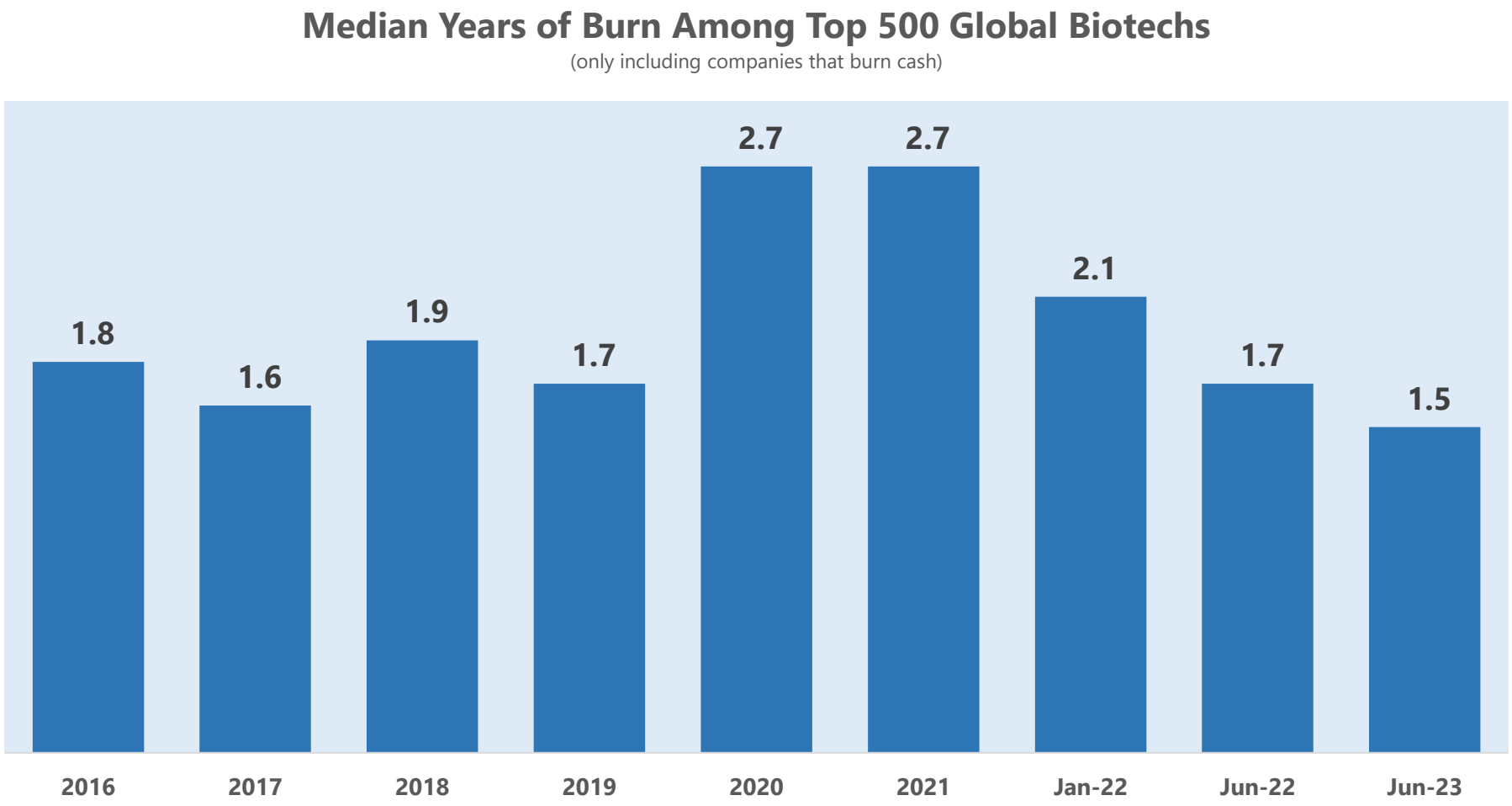


Years of Burn vs. Market Cap, Sep 22, 2023, Global Biotech Sector, Sep 2023



Source: CapitalIQ and Stifel Analysis.

Median Years of Burn of Top 500 Public Biotechs Continues its Sharp Decline



The previous page looked at all biotechs. This page looks at the top 500 biotech survivors from September 2021 (over 95% are still around).

Cash positions for quarter ended June 30, 2023 have now been fully reported.

The median Top 500 biotech company on June 30 quarter end had 1.5 years of burn on its balance sheet.

This is down from 2.7 years at the end of 2021.

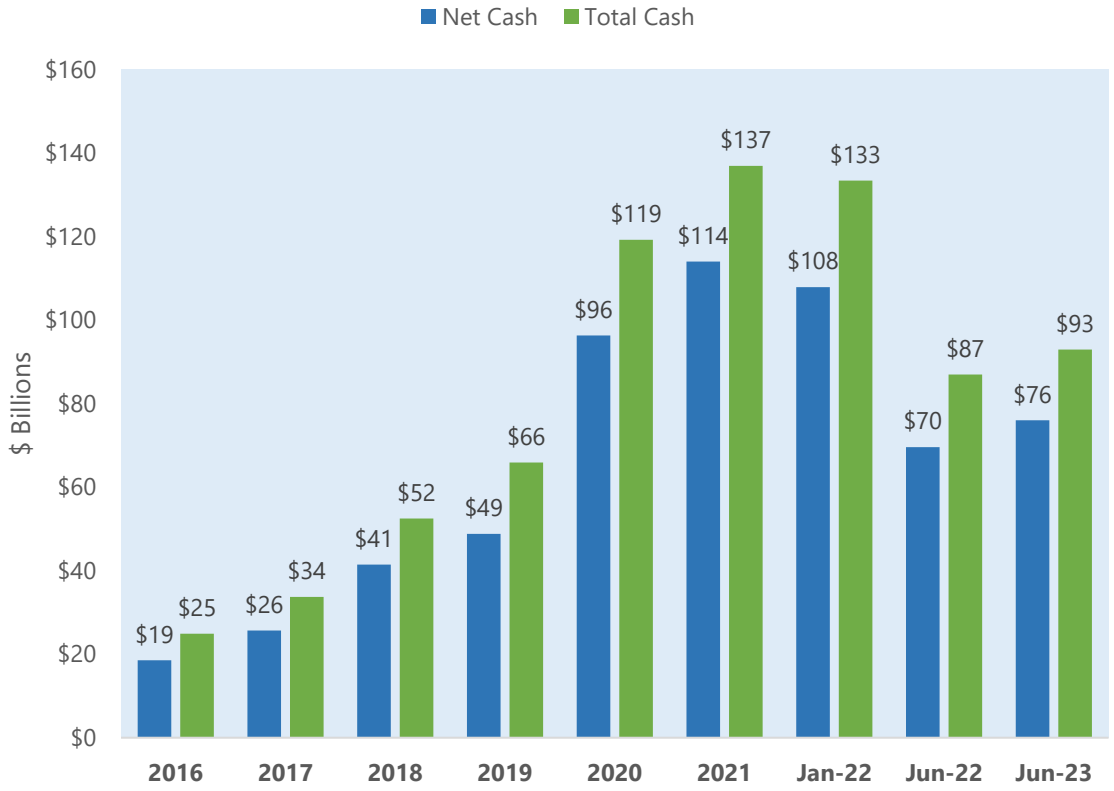
This is also below levels seen in the 2016 to 2018 period.

Notes: Data from CapitalIQ. We took all public biotech companies in Sep 2021 and chose the largest 500 by enterprise value at the time for this analysis. This chart tracks the balance sheets of this cohort to present (and back to 2016 for historic reference). Years of burn is defined as net cash at last quarter end dividend by trailing 12-month EBITDA.

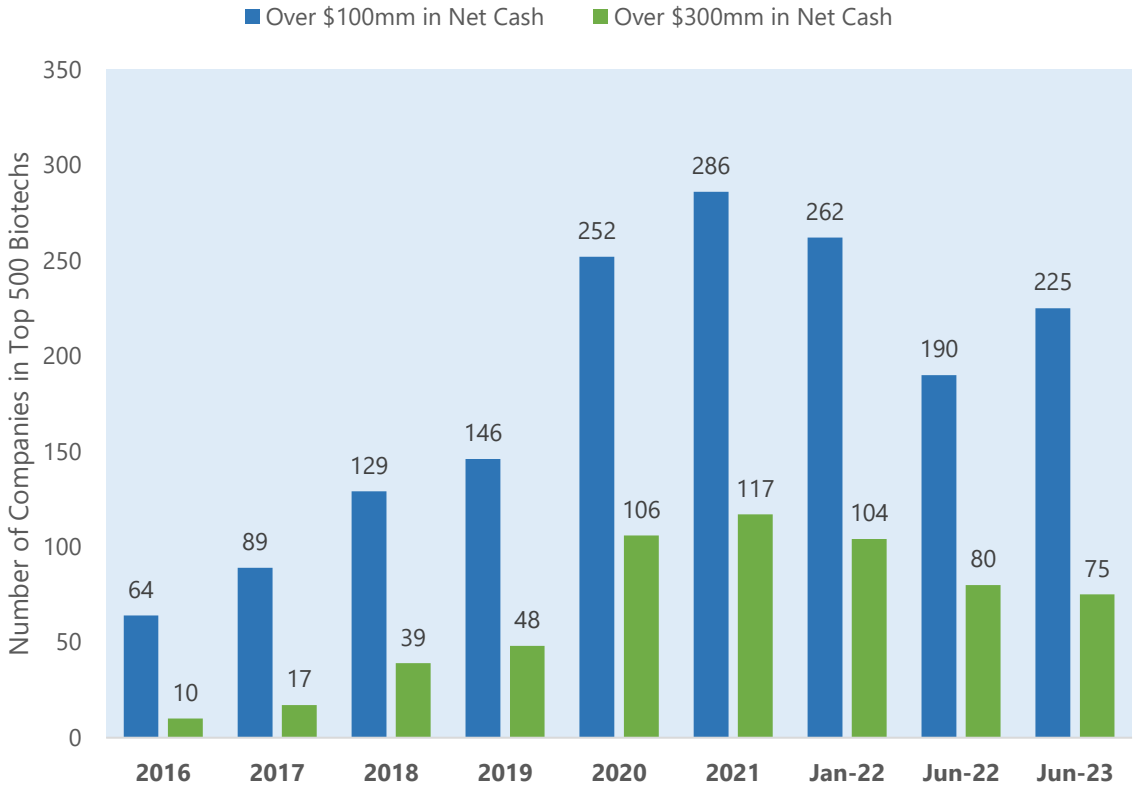
Top 500 Public Biotech Aggregate Balance Sheet Status

The total net cash held by the top 500 biotechs has fallen from $114 billion in Jan 2022 to $70 billion as of June 30, 2022. Since then, the picture has improved with industry net cash up to $76 billion, reflecting reopening of the follow-on Market. The number of biotechs with more than $100mm in net cash has improved in the last 12 months. But, the number with more than $300mm in net cash has shrunk.

Aggregate Balance Sheet Position of Top 500 Global Biotechs



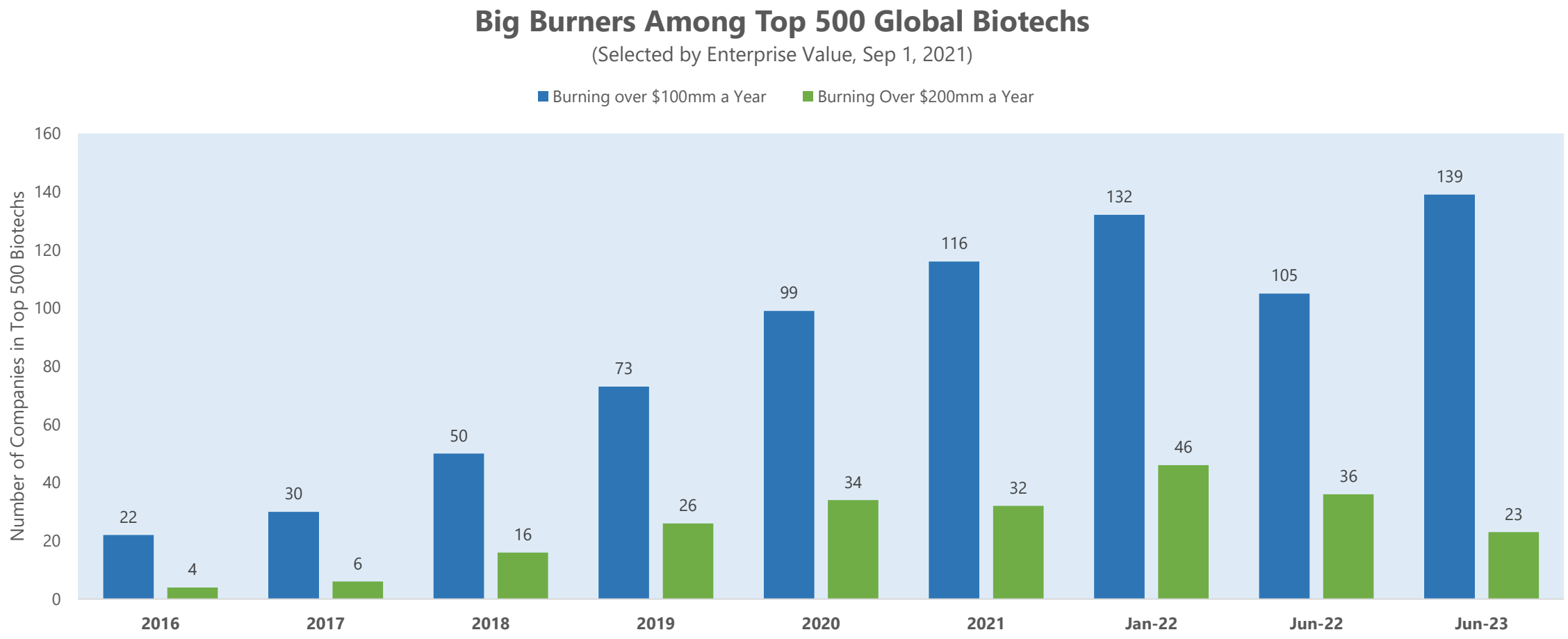
Summary Cash Position of Top 500 Global Biotechs



Source: CapitalIQ, Biotechs were defined as companies in the biopharma sector that do not yet have a commercial product.

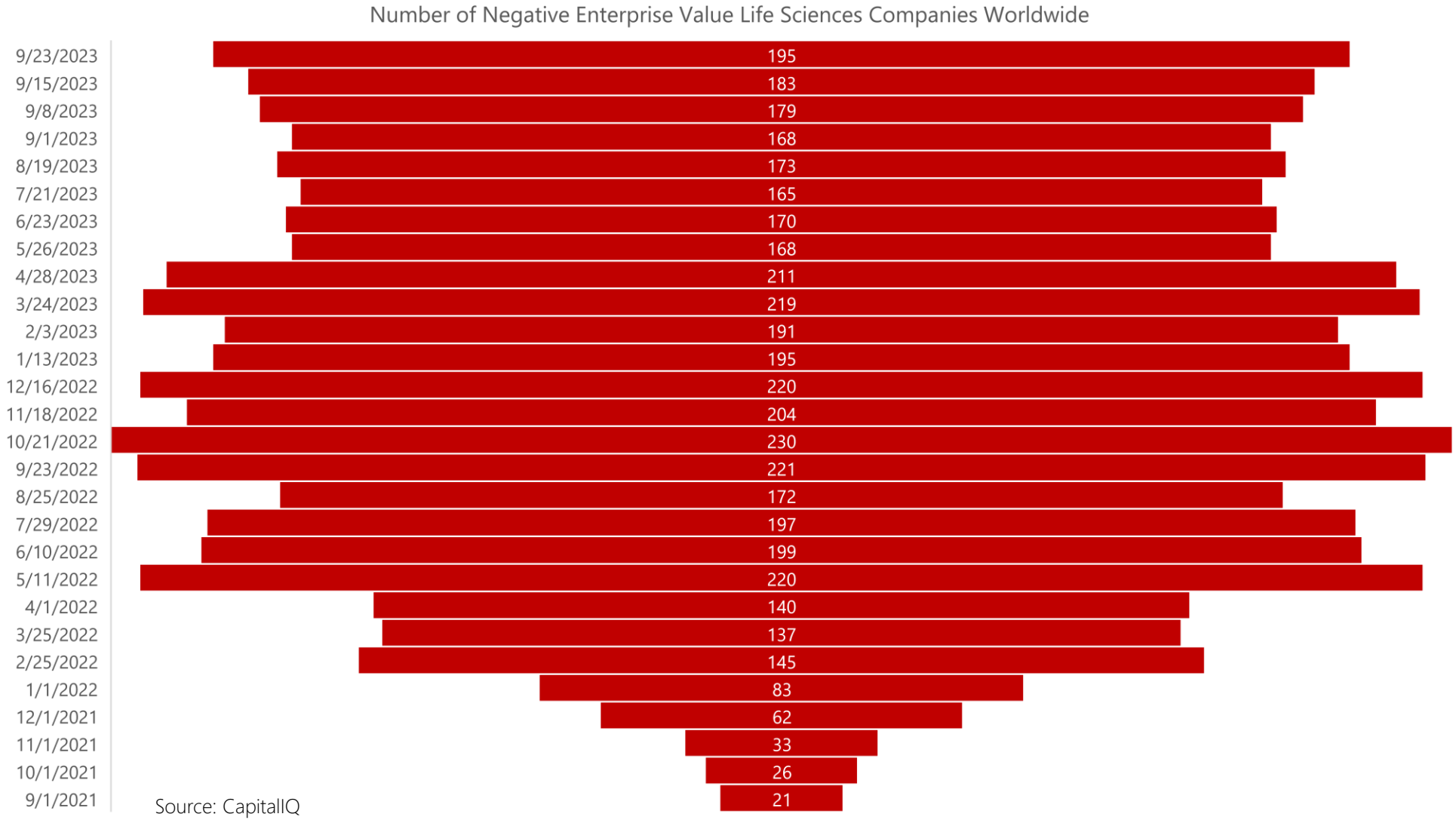
Top 500 Public Biotech Spend Behavior

Biotechs have not restrained spend, on average, through end of year 2022. The number of companies burning over $100mm a year has jumped up in the last 12 months. On the other hand, today, there are far fewer companies burning over $200mm a year.



Source: CapitalIQ, Biotechs were defined as companies in the biopharma sector that do not yet have a commercial product.

Number of Negative Enterprise Value Life Sciences Companies Rose to 195 in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide rose from 183 a week ago to 195 last Friday.

Public Life Sciences Sector Value Fell Last Week

The total enterprise value of the publicly traded life sciences sector fell by 2.6% last week ($236 billion). The sectors that dropped the most were biotech, CDMO's, HCIT, diagnostics, pharma services and life science tools.

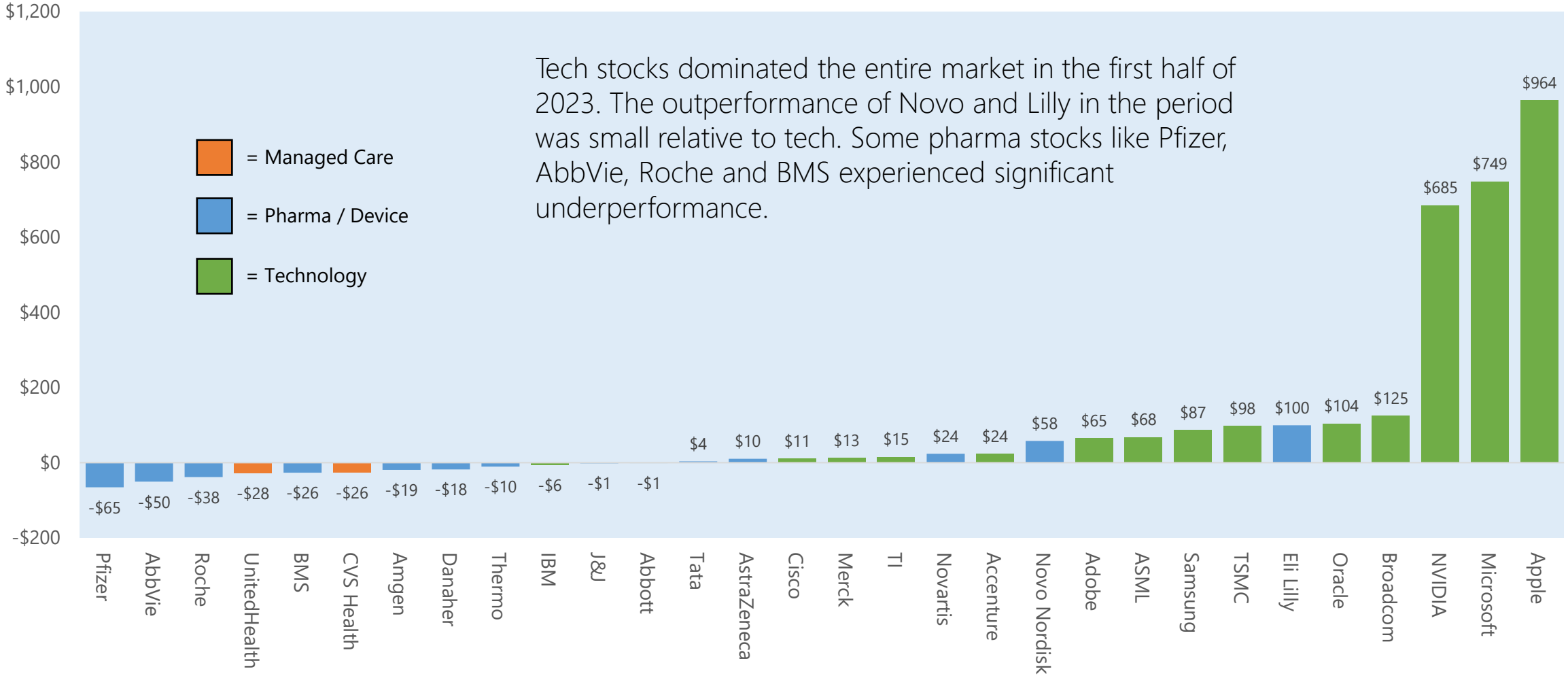
Sector	Firm Count	Enterprise Value (Sep 22, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$79,241	-2.2%	2.8%	-0.3%
Biotech	818	$179,800	-7.3%	-4.3%	-5.1%
CDMO	40	$156,252	-7.0%	-6.8%	-4.3%
Diagnostics	83	$230,763	-3.7%	-7.1%	11.6%
OTC	32	$29,806	-2.1%	-4.2%	5.7%
Pharma	724	$5,784,696	-2.0%	-1.8%	13.3%
Services	41	$204,417	-3.3%	-3.3%	10.3%
Tools	54	$668,292	-3.3%	-4.8%	-6.2%
Devices	181	$1,529,334	-3.0%	-2.8%	6.0%
HCIT	11	$22,127	-3.6%	-3.7%	-9.2%
Total	**2065**	**$8,887,045**	**-2.6%**	**-2.5%**	**9.5%**

Source: CapitalIQ

First Half of 2023: Tech Stocks Blew Pharma Away

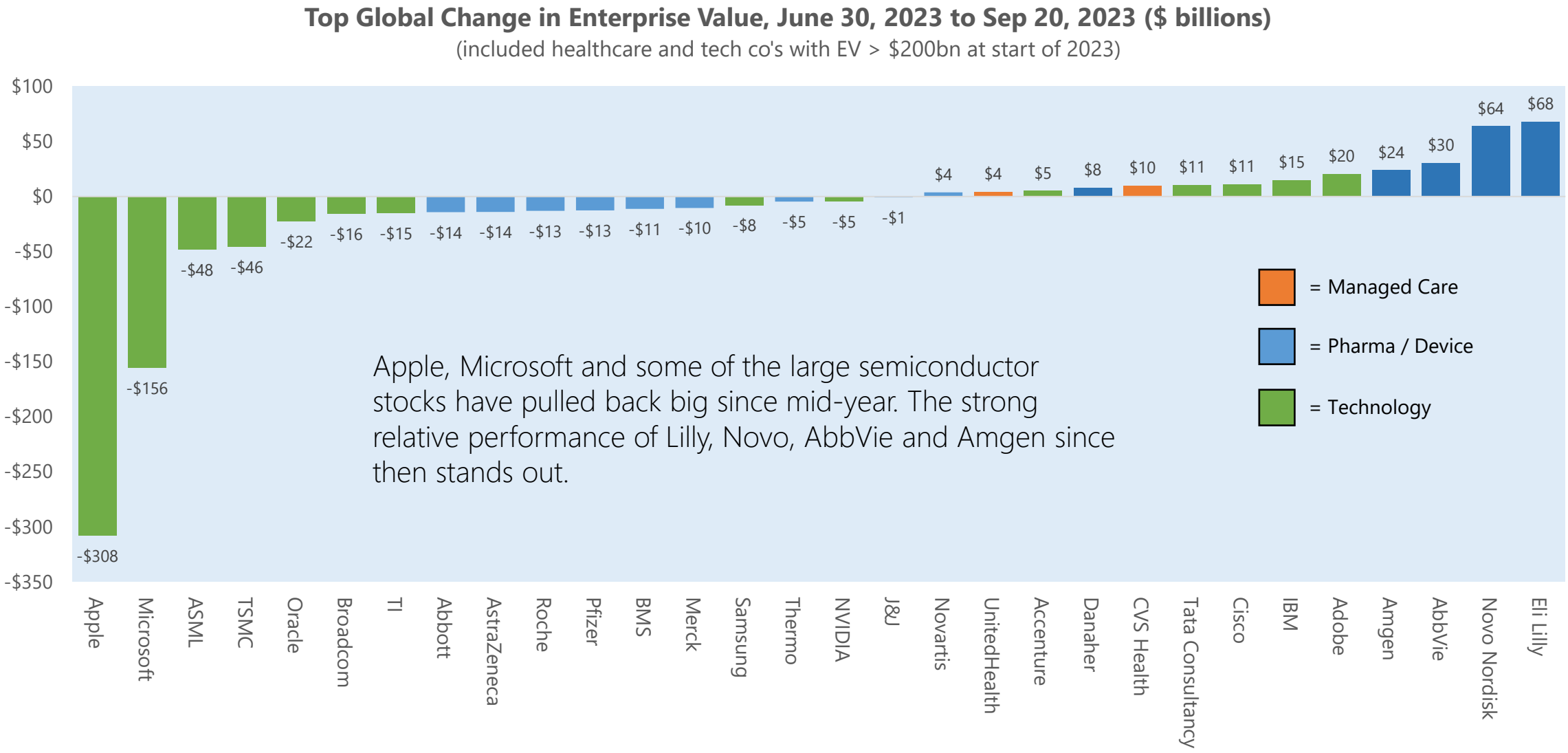
Top Global Change in Enterprise Value, Jan 1, 2023 to June 30, 2023 ($ billions)

(included healthcare and tech co's with EV > $200bn at start of 2023)



Source: CapitalIQ

Since Mid-Year Select Pharmas are Leading the Pack While Big Tech Has Been in the Back Seat



Source: CapitalIQ

Biotech Market Outlook

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

The Summer of Hope

We went into the Summer full of hope. The XBI had marched from 75 to 90. It felt like it would just take a month or two to see some real sunshine in biotech with the XBI over 100. Seeing the market momentum, biotech boards were starting to ask their better companies to “org up” and get ready for the obvious “IPO window”. You could start to feel that biotech sizzle was on the way.

Unfortunately, things didn’t go according to plan. Mr. Powell and his gloomy friends at the Fed spent their Summer holiday in Jackson Hole explaining that inflation would not easily be squashed and that it will be essential to keep rates high. As we returned from holiday bliss in September, we started hearing the alarming phrase “higher for longer”. As we survey the market today, we now face the reality of those pesky Fed “dot plots” which show the expected interest rate trajectory well into 2024. It’s clear that the Fed is telegraphing an intention to keep rates up way longer.

It’s with this backdrop that we have seen appalling performance of biotech stocks in the last month. Our Summer Sizzle has turned into Autumn Fizzle. And we are now looking at “Lower for Longer” in biotech.

They Don’t Ring a Bell At The Bottom

Of course, the implications of the Fed’s messaging go well beyond biotech. Growth stocks everywhere are struggling, and many parts of the global innovation ecosystem are in trouble. Capital markets activities are slowing and M&A volume in pharma has been inexplicably vaporized.

We have many conversations with market participants each week and can report that the drumbeat of pessimism has gotten quite a bit louder recently.

It’s starting to feel like we are nearing a nadir. High pessimism tends to market a bottom. Phrases we have heard in the last week include “we are past the point of denial”, it’s “hang up the cleats time”, and “we are in the bottom of the biotech hype cycle”.

It’s typically a point of pessimism like this when a market bottoms out. We have no great soothsaying abilities but would simply note the old Wall Street adage: “they don’t ring a bell at the bottom.” It feels like we are there.

The Market Will Ultimately Get a Lot Better

The Fed is doing its job and Mr. Powell is trying to keep the post-Pandemic economy afloat. He is very different stylistically than Paul Volcker shown at right. Mr. Volcker faced much higher inflation (13.3% in 1979) and forced Fed Funds to 20% by June 1981. The economy plunged into recession which wrung out the inflation. It was a period of great economic pain.

It's also important to remember what followed. With low inflation and an innovation-laden economy ahead, the Dow Jones Industrial Average rose by fourteen times from 1981 to 2001.

We are not saying that we are in store for the same thing. But we would note that some quarters wish that Mr. Powell would get on with it and take rates up as high as needs to get inflation behind us. The biotech market wouldn't be likely to get much worse. One would hope that with the current "higher for longer" approach behind us, we would see a major reinvigoration of the equities market in time.

History would say that the market will not just get better – but, instead, it will get a lot better. This is important to know as we navigate today's stressed market circumstances.

Paul Volcker, Former Fed Chairman

Finding Our Way Out

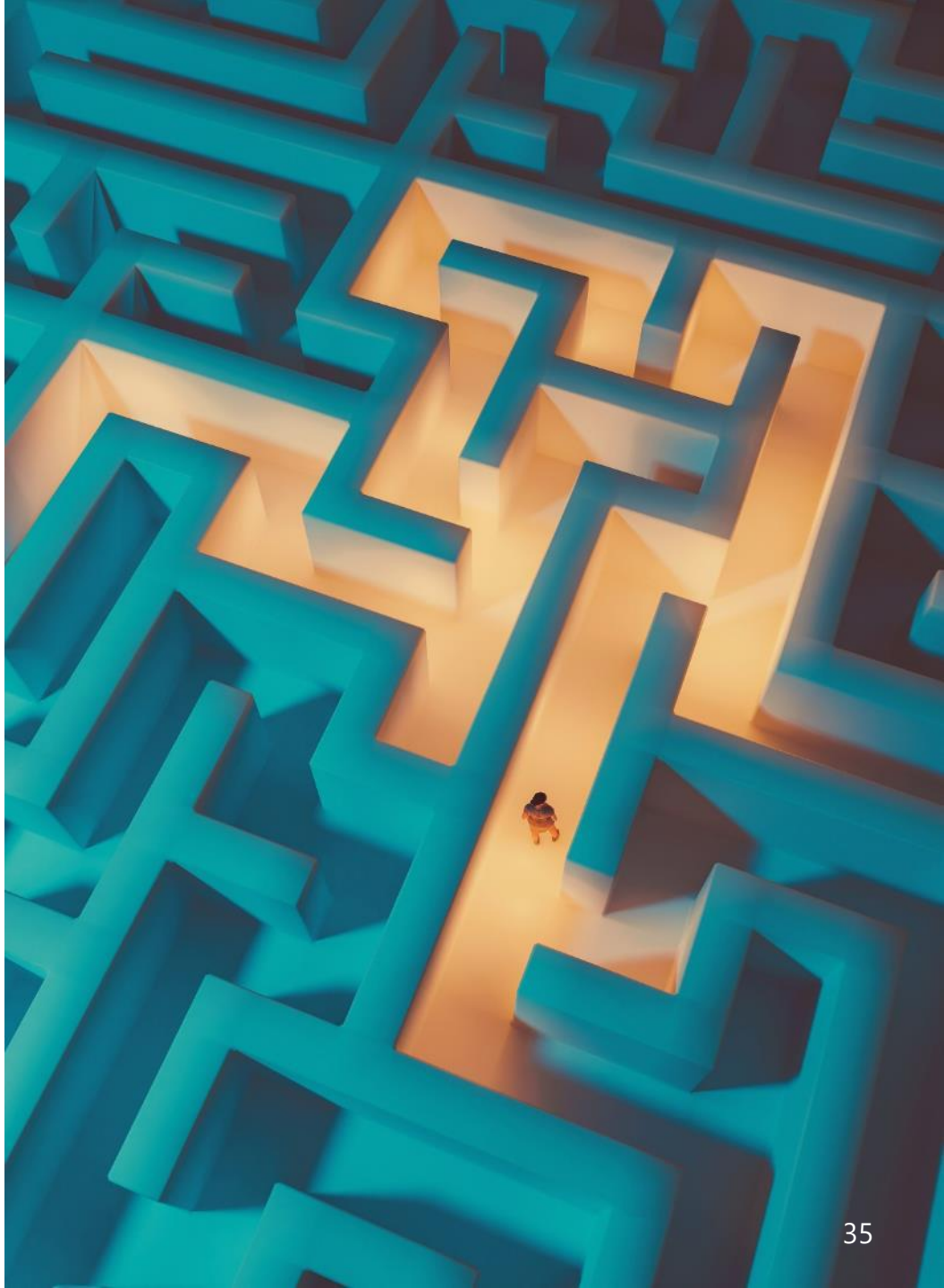
The fact that the market will improve *eventually* is little solace for a biotech CEO facing a dwindling cash pile and little prospect for financing.

We would simply the note that we are amazed by how well the biotech population has done throughout the last two years. Despite liquidations here and a few capitulations there, the reality is that the public population of global biotech companies has shrunk by less than 10 percent over two years.

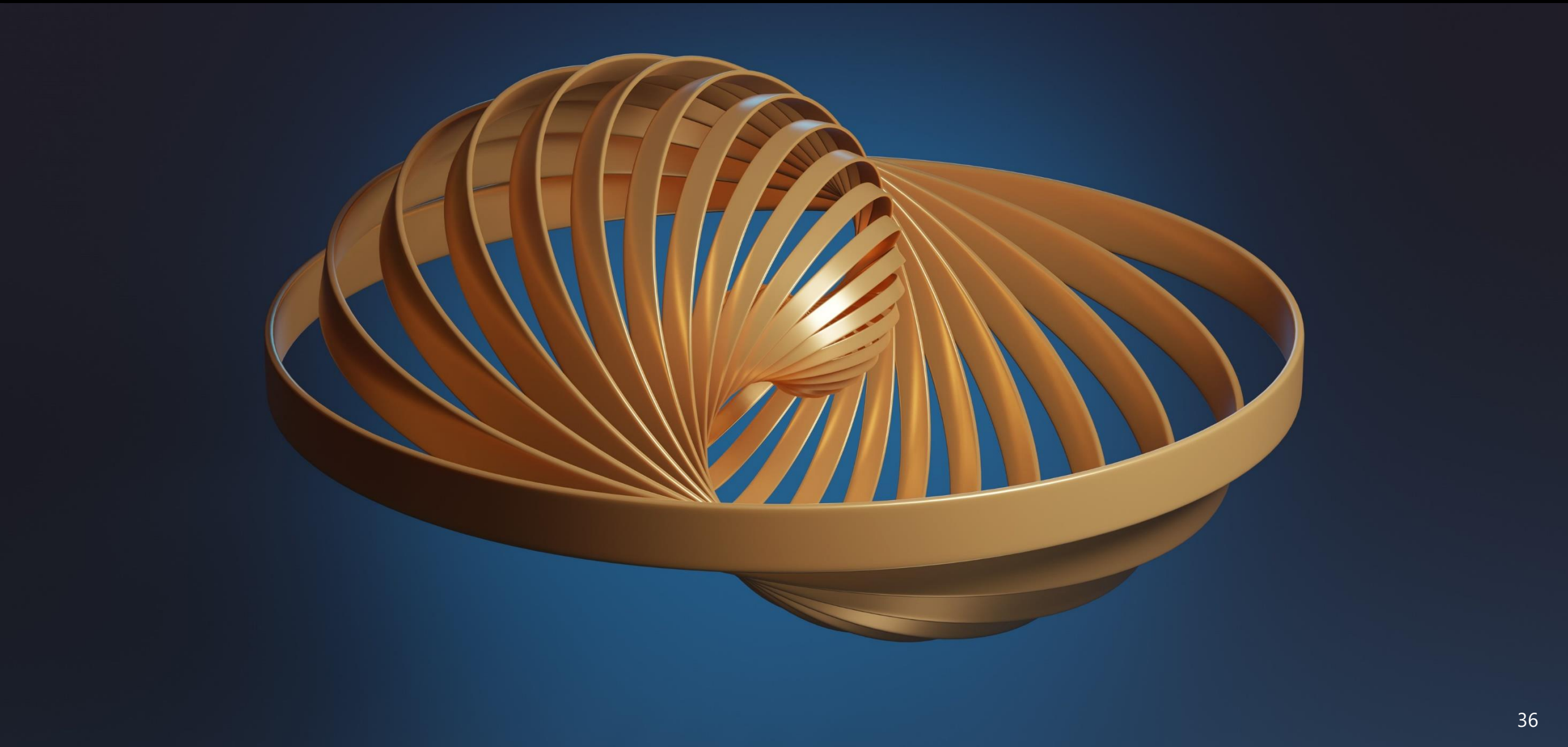
Going forward, the next year or two could obviously be quite tough as shown in the balance sheet statistics in the previous section. Too many companies have two years or less of cash remaining. This is time for creativity, thrift, thought and focus.

Phrases that we have heard lately include “prep for the worst; hope for the best”, “uncertainty creates opportunity” and this industry is a “serendipitous marathon” – you must “stay in the game”.

Business plans and strategy are key. One must pick a plan and clinical strategy that can be financed. The markets are open and will fund plans that make sense to investors.

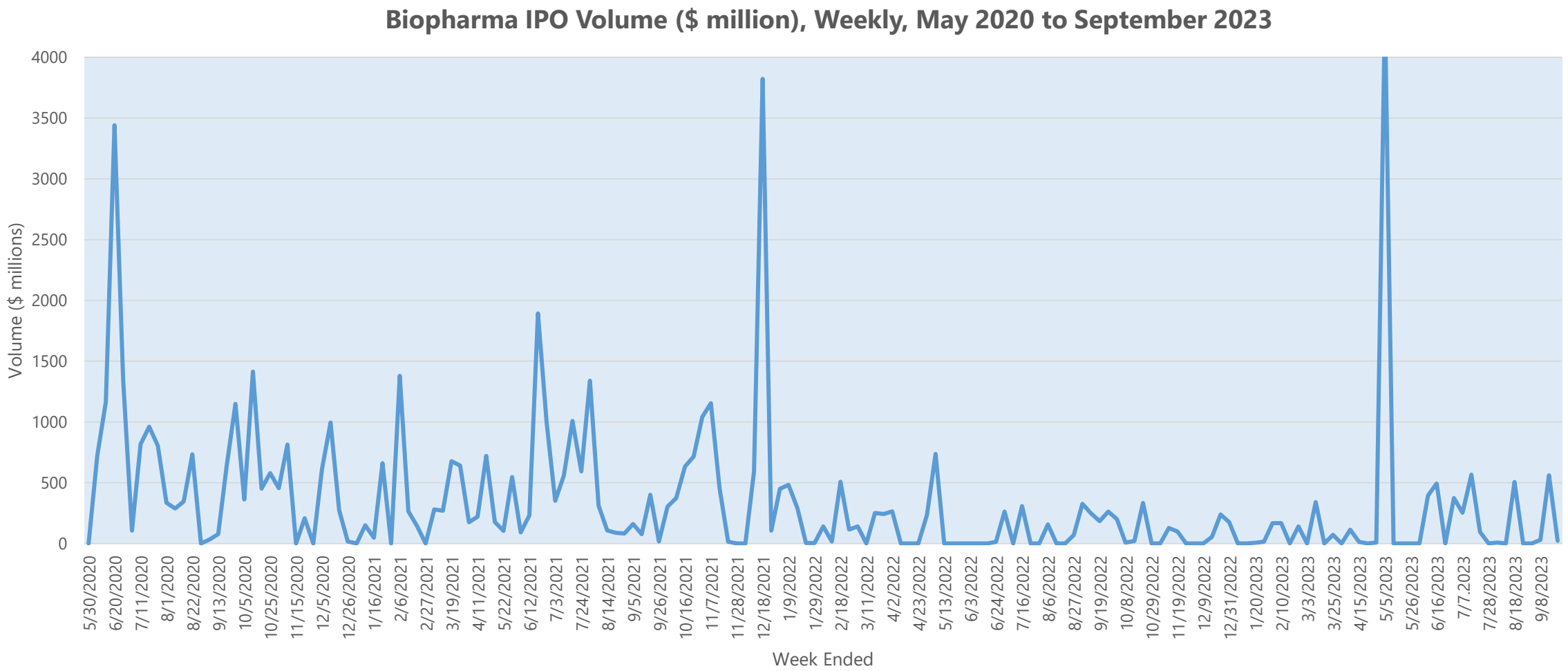


Capital Markets and Deals Environment



IPO Market Quiet

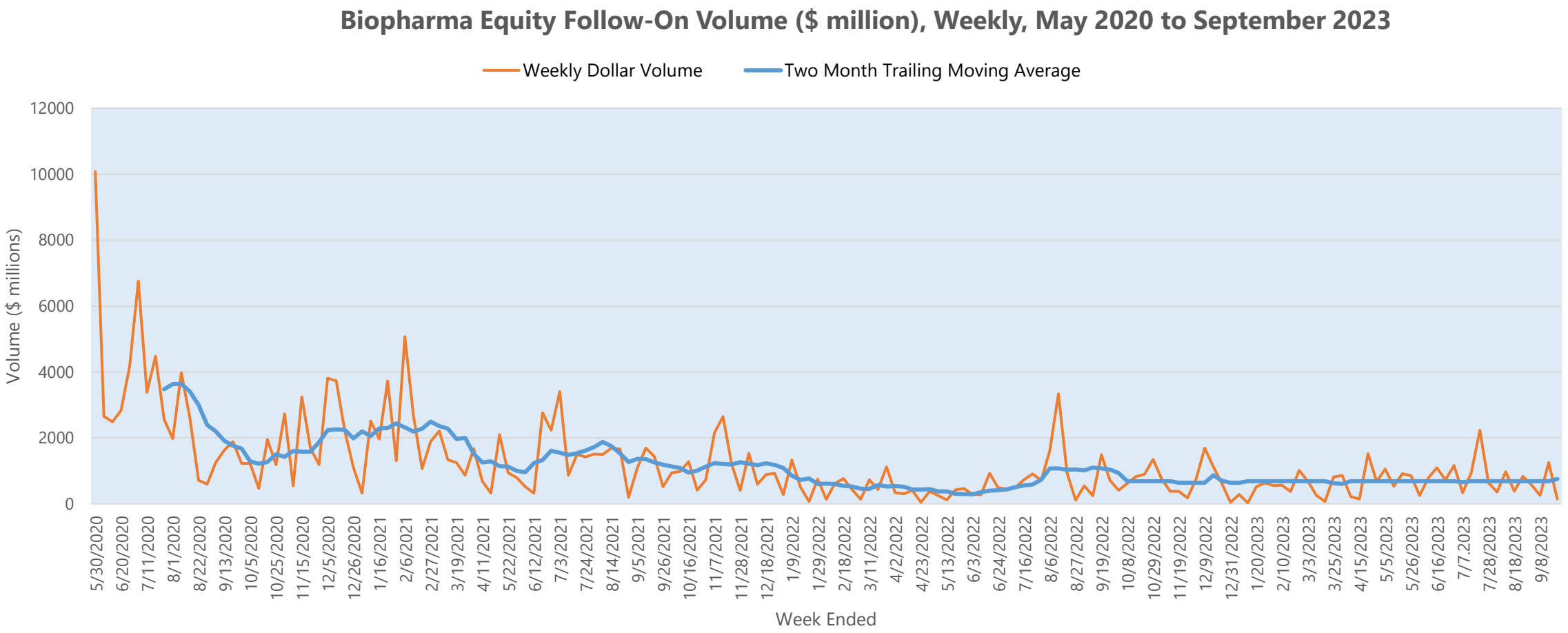
Last week saw one small IPO in China. Otherwise, the market was closed. Some recent issues have not traded as well as hoped.



Source: Data from CapitalIQ and Stifel research.

Last Week Was Soft for Follow-On Offerings

Last week saw $143 million in follow-on volume as the market digested negative Fed news. This was the third quietest week of the year.



Source: Data from CapitalIQ and Stifel research.

HilleVax Announces Pricing of Public Offering of Common Stock

BOSTON, Sept. 19, 2023 (GLOBE NEWSWIRE) -- HilleVax, Inc. (Nasdaq: HLVX), a clinical-stage biopharmaceutical company focused on developing and commercializing novel vaccines, today announced the pricing of its public offering of 8,000,000 shares of its common stock at an initial price to the public of $12.50 per share. All of the shares are being offered by HilleVax. The gross proceeds from the offering, before deducting underwriting discounts and commissions and other offering expenses, are expected to be $100.0 million. The offering is expected to close on September 22, 2023, subject to the satisfaction of customary closing conditions. In addition, HilleVax has granted the underwriters a 30-day option to purchase up to an additional 1,200,000 shares of common stock at the initial price to the public, less underwriting discounts and commissions.

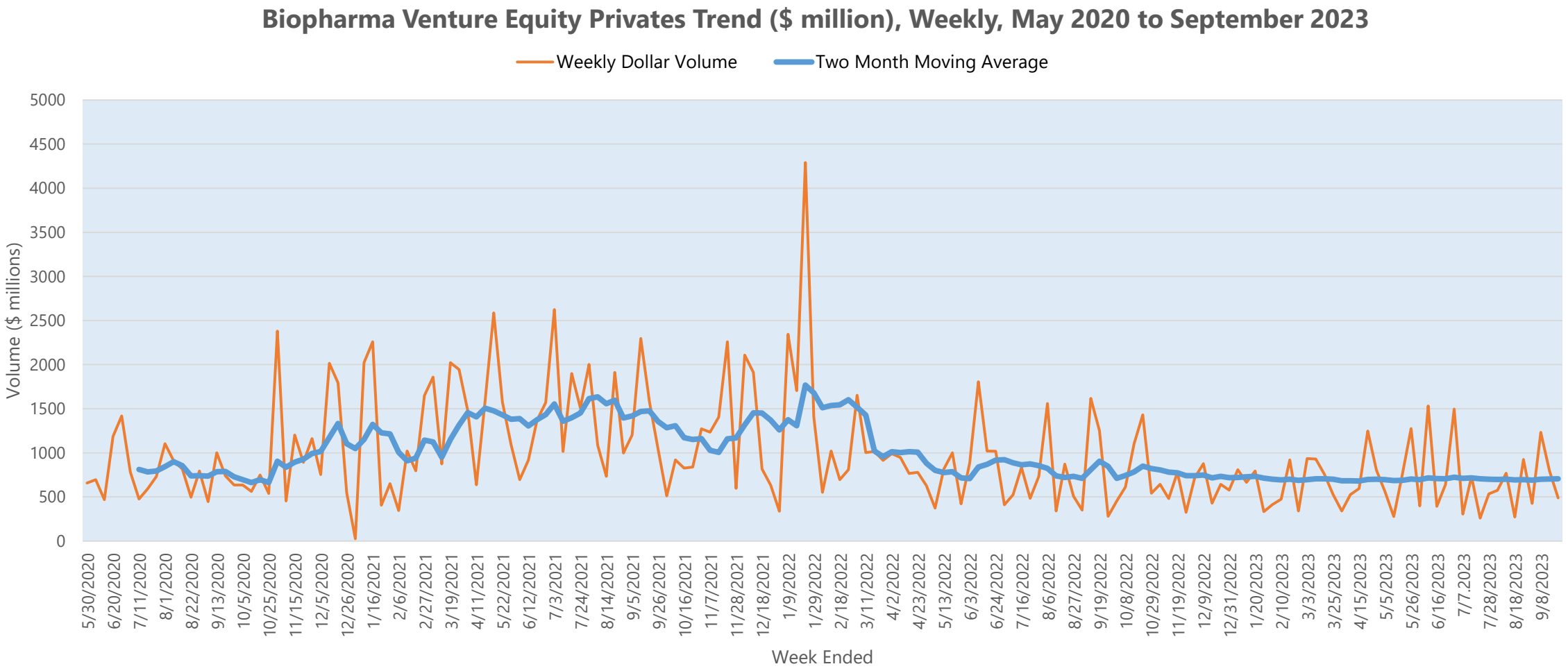
HilleVax intends to use the net proceeds from the offering to fund the clinical development of HIL-214, including certain manufacturing activities, and for working capital and general corporate purposes.

J.P. Morgan, Leerink Partners, Stifel and Guggenheim Securities are acting as joint book-running managers for the offering.

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

Venture Equity Market Quiet Last Week

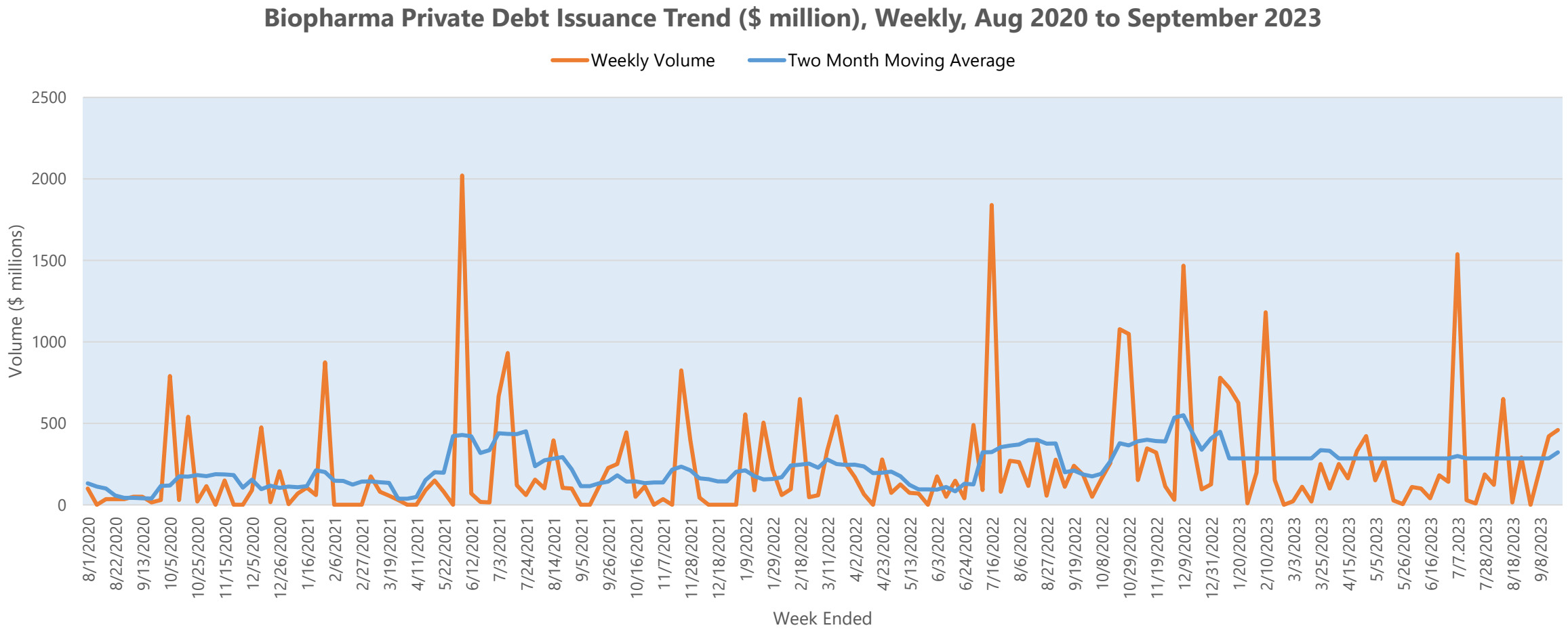
Last week saw 35 companies raise $490 million in the venture equity market.



Source: Data from CapitalIQ, Crunchbase.

Weekly Global Biopharma Private Debt Placements

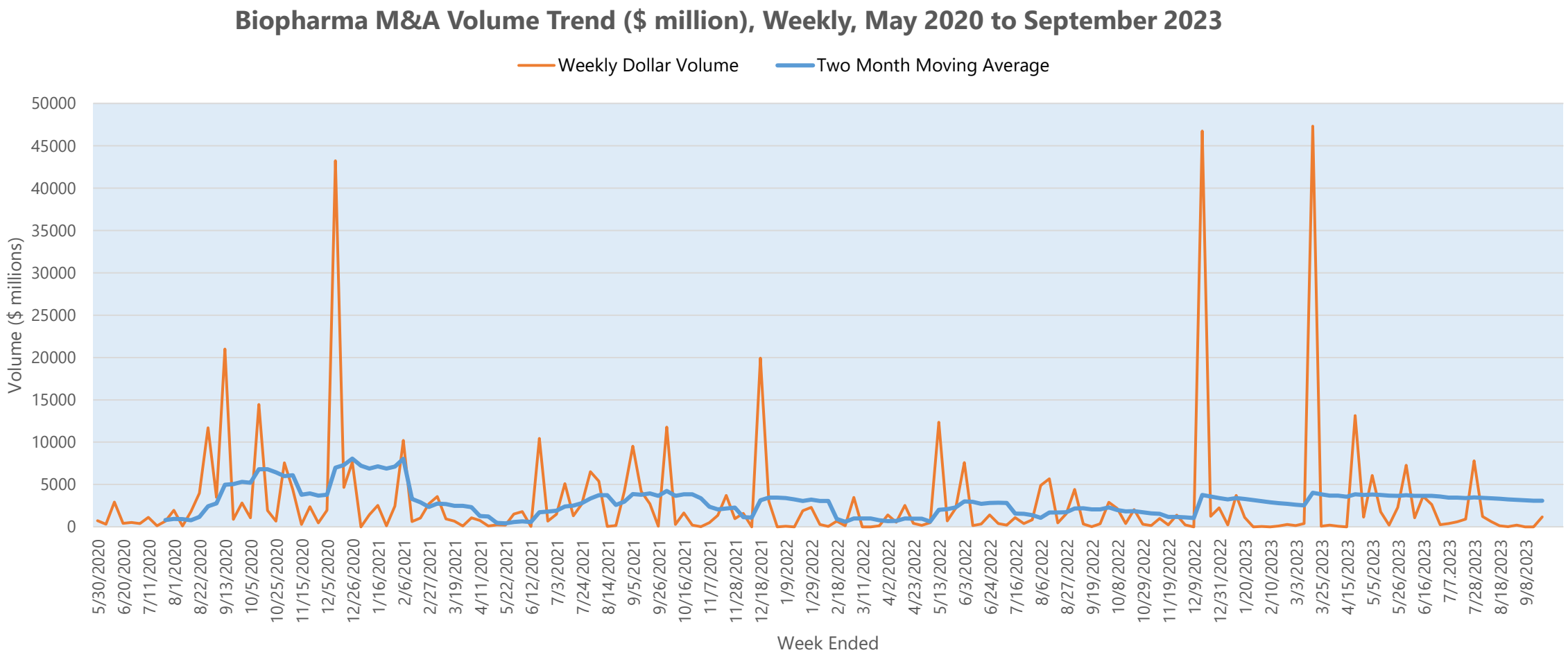
We saw five deals in the private debt market last week with $459mm raised. The debt market continues to function well despite a difficult rate environment.



Source: Data from CapitalIQ, Crunchbase.

Slight M&A Pick Up Last Week

While there were no M&A deals of over $50mm in biotech last week we saw one meaningful pharma sale (M8 Pharma to Acino) and one meaningful API deal (Glenmark Life Sciences sale to Nirma Limited). Stifel was pleased to represent M8 Pharma on its sale to Acino.



Source: S&P, CapitalIQ

Marlboro Maker Hits Reset on $2 Billion Bet on Medicine

Philip Morris considers selling a stake in a recently acquired pharmaceutical business after setbacks

Ben Dummett and Jennifer Maloney, *Wall Street Journal*, Sep 19, 2023

Philip Morris International's push into healthcare is faltering, prompting the tobacco giant to consider options such as selling a stake in its biggest pharmaceuticals unit.

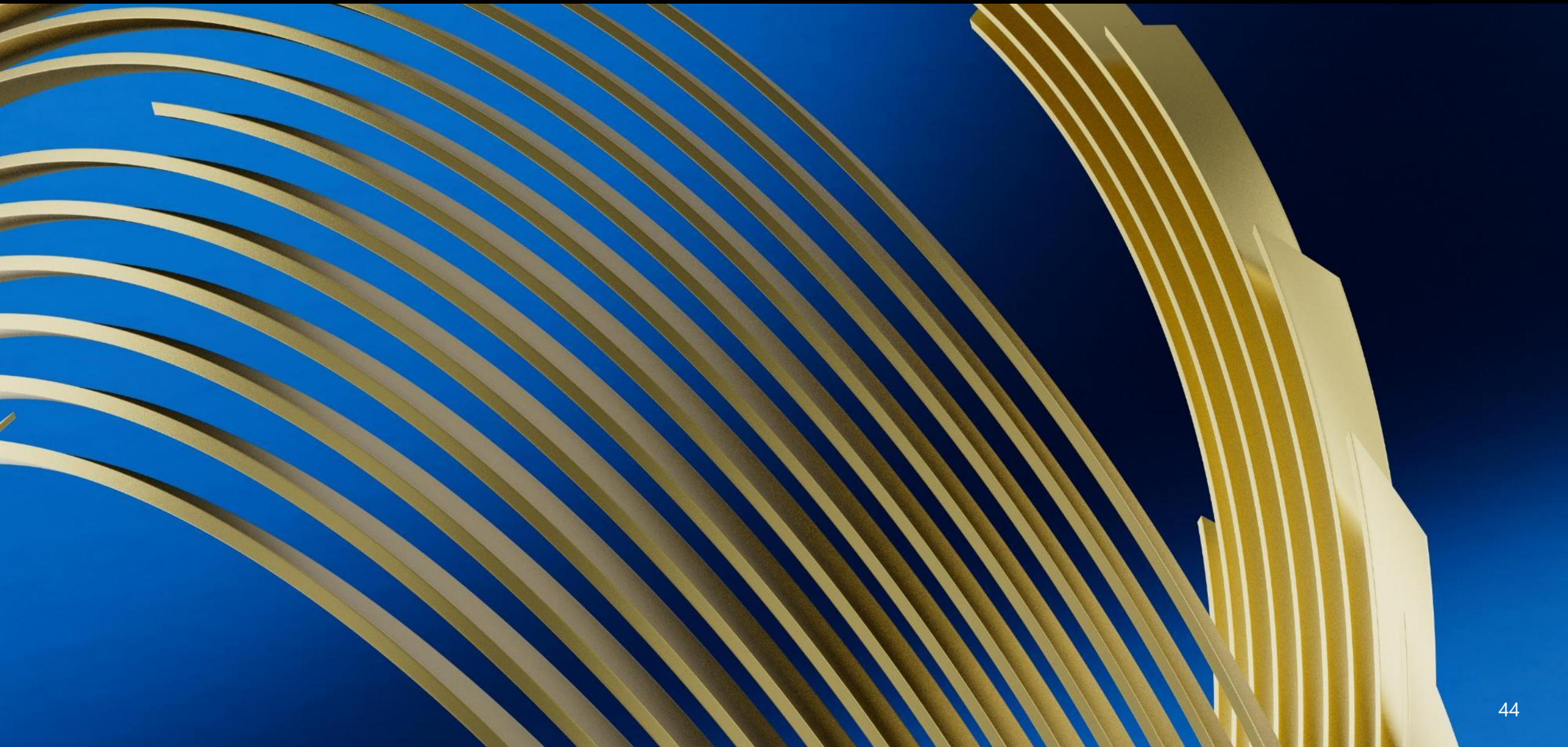
In 2021, the tobacco giant agreed to acquire three pharmaceutical companies for a total of more than $2 billion as part of a plan to pivot away from cigarette sales. The deals inserted the Marlboro maker into the market for inhalers and other treatments for respiratory diseases that are linked to cigarette smoking.

Philip Morris's struggles came into view over the summer, when the company took a $680 million charge on its wellness and healthcare business and postponed its ambitious revenue goals for the business.

Now, Philip Morris is considering the possible sale of a stake in its biggest pharmaceuticals unit, as it searches for a new partner to help it make the business work. Philip Morris acquired that business, an inhaled-medication company called Vectura Group, in a $1.24 billion deal after winning a bidding war against private-equity firm Carlyle Group.

Source: https://www.wsj.com/business/marlboro-maker-hits-reset-on-2-billion-bet-on-medicine-110e4df7

Industry News



Orphan Cures Act on Deck

BIO, "ORPHAN Cures Act a "welcome and bipartisan fix" to the IRA's negative impact on drug development," September 18, 2023

Representatives John Joyce, M.D. (R-PA) and Wiley Nickel (D-NC) today introduced the Optimizing Research Progress Hope And New Cures (ORPHAN Cures Act). BIO President and CEO, Rachel King, made the following remarks:

"This legislation is a welcome bipartisan fix to the Inflation Reduction Act's (IRA) negative impact on the development of drugs to treat rare diseases.

"Encouraging R&D for drugs to treat rare diseases is difficult as is. By definition, orphan drugs benefit small patient populations, making investment in this space incredibly risky. But there is tremendous need for these treatments. Fewer than 5 percent of rare diseases have an FDA approved treatment. We have repeatedly warned that the IRA -- by subjecting drugs that can treat more than one rare disease to government price controls -- creates even more barriers to investment into follow-on research and development for orphan drugs.

"The new bill, introduced by Representatives John Joyce, M.D. (R-PA) and Wiley Nickel (D-NC), changes the incentive structure within IRA to encourage follow-on investment into orphan drug development. Reversing IRA's perverse incentives will eliminate the significant barrier for scientists to usher in new waves of rare disease drug innovation – all to the benefit of the thousands of patients currently suffering from rare diseases for which no treatments exist.

"BIO looks forward to working with lawmakers to get the Optimizing Research Progress Hope And New Cures (ORPHAN Cures Act) across the finish line as quickly as possible."

One of the many oddities of the IRA was that one can avoid negotiation if an orphan drug is approved for one indication. But, once a second indication is added on, the drug becomes eligible for negotiation. Obviously, this is a major disincentive to developing drugs for many patients in severe need.

The ORPHAN Cures Act being set up for debate in Congress proposes to remove this illogical policy.

We hope that this gets passed quickly to renew incentives for multi-indication orphan drugs.

Source: https://www.bio.org/press-release/orphan-cures-act-welcome-and-bipartisan-fix-iras-negative-impact-drug-development

ARS, Intarcia and Taysha Had a Tough Week at the FDA

Greg Slabodkin, *Biospace*, Sep 22, 2023 (excerpt)

Several companies this week got stark reminders that the FDA's regulatory gauntlet is difficult to navigate in terms of getting treatments approved. Though it received backing from the Pulmonary-Allergy Drugs Advisory Committee in May, the FDA on Tuesday rejected ARS Pharmaceuticals' neffy as a nasal spray for allergic reactions—a reminder that the regulator doesn't have to follow the advice of its advisory committees. ARS plans to file a Formal Dispute Resolution Request appealing the FDA's Complete Response Letter (CRL).

On Thursday, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 19-0 against Intarcia Therapeutics' ITCA 650 implantable drug-device combination for the treatment of type 2 diabetes. The advisory committee defeat is the latest in ITCA 650's troubled regulatory history, which has included two CRLs.

Taysha this week dropped its lead experimental gene therapy candidate for giant axonal neuropathy after the FDA reiterated the need for a randomized, double-blind, placebo-controlled trial. Adding insult to injury, in Tuesday's announcement Taysha reported that Astellas will not be exercising its option to obtain an exclusive license to the therapy.

Source: https://www.biospace.com/article/fda-regulatory-gauntlet-isn-t-getting-any-easier-just-ask-these-companies/

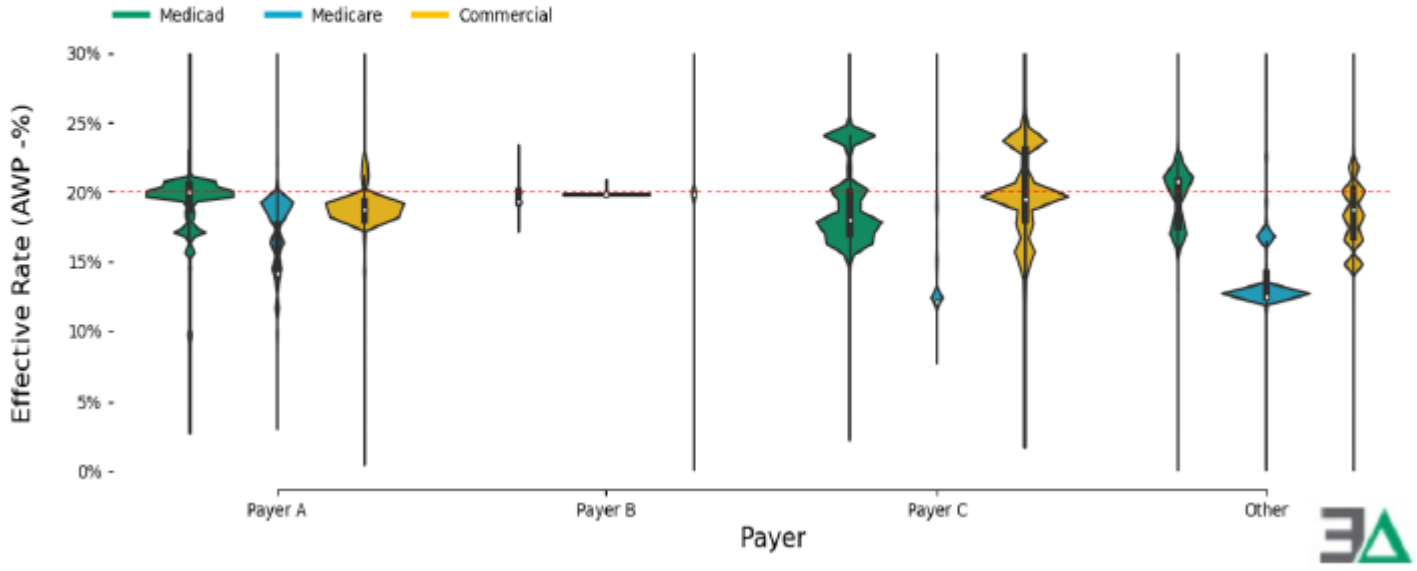
Independent Pharmacy Group Releases Study of Drug Pricing: PBM's Set Drug Prices for Patients

The attention paid to the costs of pharmaceuticals is understandable when one considers that, in many ways, medicines are arguably the backbone of the U.S. healthcare delivery system. Whether a person is seeking treatment for a simple infection or complex diseases like cancer or multiple sclerosis, prescription drugs are the primary tools employed by our nation's healthcare professionals to address illness. Moreover, prescription drugs are often the goal of researchers who are looking to offer solutions for medical conditions without current treatments. However, informed debate over drug prices is challenging because the nature of drug prices requires layers of context. That said, the common understanding of the American public appears to be that the pricing practices of drug manufacturers are primarily to blame for high drug costs. While there is certainly truth to the notion that drug manufacturers are key contributors to the prices paid for medicines, our study of 32.6 million retail pharmacy claims from independent, small chain, and mid-size chain pharmacies over a 12-month period between January 1, 2020 and December 31, 2020 finds that a great deal more context is needed to understand drug prices at the pharmacy counter.

Source: https://www.3axisadvisors.com/projects/2023/9/19/unravelling-the-drug-pricing-blame-game

PBM's Setting Drug Prices – Not Pharmas

Chart 1: Distribution of Brand Average Wholesale Price (AWP) Discounts by Payer and Line of Business for Claims where the Drug Manufacturer's List Price was Used by the PBM as the Basis of Payment (Studied Pharmacy Data, 2020)



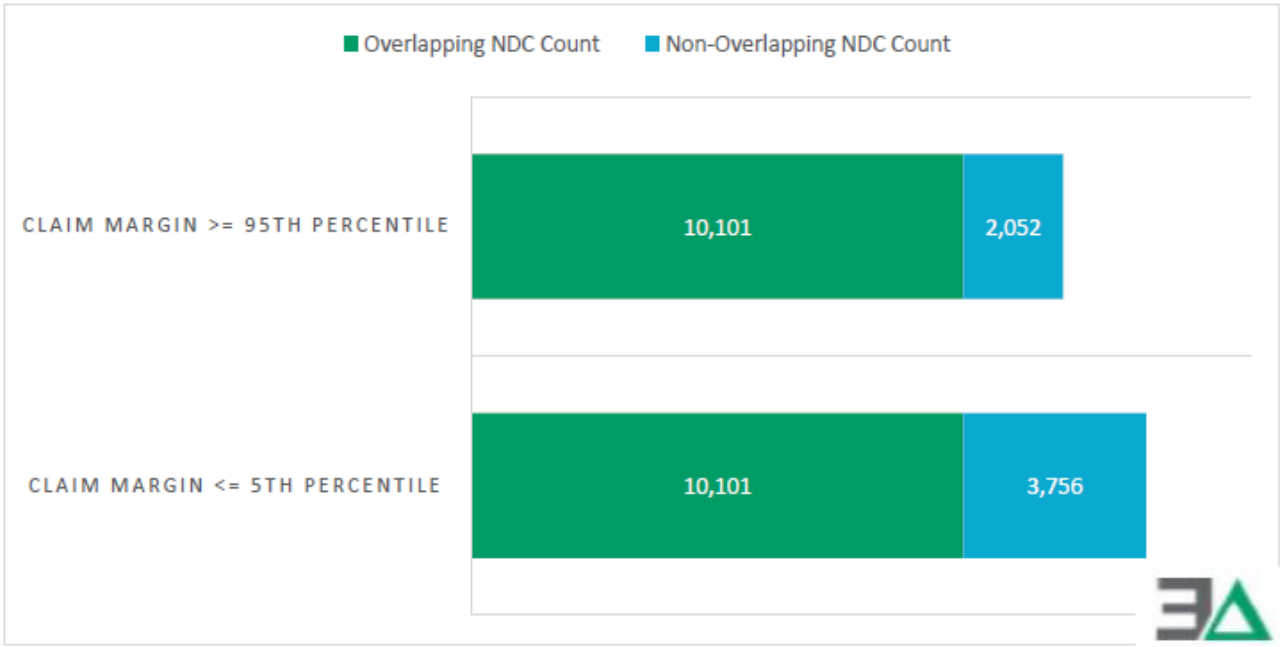
In our analysis, we find that the overwhelming majority of the prices paid at the pharmacy counter are based on price points established by the drug supply chain intermediaries known as pharmacy benefit managers (PBMs). For expensive brand medications, the data demonstrates that PBMs establish variable payment rates based upon differentiating the discounts offered to manufacturer price points (Chart 1 at left).

Source: https://www.3axisadvisors.com/projects/2023/9/19/unravelling-the-drug-pricing-blame-game

Drug Prices in the Pharmacy Disconnected from Manufacturer Price – Highly Variable

For generic medications, the most routinely utilized of all drug therapies, we observed that proprietary PBM prices (i.e., maximum allowable cost, or MAC) were used for setting the majority of all prescription costs and that like their brand counterparts, generic drug prices were highly variable and disconnected from the manufacturer or pharmacy established price for the medication. For example, we identified that within the claims where pharmacies lost and made the most money (i.e., margin), the same national drug codes (NDCs) were present in both extremes 44.6% of the time – meaning that the same drug could be responsible for both the highest profits and the biggest losses for pharmacies (Chart 3 at right).

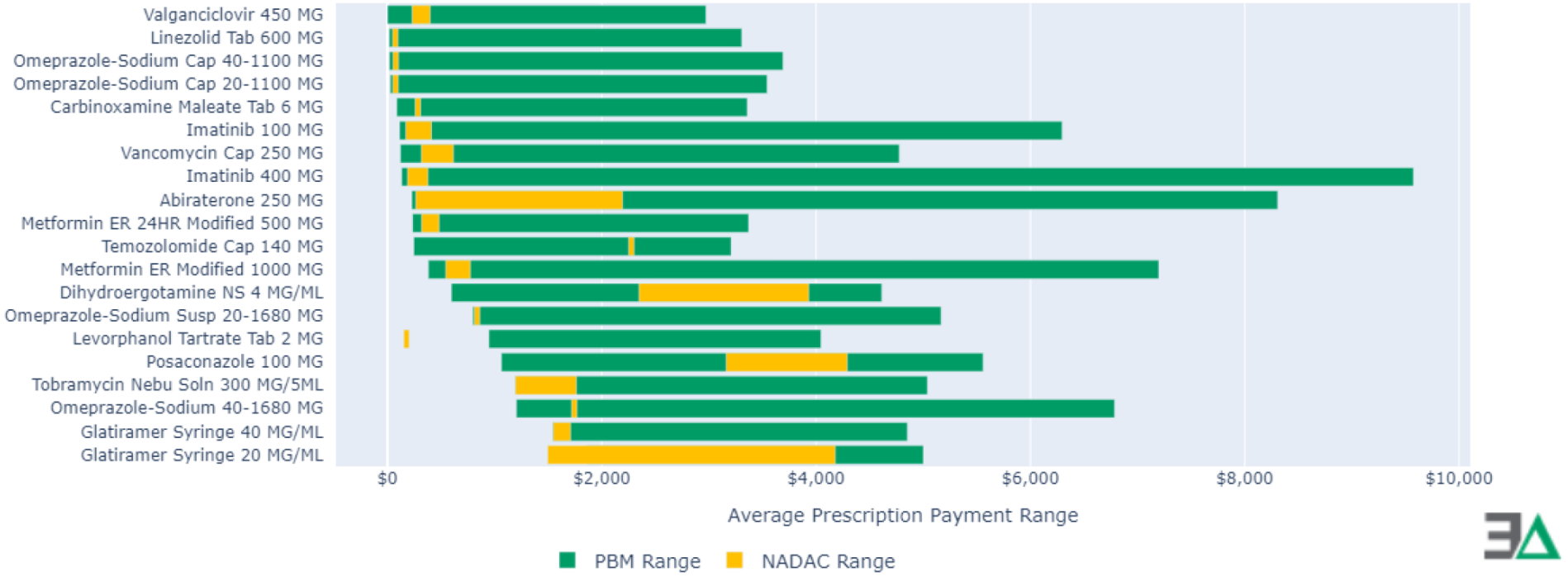
Chart 3: Count of Overlapping Unique NDCs Between Lowest and Highest Percentile of Claims by Margin Relative to National Average Drug Acquisition Cost (NADAC), (Studied Pharmacy Data, 2020)



Source: https://www.3axisadvisors.com/projects/2023/9/19/unravelling-the-drug-pricing-blame-game

PBM's Set Highly Disparate Prices for Common Generic Drugs

Figure 26: Generic Products with the Greatest PBM Payment Ranges (Min-Max Delta) within Studied Pharmacy Data (2020)



Source: https://www.3axisadvisors.com/projects/2023/9/19/unravelling-the-drug-pricing-blame-game

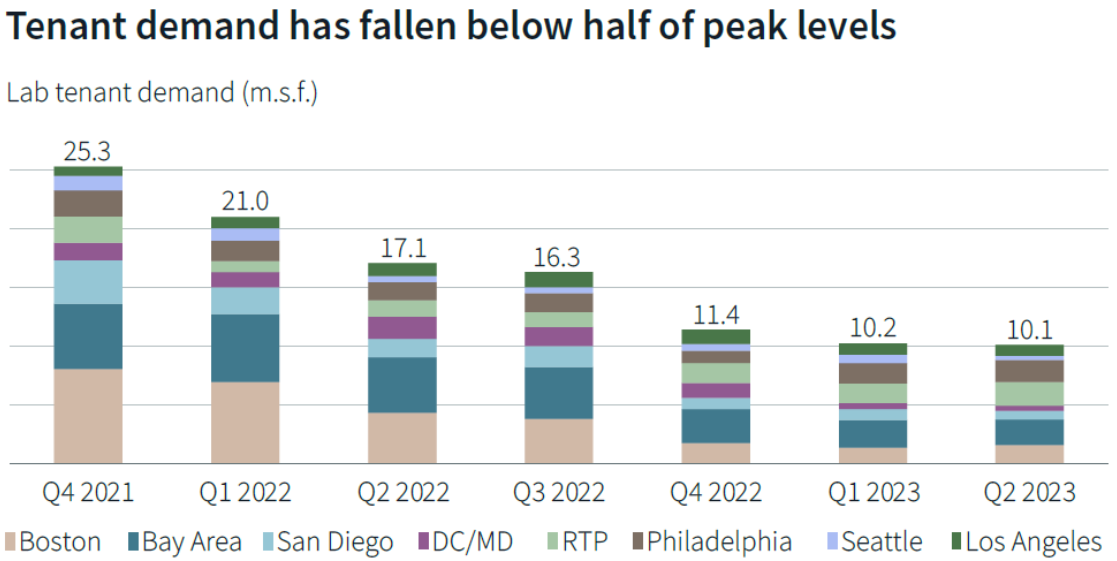
Lab Space Demand Down Over 50% since Q4 2021

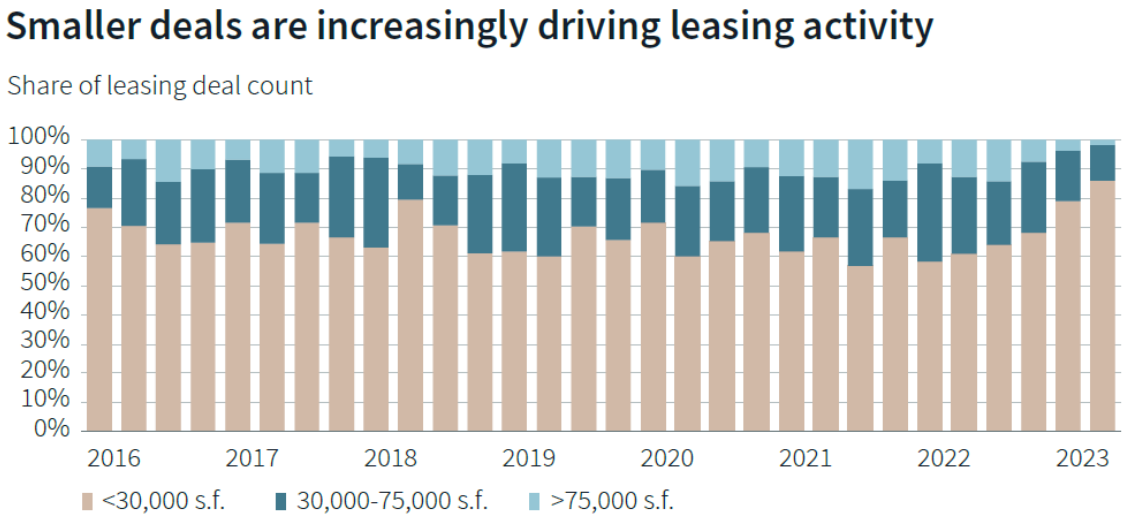
Research

2023 Life Sciences Industry and Real Estate Perspective

Assessing the future landscape for biopharma, medtech and biomanufacturing

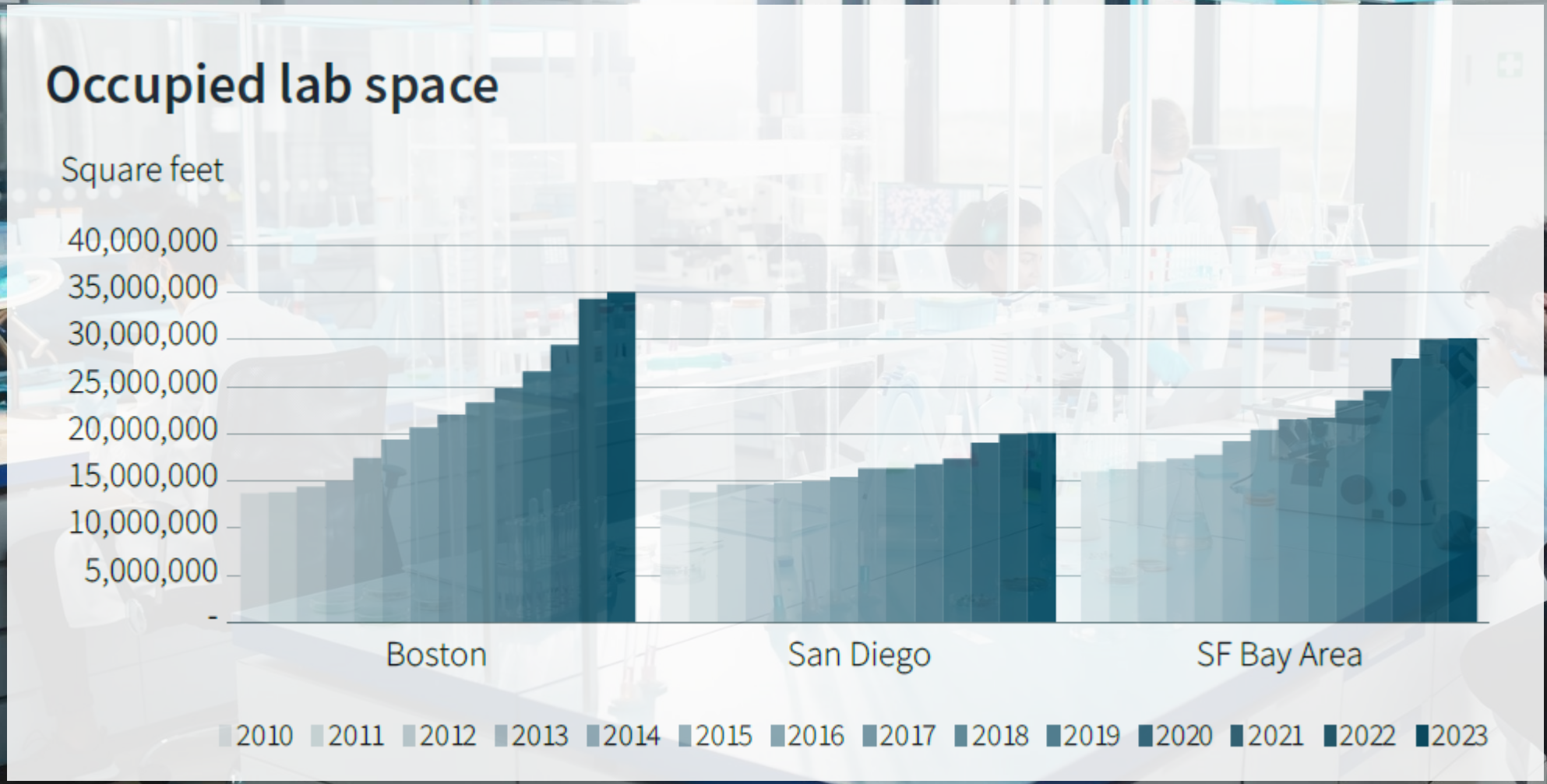
Sep 19, 2023





Source: https://www.us.jll.com/en/trends-and-insights/research/life-sciences-real-estate-outlook

JLL Report: 85 Million Square Feet of Lab Space in Top 3 U.S. Markets – All Time Record

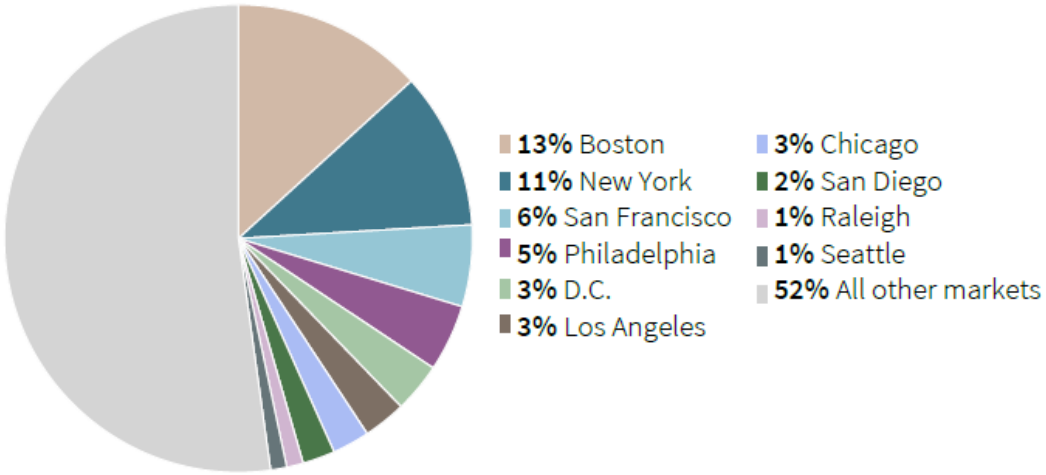


Source: https://www.us.jll.com/en/trends-and-insights/research/life-sciences-real-estate-outlook

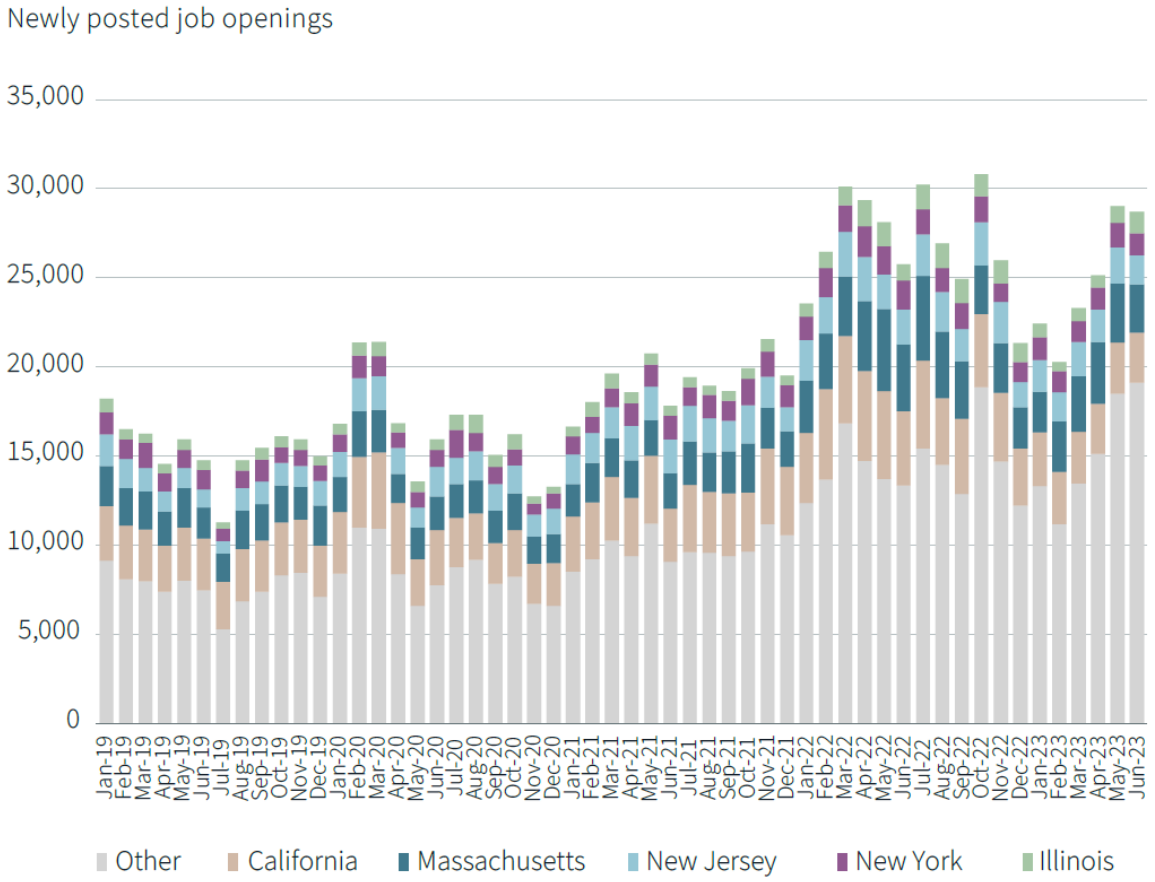
Job Market Showing Strength

JLL Sep 2023

H1 2023 job postings by metro



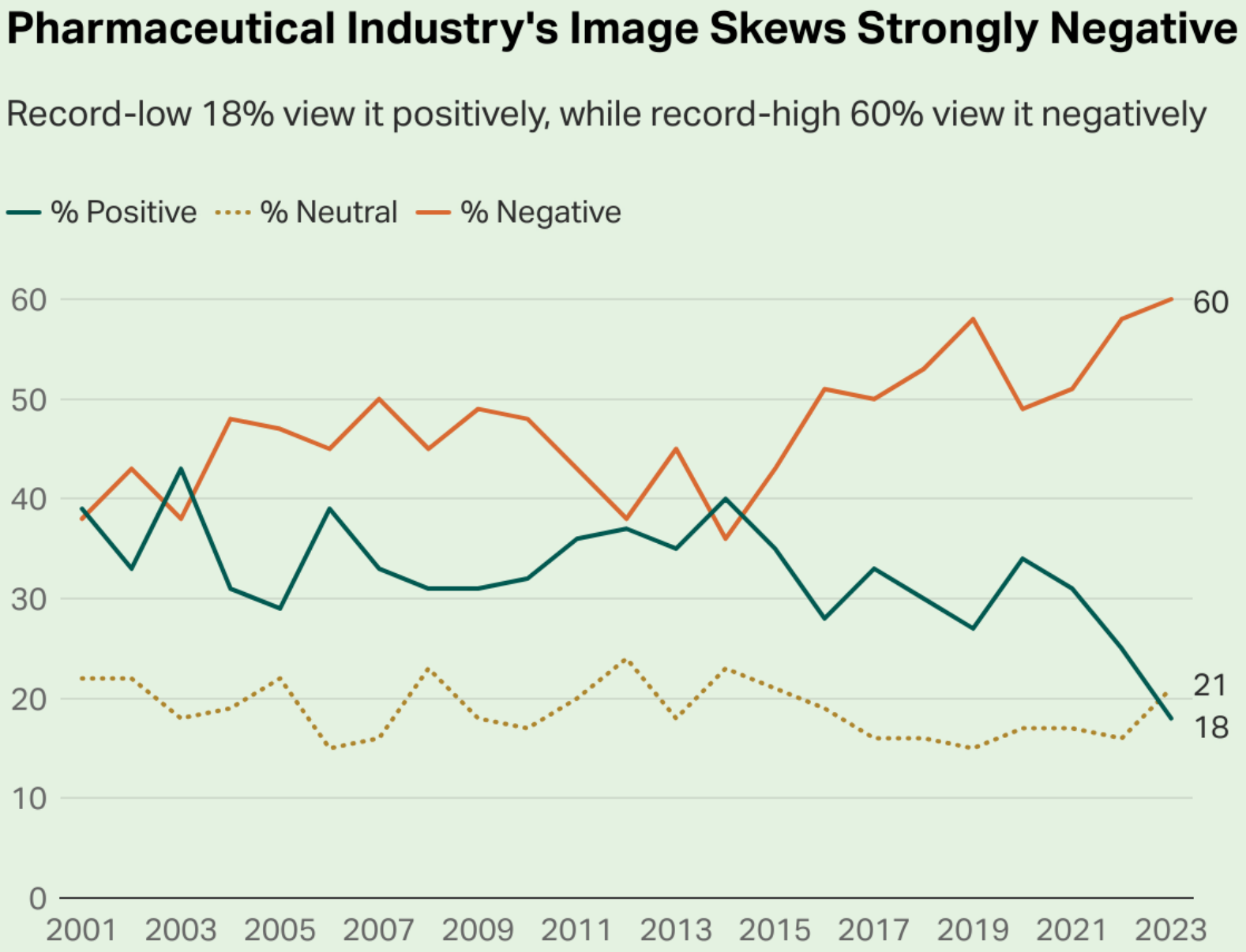
Biopharma job openings pick up substantially through Q2 2023



Source: https://www.us.jll.com/en/trends-and-insights/research/life-sciences-real-estate-outlook

Gallup Poll: Pharma Reputation Hits Record Low

The latest deterioration in the pharmaceutical industry's positive score accentuates its already-negative image. Currently, 18% of Americans have a positive view of it and 60% a negative view, with 21% feeling neutral.



Source: https://news.gallup.com/poll/510641/retail-pharmaceutical-industries-slip-public-esteem.aspx

Manufacturing Issues Hindering Carvykti® Sales

David Wainer, Wall Street Journal, Sep 21, 2023

Cell therapy is one particular area of great hope, with clinical data from Johnson & Johnson's Carvykti driving excitement in the medical field and on Wall Street. A late-stage study released earlier this year showed the treatment cut the risk of relapse by 74% compared with the standard of care—a level of efficacy seen as game-changing by experts, though with potentially serious side effects.

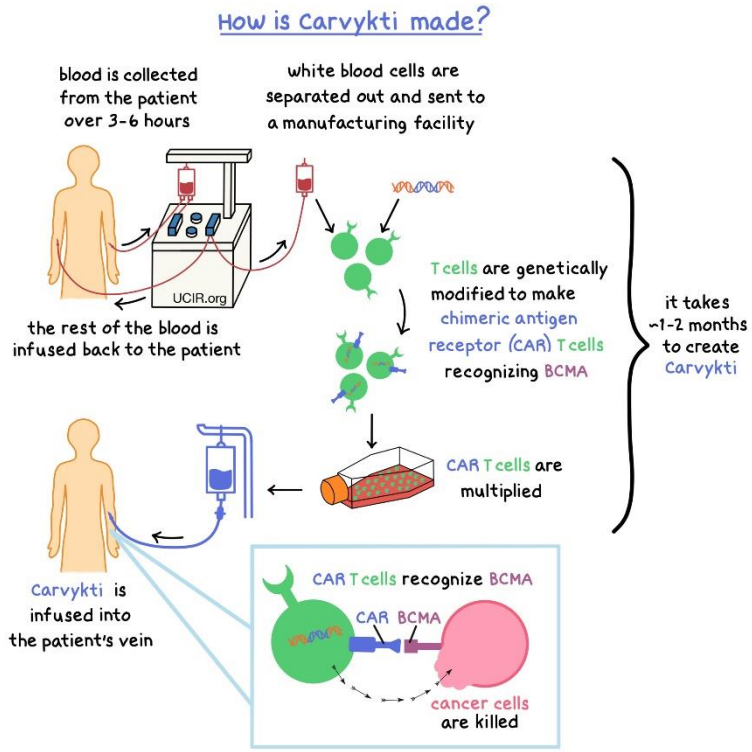
There is a major hitch, though: J&J and Legend Biotech can't keep up with demand, which means some patients die on wait lists. The companies have vowed to scale up manufacturing as quickly as possible, but it won't be easy. The issue isn't limited to J&J: A similar therapy from competitor Bristol-Myers Squibb Abecma, also faces manufacturing hurdles.

While J&J and Legend say they are doing everything they can to increase manufacturing, the process is basically bespoke, which means economies of scale don't apply.

"Intrinsically, it's very, very different from the typical manufacturing methodology for pharmaceuticals," explains Legend Chief Executive Officer Ying Huang.

While that is arguably already close to being priced into Legend's stock, encouraging signs that they can meet that goal and eventually expand beyond that would drive the shares higher. For J&J, while incremental moves on Carvykti might not be equally material, its expansion will go a long way in cementing the company's position as a leader in multiple myeloma while helping to replace revenue from blockbuster drugs going off patent.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion



Source: https://www.wsj.com/health/pharma/blockbuster-cancer-treatment-stymied-by-supply-chainfor-now-92723823

R&D Reshuffle at GSK

Gabrielle Masson, *Fierce Biotech*, September 18, 2023 (excerpt)

GSK's senior vice president and head of research John Lepore, M.D., has left the company at the same time the U.K. pharma undergoes a slight shuffling of its R&D operations.

Lepore leaves after nearly 15 years with GSK and more than five in his most recent position. His departure, as first reported by Endpoints, was confirmed by a GSK spokesperson, who said the pharma was welcoming new leader Kaivan Khavandi, Ph.D., who rejoins from BenevolentAI to head up GSK's newly reorganized respiratory and immunology sector.

In an apparent R&D revamp, GSK has divided its research into a trio of teams that are "more closely aligned" with its core therapeutic groups: respiratory and immunology, vaccines and infectious diseases, and oncology. Senior Vice President and Global Head of Vaccines Phil Dormitzer, M.D., Ph.D., will lead the vaccine and infectious disease unit while Senior Vice President and Global Head of Oncology Development Hesham Abdullah, M.D., will lead the oncology arm. GSK will continue work in HIV through its separate company ViiV.

Source: https://www.fiercebiotech.com/biotech/gsks-rd-head-john-lepore-out-door-amid-research-reorganization

Eight Principles from Dan Skovronsky's Playbook

Angelos Georgakis, Twitter, Sep 23, 2023 on Lilly Head of R&D, Dan Skovronsky

1. **Work on something really hard for a long time.** Dan Skovronsky was at home when he got a call from Lilly's statisticians informing him that their drug was effective. Donanemab could slow the progression of Alzheimer's by 35%. "Any words I use to describe my emotions at seeing the data will fall short. I've been pursuing the same enemy for 25 years. I was a kid when I started at this! Working on something hard for a long time and seeing it come to some meaningful fruition is hugely rewarding". "Work on really hard problems for a long time, slowly building up the scientific evidence until we can make meaningful drugs, and then, do bold trials and see the results."

2. **Be bold and critical.** "One reason he succeeded, he believes, is that he was willing to be critical because he already had success." That made him bold, he said, and led him to point out how slowly Lilly moved in developing new medicines.

3. **Marry the best of both worlds, biotech and pharma.** What's incredible about pharma is the resources, the people, the money—and the stability and continuity of that—which leads to institutional learning, investing in functional know-how, and the development of expertise. What's incredible about biotech is the conviction, a sink-or-swim around a conviction, an asset, a technology or an idea. The focus that comes with that conviction is hugely valuable. The inadequate resources force you to focus on the best opportunities.

4. **Allow team to see their impact.** What motivates people is not the rewards but their personal impact on the work. "When we think about biotech, people usually jump to the asymmetry and the outsized financial rewards for risk-taking, but I haven't found that to be the real problem. It's all about being able to see your personal impact on the work—and that's the valuable thing about biotech that you have to create in a big pharma company. People have to see how their work matters, how it impacts the project, how they're making a difference."

5. **Delegation becomes easy when you have the right people.** "Giving up power and delegating is not easy; we all struggle with it. That's why people are the most important ingredient. If you have great people whom you can trust, why would you be uncomfortable delegating to them?

6. **Persevere when everyone else gives up.** In 2016, Lilly's lead Alzheimer's drug, solanezumab, failed dramatically and caused a multi-billion-dollar plunge in Lilly's market value. "Dave Ricks wasn't yet our CEO at the time but he was running the business unit that controlled that asset. So Dave asked me to do a special project, which was to write up a rationale to show to our board of directors what we would do next if solanezumab failed. When I showed it to Dave, he said, "This is great, except you forgot the #1 reason why we're not giving up on Alzheimer's. And I was like, oh no, what is it? The #1 reason, Dave said, is the patients who are suffering. And if we don't do it, no one else will. He was right..."

7. **Learn from your mistakes and make smart decisions.** Picking up the pieces, Skovronsky and the team would target only what could be reliably measured in the brain going forward. Drugs would also have to hit their targets hard to advance to later stage development.

8. **Be transparent and thorough**—especially when the community is sceptical.

Sources: https://twitter.com/angelosgeo/status/1705551352187719899 and https://mem.ai/p/UEhKU8RiO6sVl0bMuoJK

Israeli Study Shows that AI-Generated Diagnoses in a Primary Care Setting Generally Get it Right

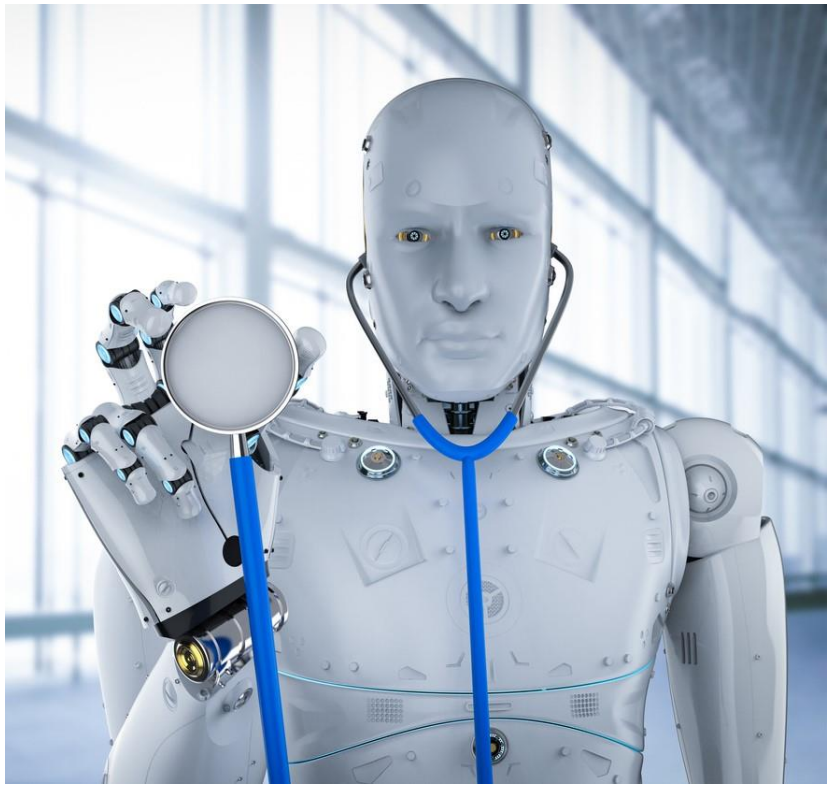
Zeltzer et.al., "Diagnostic Accuracy of Artificial Intelligence in Virtual Primary Care," *Mayo Clinic Proceedings: Digital Health*, Sep 20, 2023.

Objective: To evaluate the diagnostic accuracy of artificial intelligence (AI)-generated clinical diagnoses.

Patients and Methods: A retrospective chart review of 102,059 virtual primary care clinical encounters from October 1, 2022, to January 31, 2023 was conducted. Patients underwent an AI medical interview, after which virtual care providers reviewed the interview summary and AI-provided differential diagnoses, communicated with patients, and finalized diagnoses and treatment plans. Our accuracy measures were agreement between AI diagnoses, virtual care providers, and blind adjudicators. We analyzed AI diagnostic agreement across different diagnoses, presenting symptoms, patient demographic characteristics such as race, and provider levels of experience. We also evaluated model performance improvement with retraining.

Results: Providers selected an AI diagnosis in 84.2% (n = 85,976) of cases and the top-ranked AI diagnosis in 60.9% (n = 62,130) of cases. Agreement rates varied by diagnosis, with greater than or equal to 95% provider agreement with an AI diagnosis for 35 diagnoses (47% of cases, n = 47,679) and greater than or equal to 90% agreement for 57 diagnoses (69% of cases, n = 70,697). The average agreement rate for half of all presenting symptoms was greater than or equal to 90%. Adjusting for case mix, diagnostic accuracy exhibited minimal variation across demographic characteristics. The adjudicators' consensus diagnosis, reached in 58.2% (n = 128) of adjudicated cases was always included in the AI differential diagnosis. Provider experience did not affect agreement, and model retraining increased diagnostic accuracy for retrained conditions from 96.6% to 98.0%.

Conclusion: Our findings show that agreement between AI and provider diagnoses is high in most cases in the setting of this study. The results highlight the potential for AI to enhance primary care disease diagnosis and patient triage, with the capacity to improve over time.



Source: https://www.mcpdigitalhealth.org/article/S2949-7612(23)00070-6/fulltext

Insight: Big Pharma bets on AI to speed up clinical trials

Natalie Grover and Martin Coulter, Reuters, Sep 22, 2023

LONDON, Sept 22 (Reuters) - Major drugmakers are using artificial intelligence to find patients for clinical trials quickly, or to reduce the number of people needed to test medicines, both accelerating drug development and potentially saving millions of dollars.

Human studies are the most expensive and time-consuming part of drug development as it can take years to recruit patients and trial new medicines in a process that can cost over a billion dollars from the discovery of a drug to the finishing line.

Reuters interviews with more than a dozen pharmaceutical company executives, drug regulators, public health experts and AI firms show, however, that the technology is playing a sizeable and growing role in human drug trials.

Companies such as Amgen (AMGN.O), Bayer (BAYGn.DE) and Novartis (NOVN.S) are training AI to scan billions of public health records, prescription data, medical insurance claims and their internal data to find trial patients - in some cases halving the time it takes to sign them up.

"I don't think it's pervasive yet," said Jeffrey Morgan, managing director at Deloitte, which advises the life sciences industry. "But I think we're past the experimentation stage."

German drugmaker Bayer said it used AI to cut the number of participants needed by several thousand for a late-stage trial for asundexian, an experimental drug designed to reduce the long-term risk of strokes in adults.

It used AI to link the mid-stage trial results to real-world data from millions of patients in Finland and the United States to predict the long-term risks in a population similar to the trial.

Source: https://www.reuters.com/technology/big-pharma-bets-ai-speed-up-clinical-trials-2023-09-22/

AZ/Daiichi Trop2 Breast Cancer Data

"Datopotamab deruxtecan demonstrated statistically significant and clinically meaningful progression-free survival benefit in patients with HR-positive, HER2-low or negative breast cancer in TROPION-Breast01 Phase III trial," AZ Press Release, Sep 22, 2023

Positive high-level results from the TROPION-Breast01 Phase III trial showed datopotamab deruxtecan (Dato-DXd) demonstrated a statistically significant and clinically meaningful improvement for the primary endpoint of progression-free survival (PFS) compared to investigator's choice of chemotherapy in patients with inoperable or metastatic hormone receptor (HR)-positive, HER2-low or negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer previously treated with endocrine-based therapy and at least one systemic therapy.

A trend in improvement for the dual primary endpoint of overall survival (OS) was observed for datopotamab deruxtecan versus chemotherapy. Data for OS were not mature at this interim analysis and the trial will continue as planned to assess OS.

Datopotamab deruxtecan is a specifically engineered TROP2-directed DXd antibody drug conjugate (ADC) being jointly developed by AstraZeneca and Daiichi Sankyo.

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "Today's TROPION-Breast01 news is a significant development for patients with HR-positive, HER2-low or negative metastatic breast cancer whose tumours have become insensitive to endocrine therapy and who currently face poor outcomes. We are encouraged by these positive results."

More than two million people worldwide are diagnosed with breast cancer each year. HR-positive, HER2-low or negative breast cancer is the most common subtype, accounting for more than 65% of diagnosed cases. Standard initial treatment for these patients is endocrine therapy but most patients with advanced disease will develop resistance, underscoring the need for additional options. TROP2 is a protein broadly expressed in HR-positive, HER2-low or negative breast cancer.

A few weeks ago, we saw AZ/Daiichi's TROP2 data in lung cancer.

This week, AZ is signaling that they are hitting in breast cancer as well.

There appears to be some benefit in OS.

This is obviously relevant to the competition with Gilead's Trodelvy®. It's early days in the development of datasets here.

It's exciting to see patients get another option for TROP2 driven cancer.

Source: https://www.astrazeneca.com/media-centre/press-releases/2023/dato-dxd-improved-pfs-in-breast-cancer.html

Agenus Reports Positive Colorectal Cancer Data in Neo-Adjuvant Setting

Alex Knapp, *Forbes*, Sep 20, 2021

Pathologist Erika Hissong (L) and Oncologist Pashtoon Kasi (R) were two of the scientists involved in a new study demonstrating efficacy of a new immunotherapy against colorectal cancer. WEILL-CORNELL MEDICINE

A combination immunotherapy developed by biotech company Agenus administered before surgery destroyed over 80% of a tumor before it was removed.

"...a new report published in the journal *Oncogene* Thursday found that in a small-scale study, patients treated with an experimental immunotherapy prior to having their tumors surgically removed saw about 80% to 90% of the cancer cells killed in a manner that suggests it's less likely that the cancer will return.

"Within weeks, it was like it had shriveled down to nothing," Pashtoon Kasi, director of colon cancer research at Weill Cornell Medicine and lead author of the study, told Forbes.

In the study, 12 patients with advanced colon and rectal cancers that hadn't yet spread to other parts of the body were treated with a combination of two immunotherapies discovered and being developed by Massachusetts-based biotech company Agenus: botensilimab and balstilimab. These drugs target different ways in which tumors "hide" from the immune system, enabling the body to attack these tumors. The treatment took place a few weeks prior to a surgical removal of their cancers. Because these types of treatments create an inflammatory response, which can increase the risk of infection from the surgery, only half of a typical dose was given, Kasi said."

Source: https://www.forbes.com/sites/alexknapp/2023/09/20/new--drug-combo-shows-promising-results-against-earlier-stages-of-colorectal-cancer/?sh=2c986682175f

Review Article in JACC Last Week Highlights Benefit of Colchicine in Reducing Cardiac Events in Patients with Inflammation

Nelson K, Fuster V, Ridker PM. Low-Dose Colchicine for Secondary Prevention of Coronary Artery Disease: JACC Review Topic of the Week. J Am Coll Cardiol. 2023 Aug 15;82(7):648-660.

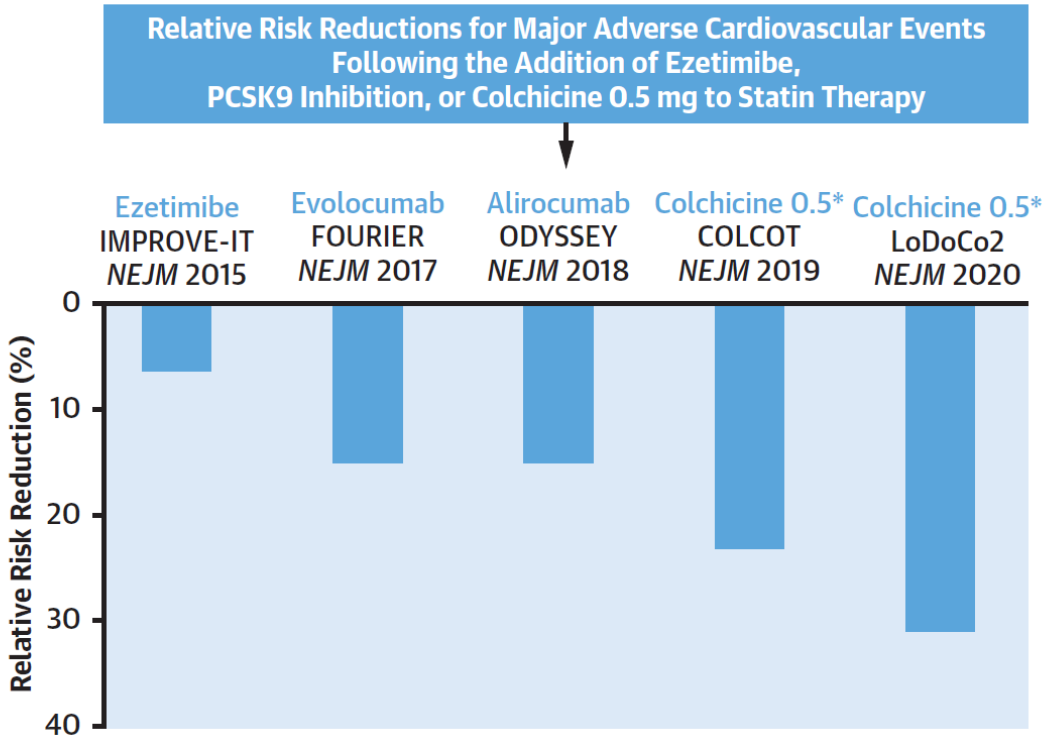
Low-Dose Colchicine for Secondary Prevention of Coronary Artery Disease

JACC Review Topic of the Week

Kyle Nelson, MD,[a] Valentin Fuster, MD,[a,b] Paul M Ridker, MD, MPH[c]

ABSTRACT

Among statin-treated patients, inflammation assessed by means of high-sensitivity C-reactive protein (hsCRP) is a more powerful determinant of cardiovascular death and all-cause mortality than low-density-lipoprotein cholesterol (LDL-C). Several therapies that target residual inflammatory risk significantly reduce vascular event rates. For coronary artery disease patients already taking guideline-directed medical care, including statins, low-dose colchicine (0.5 mg/d orally) has been shown to safely lower major adverse cardiovascular events by 31% among those with stable atherosclerosis and by 23% after recent myocardial infarction. These magnitudes of benefit are larger than those seen in contemporary secondary prevention trials of adjunctive lipid-lowering agents. Low-dose colchicine is contraindicated in patients with significant renal or liver dysfunction and should be temporarily discontinued when taking concomitant agents such as clarithromycin, ketoconazole, and cyclosporine that share metabolism pathways. Lipid lowering and inflammation inhibition are not in conflict but are synergistic. In the future, combined use of aggressive LDL-C–lowering and inflammation-inhibiting therapies may become standard of care for most atherosclerosis patients. In June 2023, the U.S. Food and Drug Administration approved the use of low-dose colchicine to reduce the risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease. (J Am Coll Cardiol 2023;82:648–660)



Source: https://pubmed.ncbi.nlm.nih.gov/37558377/

WSJ Article on Sep 23rd Highlights Colchicine Data and Talks About Why U.S. Hasn't Adopted it in Heart Disease Prevention

Ron Winslow, *Wall Street Journal*, September 23, 2023 (excerpt)

The drug colchicine has been used for more than 2,000 years to treat the fiery joint-pain ailment called gout. It also is a remedy for a genetic disorder called familial Mediterranean fever, and for pericarditis, an inflammation of the sac around the heart.

Now colchicine may be set for a surprising new role. In June, the Food and Drug Administration approved a new low-dose version of the drug as the first-ever medicine to treat cardiovascular inflammation, marking a new approach for heart-attack prevention.

Several things could limit the adoption of colchicine by cardiologists, at least at first, including side-effect concerns and the emergence of several other new options for reducing the risk of heart attacks. But the drug's approval provides fresh validation for a concept that has been gaining momentum in cardiology over the past 25 years—that inflammation is a key culprit in atherosclerosis, the artery-clogging disease, and that treating it can reduce the risk of a heart attack.

The bedrock strategy for heart-attack prevention has long been lowering LDL cholesterol with drugs called statins. Adding low-dose colchicine—which in one study reduced cardiovascular risk by 31% in patients already treated with statins and other preventive medicines—would enable doctors to simultaneously hit two biological targets that cause heart attacks.

"This is about combining therapies" that are both effective ways to reduce risk, says Dr. Paul Ridker, director of the Center for Cardiovascular Disease Prevention at Harvard-affiliated Brigham and Women's Hospital, Boston. "They're not in conflict, they're synergistic."

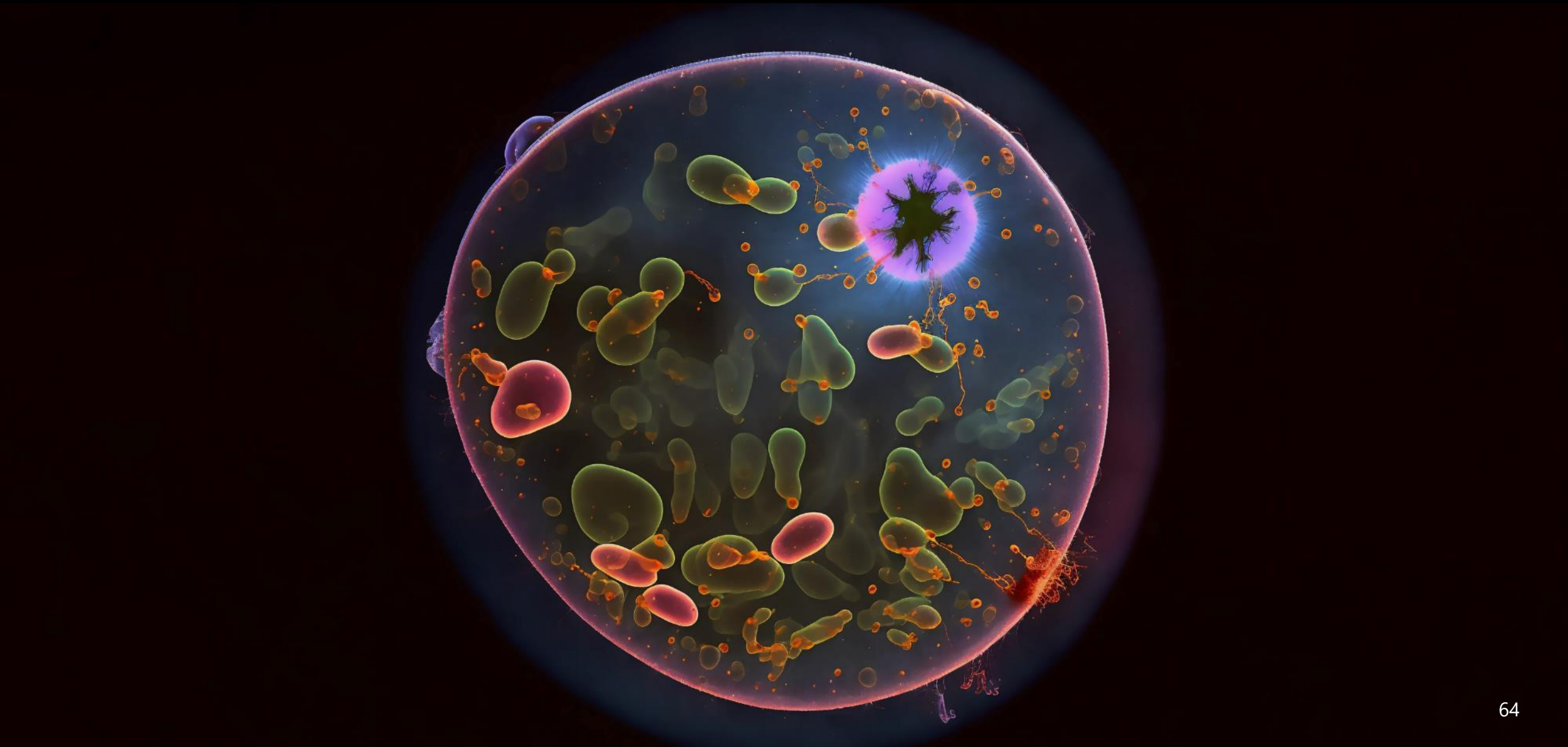
Ridker is a scientific adviser to Agepha Pharma, the company that owns the rights to market 0.5-milligram colchicine for cardiovascular-risk reduction, but wasn't involved in the studies that led to the drug's approval.

Another hurdle: lack of pharmaceutical companies marketing muscle to get the word out to clinicians and patients. The FDA gave approval for the drug to Agepha Pharma, a tiny family-owned company based in Dubai that has neither a sales force nor a presence in the U.S. market. It hasn't been able to find a partner to co-promote the drug, which it calls Lodoco.

The potential market for an anti-inflammatory agent to reduce heart risk is huge. Data from clinical trials indicate that about half of patients with atherosclerosis have elevated levels of an inflammatory marker called C-reactive protein, or CRP, despite being on intensive statin therapy. Such patients are significantly more likely to suffer a heart attack or other cardiovascular event than those with low CRP and low LDL.

Source: https://www.wsj.com/health/wellness/heart-attack-health-inflammation-drug-353dabf5

Pharma Target Identification Approaches and ‘OMICs Technology



Big Pharma R&D Business Models

Last week we spoke at some length about pharma strategy and overall business models.

A key point was that some companies appear to be doing a better job than others in finding the right target to hit for a disease and resourcing an attack on such target.

Obviously, that's the beginning of a strategy. Not the end of it.

A critical factor in R&D resource allocation goes beyond the selection of what disease to work on.

Perhaps the single most basic element of R&D strategy is what targets to work on.

It's fair to say that there are three basic approaches that pharma companies take: (1) find novel targets and develop drugs against those targets, (2) develop drugs against targets that are already known to be relevant for a disease state or (3) develop drugs without knowing the specific target (but knowing for other reasons that a drug will work).

The scale and pace of work in industry and academia on novel target identification has accelerated massively in the last decade.

Initially, the main driver was emerging understanding of the genetics of disease and efforts to exploit such understanding with novel drug constructs.

More recently, a key driver has been emerging insights from the fields of transcriptomics, proteomics, epigenomics and metabolomics and disease.

For simplicity, scientists refer to these emerging disciplines (combined with genomics) as 'OMICs.

In this section, we are going to dig into how pharma is leveraging the exploding area of 'OMICs to more rapidly develop drugs at a time when some commentators are complaining that R&D productivity is falling.

It appears to us that we are in early days of leveraging 'OMICs insights in drug development – and related areas like diagnostics.

Our hope is that more biotechs and pharmas will exploit these emerging technologies, along with growing capabilities in machine learning, to deliver more and better solutions to patients in the years ahead.

Target ID: Harder Than You Might Think

Written by:

Steve Rees

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AstraZeneca

2021

"Target identification lies at the heart of modern drug discovery. On paper, the process sounds simple - find a biological target that plays a role in disease, then find a therapeutic that interacts with it - yet this belies the complexity of the task.

The challenge of discovering and validating targets is reflected in the failure rate of drug candidates in the clinic, where promising treatments fail to show efficacy even in relatively late stage trials. The reason for this failure is usually that the underlying hypothesis - that this drug activates or inhibits a target and modulates the disease in a particular way in a particular patient population - turns out to be wrong.

While our success rate of pipeline molecules advancing from pre-clinical investigation to completion of Phase III clinical trials is higher than industry averages, we endeavour to do better. For this reason, over the past few years we have invested in multiple technologies to help improve target discovery.

In the past, most of our drug targets have been found by combing the published scientific literature for insights into molecular pathways or genetic variants linked to disease. We're now aiming to get ahead of the curve by focusing on the identification of original novel targets through our recent investments in genomics, functional genomics, and machine learning and artificial intelligence (ML/AI).

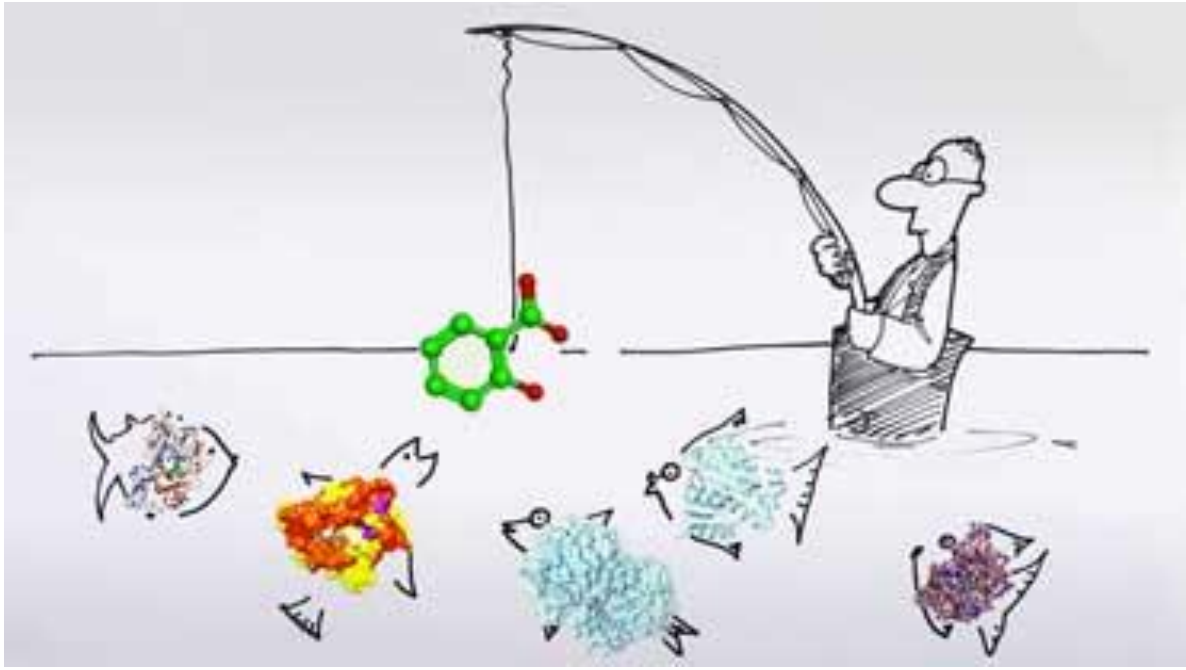
The journey to discovering better targets starts with building a deep understanding of biology. Increasingly, this comes from genomic insights, whether from patients and public biobanks or from tissue and tumour samples, aiming to identify genetic alterations underpinning disease.

Through our Centre for Genomics Research, we're aiming to analyse 2 million genomes by 2026, drawn from diverse populations and covering a wide range of diseases and clinical trials."

Source: https://www.astrazeneca.com/what-science-can-do/topics/disease-understanding/Hitting-the-bullseye-finding-better-targets-for-drug-development.html

Target ID: Roche Uses Many Different Approaches

Identifying the biological origin of a disease, and the potential targets for intervention, is the first step in the discovery of a medicine. More an art than a science, target identification is grounded in a number of different approaches and technologies, many of which are used in Roche research and early development.



Source: https://www.roche.com/stories/target-identification-in-drug-discovery

A Variety of Approaches Used in Target Identification

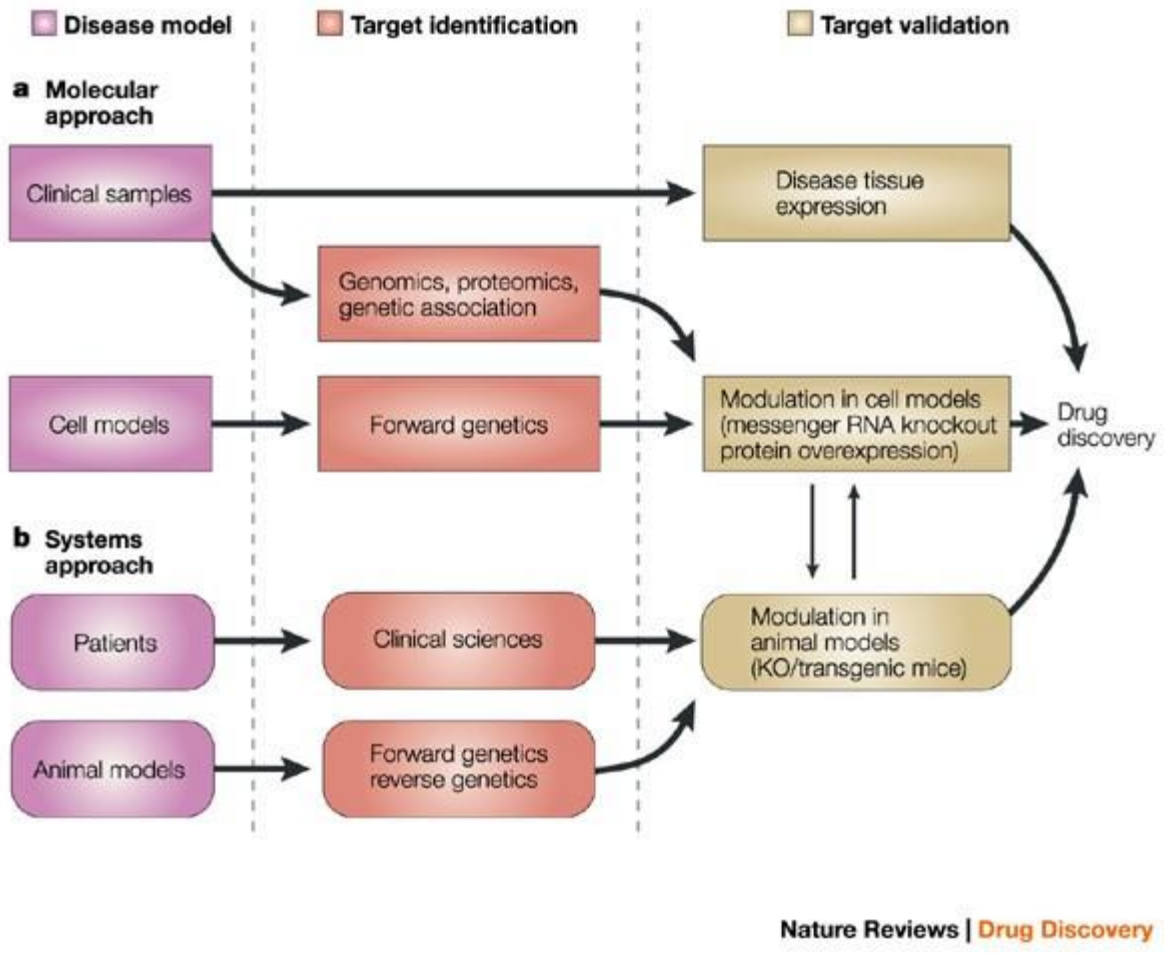
Rasul et.al., Target Identification Approaches in Drug Discovery, 2022

"Target identification is the most critical step in chemical genetics and drug discovery. A variety of novel bioactive chemical compounds have been discovered by phenotypic-based screening methods. However, identifying molecular targets for these bioactive compounds is a very laborious process. With the development and advancements in new methodologies and techniques for identification and biological analysis, various target identification methods have been established such as affinity-based methods, genetic-based techniques, computational approaches, and chemical proteomics. In this chapter, we will classify the target identification approaches, various molecular target identification methods, their work schemes, and the applications of target identification techniques in discovery of targets of small molecules, while keeping in view that each and every method is associated with some advantages as well as disadvantages. The efficient execution of every scientific process involves significant infrastructure set up and expertise in multiple disciplines (chemistry, proteomics, genomics, and bioinformatics). The collaborative work scheme comprising integrated knowledge of all of these disciplines will ensure the maximum potential is utilized in academic and industrial grounds."

Source: https://link.springer.com/chapter/10.1007/978-3-030-95895-4_3

Both Molecular Approach or a Systems Approach Can Work for Target Identification

"Target discovery, which involves the identification and early validation of disease-modifying targets, is an essential first step in the drug discovery pipeline. Indeed, the drive to determine protein function has been stimulated, both in industry and academia, by the completion of the human genome project. In this article, we critically examine the strategies and methodologies used for both the identification and validation of disease-relevant proteins. In particular, we will examine the likely impact of recent technological advances, including genomics, proteomics, small interfering RNA and mouse knockout models, and conclude by speculating on future trends."

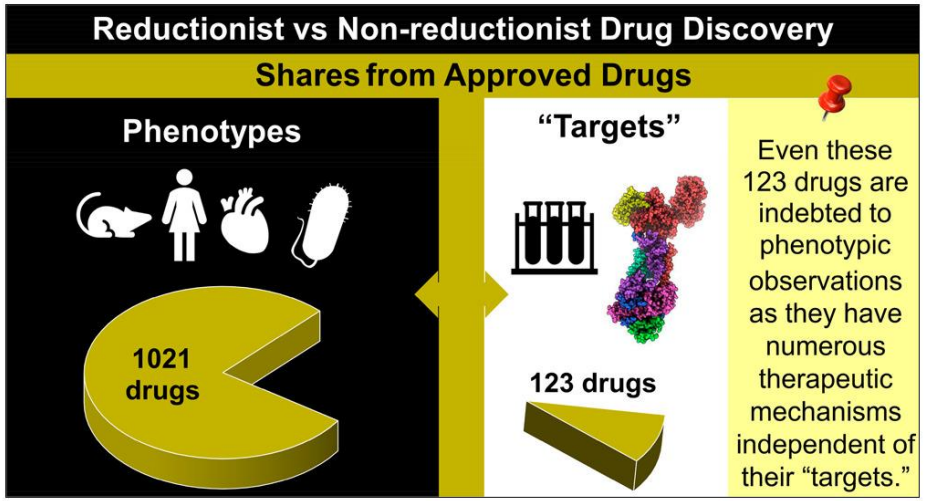


Source: https://www.nature.com/articles/nrd1202

Recent Paper Argues that Target Discovery is a Waste of Time

Sadri A. Is Target-Based Drug Discovery Efficient? Discovery and "Off-Target" Mechanisms of All Drugs. J Med Chem. 2023 Sep 6.

Target-based drug discovery is the dominant paradigm of drug discovery; however, a comprehensive evaluation of its real-world efficiency is lacking. Here, a manual systematic review of about 32000 articles and patents dating back to 150 years ago demonstrates its apparent inefficiency. Analyzing the origins of all approved drugs reveals that, despite several decades of dominance, only 9.4% of small-molecule drugs have been discovered through "target-based" assays. Moreover, the therapeutic effects of even this minimal share cannot be solely attributed and reduced to their purported targets, as they depend on numerous off-target mechanisms unconsciously incorporated by phenotypic observations. The data suggest that reductionist target-based drug discovery may be a cause of the productivity crisis in drug discovery. An evidence-based approach to enhance efficiency seems to be prioritizing, in selecting and optimizing molecules, higher-level phenotypic observations that are closer to the sought-after therapeutic effects using tools like artificial intelligence and machine learning.



Source: https://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.2c01737

Derek Lowe of Science Discusses Sadri Paper

Derek Lowe, "Target Based Drug Discovery - A Waste of Time?," *Science*, Sep 21, 2023

This new paper is going to annoy a lot of people, but I think that's fine. Its author, Arash Sadri, has undertaken an extensive review of the origins of all approved small-molecule drugs (1144 of them). His claim is that only 123 of them were discovered by purely target-based assay methods, and that the rest have to be described as discovered through phenotypic means. He notes that the share of target-based drugs in new approvals has grown over the years, but that there has never been a year when they surpassed the phenotypic ones.

That's largely due to his definitions, but they aren't bad ones. For the origins of a given discovery, he is citing "the first observation that has related a therapeutic class to the therapeutic effect". Everything subsequent in that particular therapeutic class is then assigned according to that original observation - the first-in-class drug is the standard bearer. Whenever possible, he has relied on the original accounts of people who worked on each particular project. And when you go back in that sort of detail, you find that yes indeed, it looks like an awful lot of drugs have been discovered by means that do not match up with the ways that we'd like to imagine that we use. Indeed, he says that the apparent recent increases in productivity have been more due to "the adaptation of the pharmaceutical industry to its failures rather than addressing their fundamental causes". The popularity of rare-drug monogenic disease drugs falls into this category, for example.

And even for the drugs whose discoveries were unambiguously target-based, in many cases their eventual clinical utility seems to have been enhanced by unanticipated effects that were observed phenotypically in humans. As Sadri has it, there is a survivorship bias at work, since so many drugs fail their Phase II trials. The ones that get through are not simply the ones that had the most selectivity and the most potency for their stated targets. Many, many drugs are doing something else along with (or other than) their ostensible mechanisms. Potency and selectivity for the stated target are simply not sufficient (by themselves) to make a drug, as anyone with any experience knows, but if we really believed in the "strong form" of the target-based drug discovery paradigm, wouldn't they be (outside of tox failures, of course).

Source: https://www.science.org/content/blog-post/target-based-drug-discovery-waste-time

Should we put our scientific instruments in the trash?

Our Counterpoints to Sadri Paper

In a way, the Sadri paper makes the case for the modern approach to target discovery – which focuses on genetic causes of disease and associations between genetic polymorphisms and metabolite and protein levels. This is because the history of drug discovery, which he reviews competently, was carried out without these tools.

1 Doesn't Look at the Modern Era

Almost all drugs looked at in his paper were discovered without the benefit of 'OMICs technologies and prior tools to improve target discovery (e.g., affinity tools).

2 With 15+ Year Timeline, We Won't Start to See Effect of 'OMICS Revolution for a While

Unfortunately, the time from discovering a target to getting a drug relevant to that target to patients is long.

For example, the role of PCSK9 in cardiovascular disease was discovered from a GWAS study in 2003. The first PCSK9 inhibitor, Praluent®, was not approved until 2015. This was record time to go from a target ID to a drug approval – thanks to incredibly hard work at Regeneron and Sanofi.

3 Emerging Data Support Modern Era Approach

One way of seeing if new approaches to target identification are paying off is to see what the odds are of approval using 'OMICs approaches.

A 2019 paper by King et.al., from AbbVie did the work and found that drugs developed based on genetic discoveries were more than twice as likely to be approved by the FDA as other drugs.*

Source: https://pubmed.ncbi.nlm.nih.gov/31830040/

Biology and Medicine are Largely About Function and Phenotype

Phenotype: the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment.

Biology: frequently studies the relationship between function and phenotype. Why is the tall guy tall? Why is the short guy short?

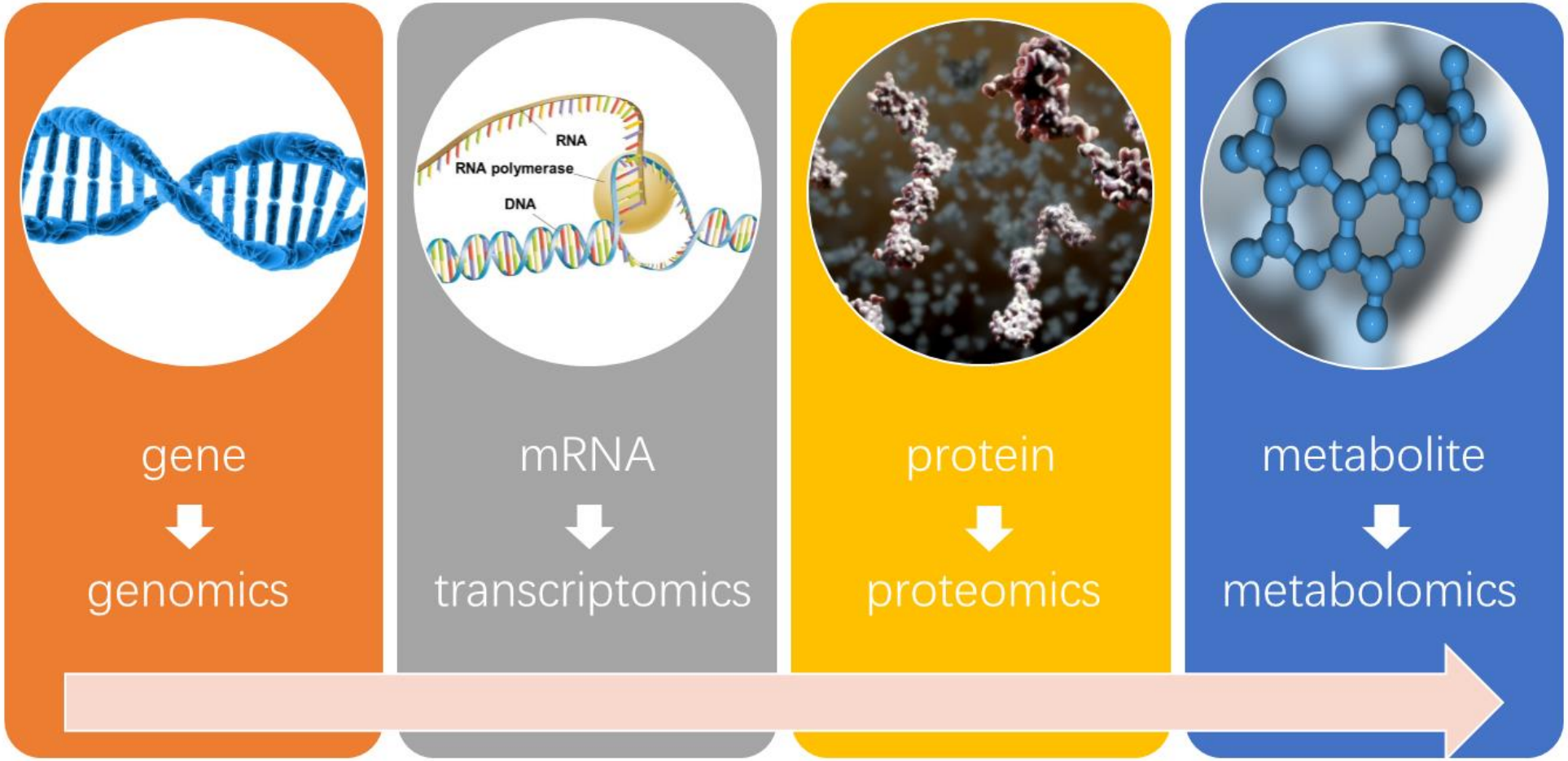
Medicine: the study of phenotypes that are not normal in some meaningful way.

Omics: underlying accessible data that might allow us to figure out which genes or environmental factors cause these differences..

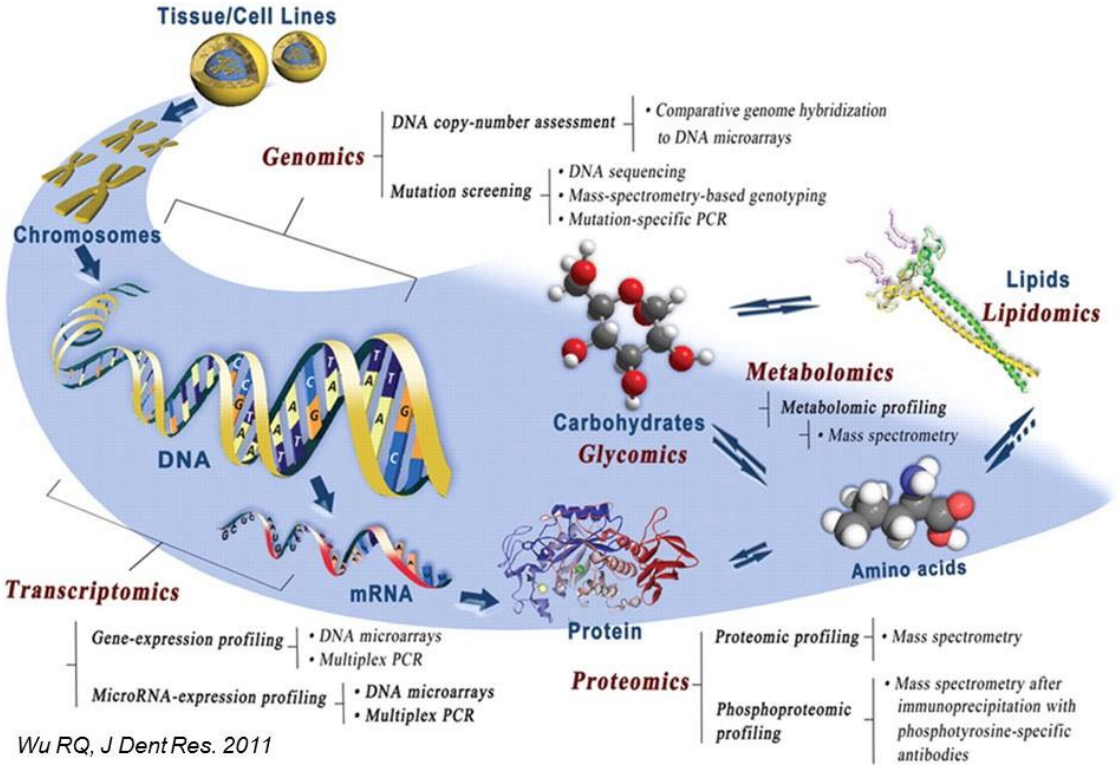
World's shortest man and tallest man

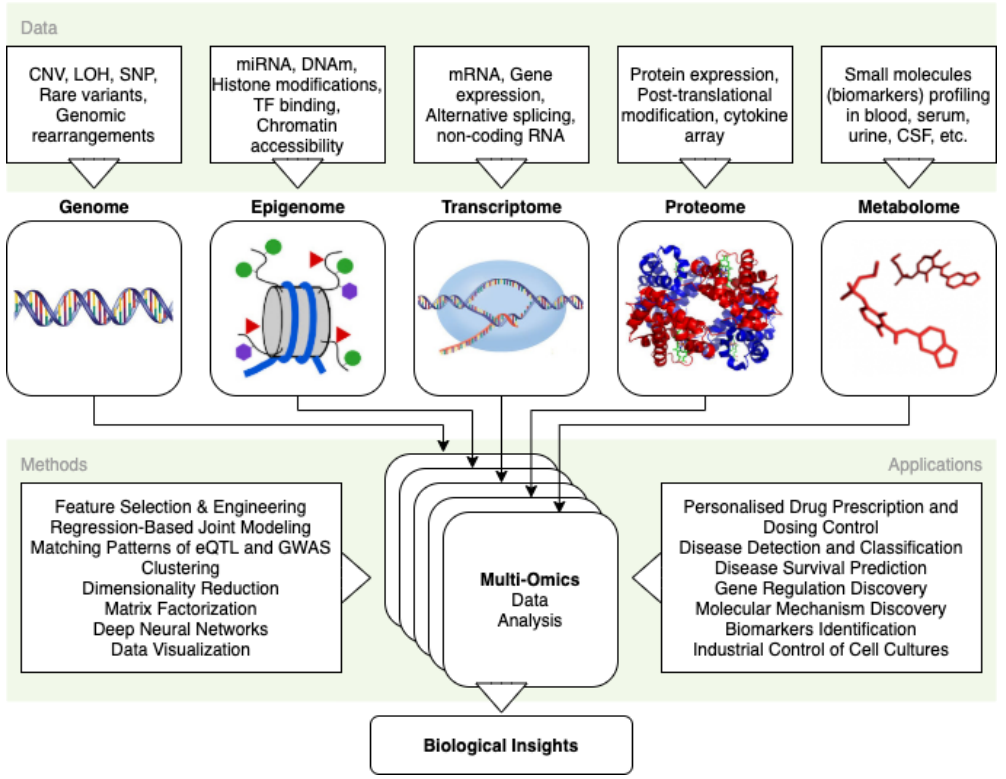
Source: Stifel analysis and Reudi Abersold, Institute of Molecular Systems Biology, ETH-Zurich.

‘OMICS Refers to the Multidisciplinary Study of Human Physiology Via Genes, RNA and their Products (Metabolites and Proteins)



‘OMICS Technologies Are One of the Main Methods Used to Obtain Biological Insights Today

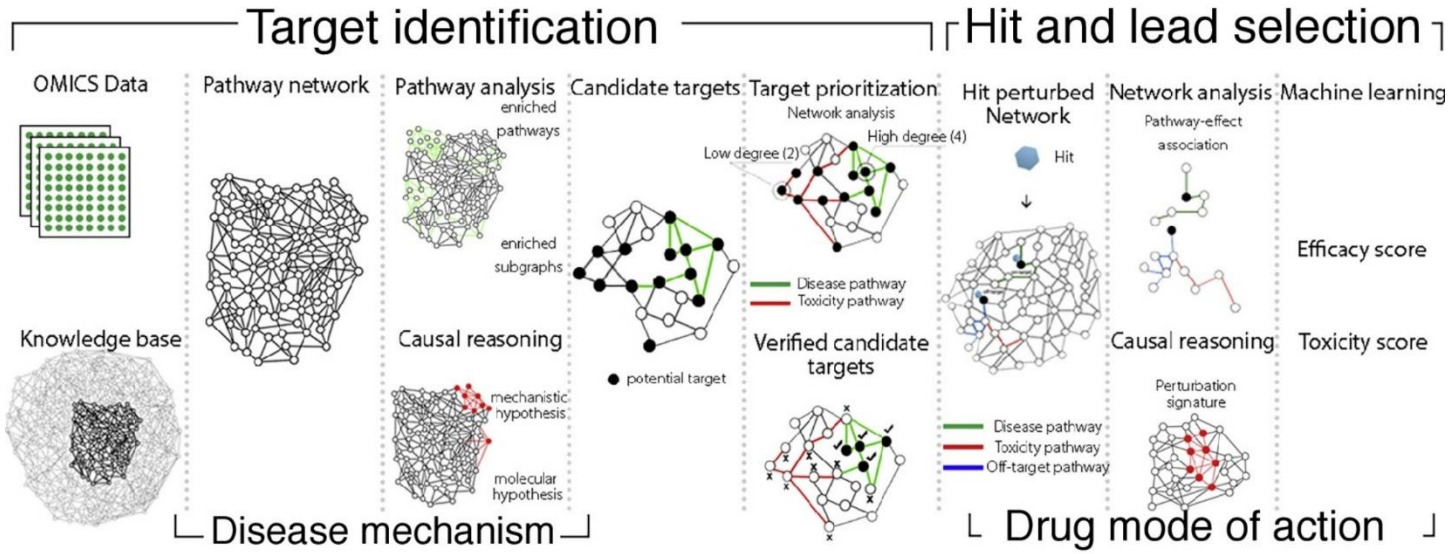




‘OMICS Data Needs to be Combined with Biological Analysis and Pathway Analysis to Get to Drug Targets

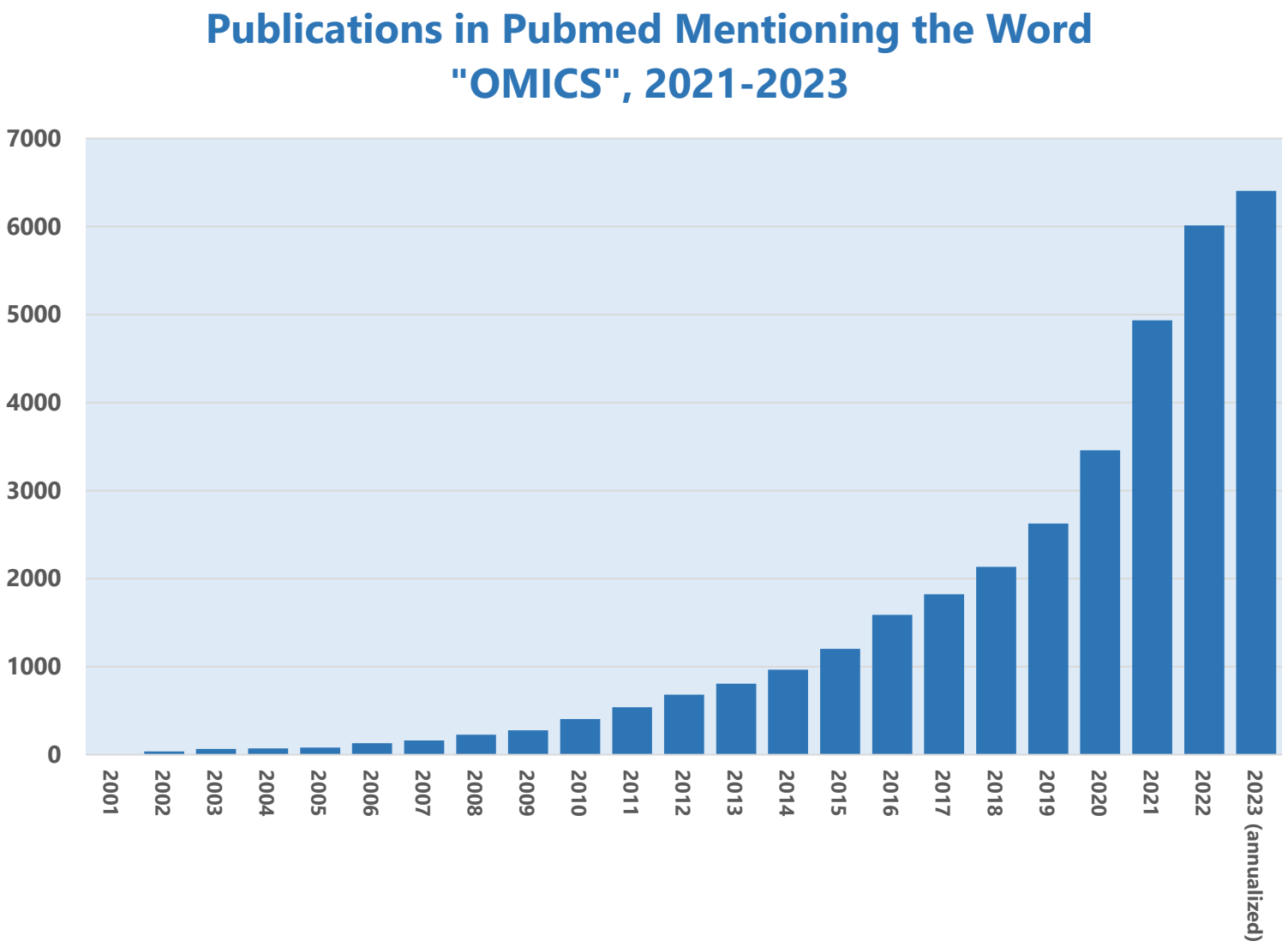
Fotis C, Antoranz A, Hatziavramidis D, Sakellaropoulos T, Alexopoulos LG. Network-based technologies for early drug discovery. *Drug Discov Today*. 2018 Mar;23(3):626-635.

Although the traditional drug discovery approach has led to the development of many successful drugs, the attrition rates remain high. Recent advances in systems-oriented approaches (systems-biology and/or pharmacology) and ‘omics technologies has led to a plethora of new computational tools that promise to enable a more-informed and successful implementation of the reductionist, one drug for one target for one disease, approach. These tools, based on biomolecular pathways and interaction networks, offer a systematic approach to unravel the mechanism(s) of a disease and link them to the chemical space and network footprint of a drug. Drug discovery can draw upon this holistic approach to identify the most-promising targets and compounds during the early phases of development.



Source: https://www.sciencedirect.com/science/article/abs/pii/S1359644617305949

Explosion in ‘OMICS Research in Last Decade

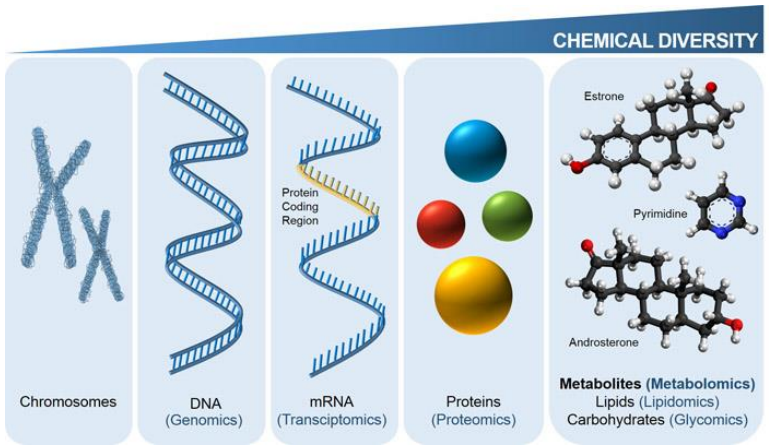


1. Explosion in ‘OMICS research and disease insights over the last two decades (chart at left)
2. OMICS factors (particularly proteins and metabolites) have major insights for medicine as the association of proteins with phenotypes often reveals relevant mechanistic information.
3. Non-genetic differences in protein and metabolite expression can account for vastly more variation in mortality.
4. It’s not that genes don’t matter. Rather, its that proteins / metabolites are ever changing so they give you a good picture of disease.

Why Not Just Study Genomics?

The big insight in biology research in the last decade has been that we can learn much more about disease by using transcriptomic, proteomic and metabolomic tools. There is increasing recognition of the value of other related tools such as the spatial placement of proteins and metabolites (spatial multi-omics) and epigenomics.

1 Vastly More Diversity in Proteins and Metabolites



2 Big Diseases Not Linked to Genes

PLOS ONE 2016

RESEARCH ARTICLE

Genetic Factors Are Not the Major Causes of Chronic Diseases

Stephen M. Rappaport*

School of Public Health, University of California, Berkeley, California, United States of America

The risk of acquiring a chronic disease is influenced by a person's genetics (G) and exposures received during life (the 'exposome', E) plus their interactions (G×E). To estimate proportions of disease risk attributable to G (plus shared exposures), published data from Western European monozygotic (MZ) twins were used to estimate population attributable fractions (PAFs) for 28 chronic diseases. Of 1.53 million Western European deaths in 2000, 0.25 million (16.4%) could be attributed to genetics plus shared exposures

3 Mortality Hard to Explain with Genetics

communications biology 2021

ARTICLE

https://doi.org/10.1038/s42003-021-02289-6 OPEN

Predicting the probability of death using proteomics

Thjodbjorg Eiriksdottir[1], Steinthor Ardal[1], Benedikt A. Jonsson[1], Sigrun H. Lund[1], Erna V. Ivarsdottir[1], Kristjan Norland[1], Egil Ferkingstad[1], Hreinn Stefansson[1], Ingileif Jonsdottir[1,2,3], Hilma Holm[1], Thorunn Rafnar[1], Jona Saemundsdottir[1], Gudmundur L. Norddahl[1], Gudmundur Thorgeirsson[1,2,3], Daniel F. Gudbjartsson[1,2], Patrick Sulem[1], Unnur Thorsteinsdottir[1,2], Kari Stefansson[1,2]✉ & Magnus O. Ulfarsson[1,2]✉

Shows that proteins are very good at predicting human mortality. When analyzing heritability, the authors found that an upper bound of genomic contributors to mortality was around 20% and that this was probably too high.

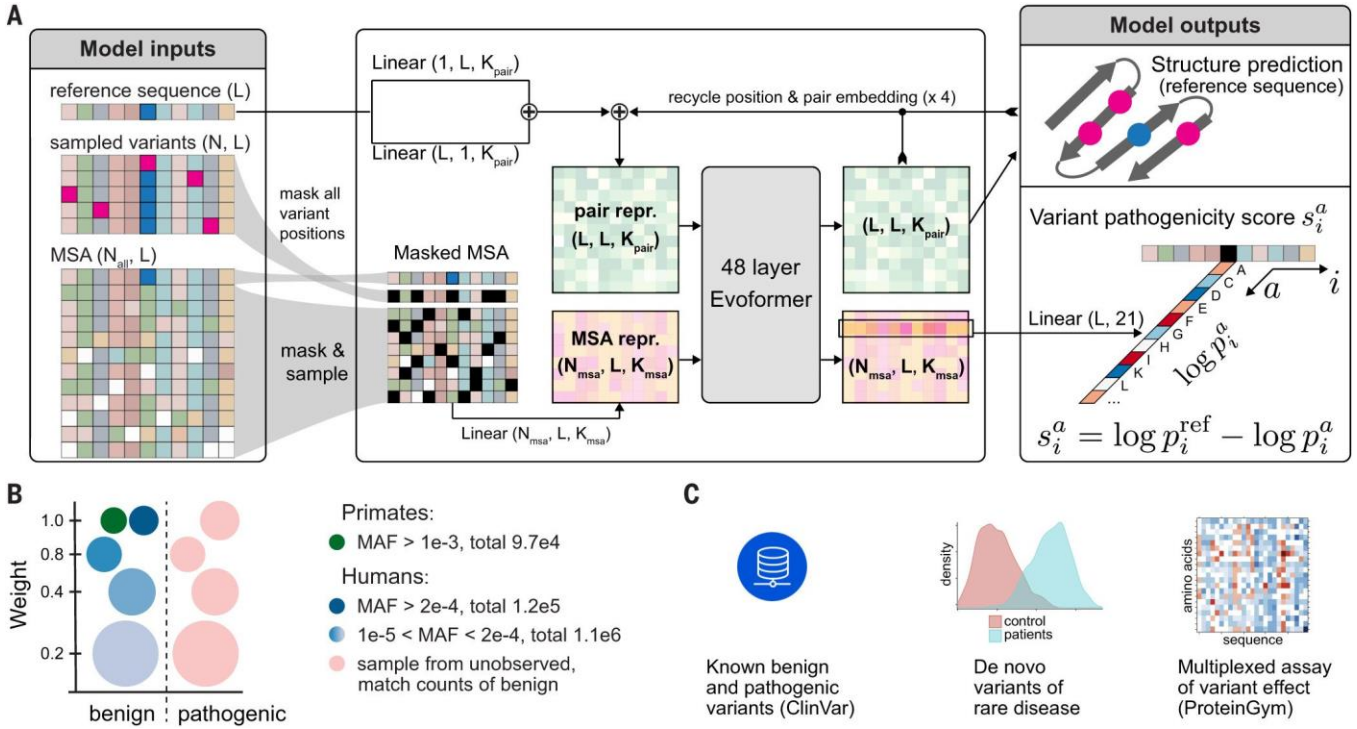
Genomics, Of Course, Making its Own Massive Progress: Understanding of Missense Mutations Progressing

Accurate proteome-wide missense variant effect prediction with AlphaMissense

JUN CHENG, GUIDO NOVATI, JOSHUA PAN, CLARE BYCROFT, AKVILĖ ŽEMGULYTĖ, TAYLOR APPLEBAUM, ALEXANDER PRITZEL, LAI HONG WONG, MICHAL ZIELINSKI, [...], AND ŽIGA AVSEC +6 authors Authors Info & Affiliations

SCIENCE · 19 Sep 2023 · Vol 381, Issue 6664 · DOI: 10.1126/science.adg7492

This article on AlphaMissense in Science last week helps to light up a key area in exploring genetics. We now know with high confidence where over 85% of missense variants are benign or pathogenics.



Source: https://www.science.org/doi/10.1126/science.adg7492

Ability to Identify Mobile Elements Such as Viruses in "Junk DNA" Progressing

Identification of mobile genetic elements with geNomad

Nature Biotechnology

Received: 6 March 2023

Accepted: 17 August 2023

Published online: 21 September 2023

Antonio Pedro Camargo[1], Simon Roux[1], Frederik Schulz[1], Michal Babinski[2], Yan Xu[2], Bin Hu[2], Patrick S. G. Chain[2], Stephen Nayfach[1] & Nikos C. Kyrpides[1]

Mobile genetic elements (MGEs) are selfish genetic entities that, unlike cellular organisms, are unable to self-replicate and, instead, rely on host cells and cellular machinery to propagate. MGEs are associated with all domains of life and encompass elements with various replication and mobility strategies, such as plasmids and viruses. Identifying and characterizing mobile genetic elements in sequencing data is essential for understanding their diversity, ecology, biotechnological applications and impact on public health. Here we introduce geNomad, a classification and annotation framework that combines information from gene content and a deep neural network to identify sequences of plasmids and viruses. geNomad uses a dataset of more than 200,000 marker protein profiles to provide functional gene annotation and taxonomic assignment of viral genomes. Using a conditional random field model, geNomad also detects proviruses integrated into host genomes with high precision. In benchmarks, geNomad achieved high classification performance for diverse plasmids and viruses (Matthews correlation coefficient of 77.8% and 95.3%, respectively), substantially outperforming other tools.

Source: https://www.nature.com/articles/s41587-023-01953-y

geNomad

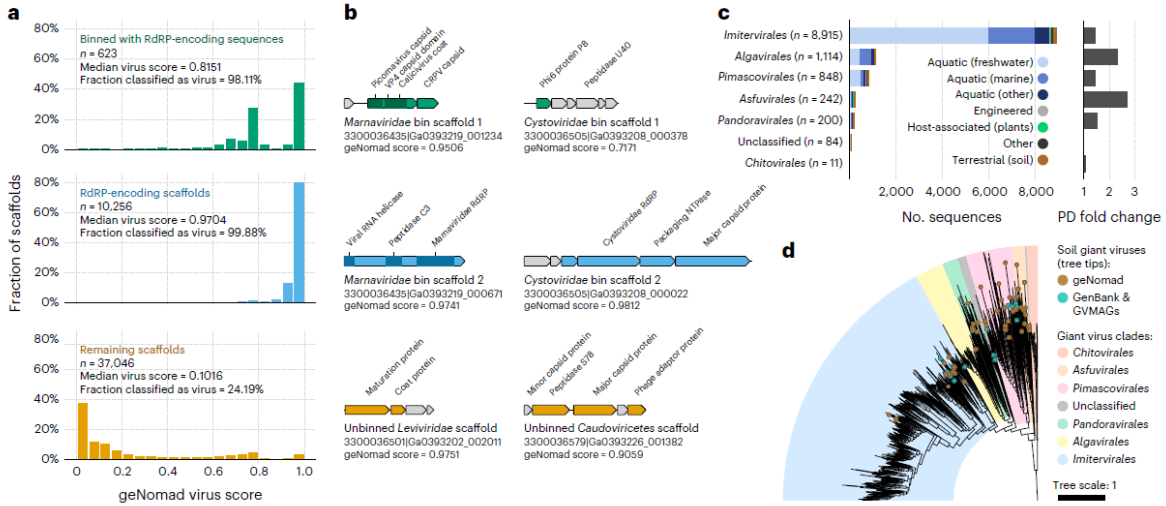
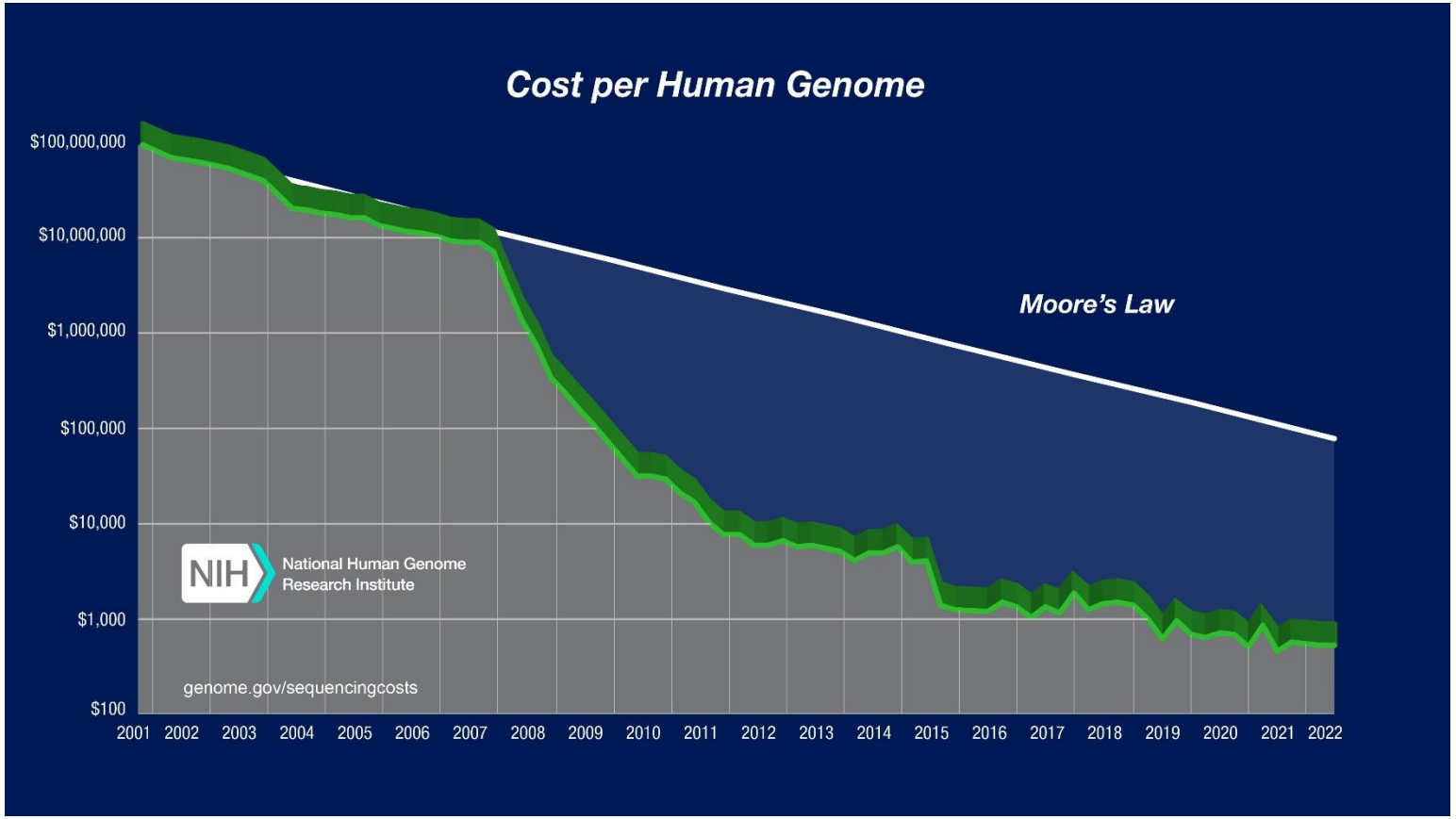


Fig. 5 | geNomad allows the discovery of RNA viruses and giant viruses in environmental sequencing data. a, Histograms showing the geNomad score distribution of three groups of scaffolds of the Sand Creek Marshes metatranscriptomes: scaffolds that binned with RdRP-encoding sequences (top row, in green); scaffolds that contain the RdRP gene (middle row, in blue); and the remaining scaffolds (bottom row, in orange). The median geNomad score and the fraction of scaffolds classified as viral are indicated for each group. large-scale survey of metagenomes of diverse ecosystems. Only scaffolds that are at least 50 kb long or more were evaluated. Bar colors represent the ecosystem types where the sequences were identified. The phylogenetic diversity (PD) fold change is shown on the right bar plot. PD fold change values correspond to the ratio between the total PD of trees reconstructed with and without geNomad-identified giant viruses. **d**, Maximum likelihood phylogenetic tree of soil giant viruses identified with geNomad (brown tree tips). Reference sequences from

Genomics, Of Course, Making its Own Massive Progress: Genetic Sequencing Costs Dropping



One can sequence a full genome today for well under $1,000.

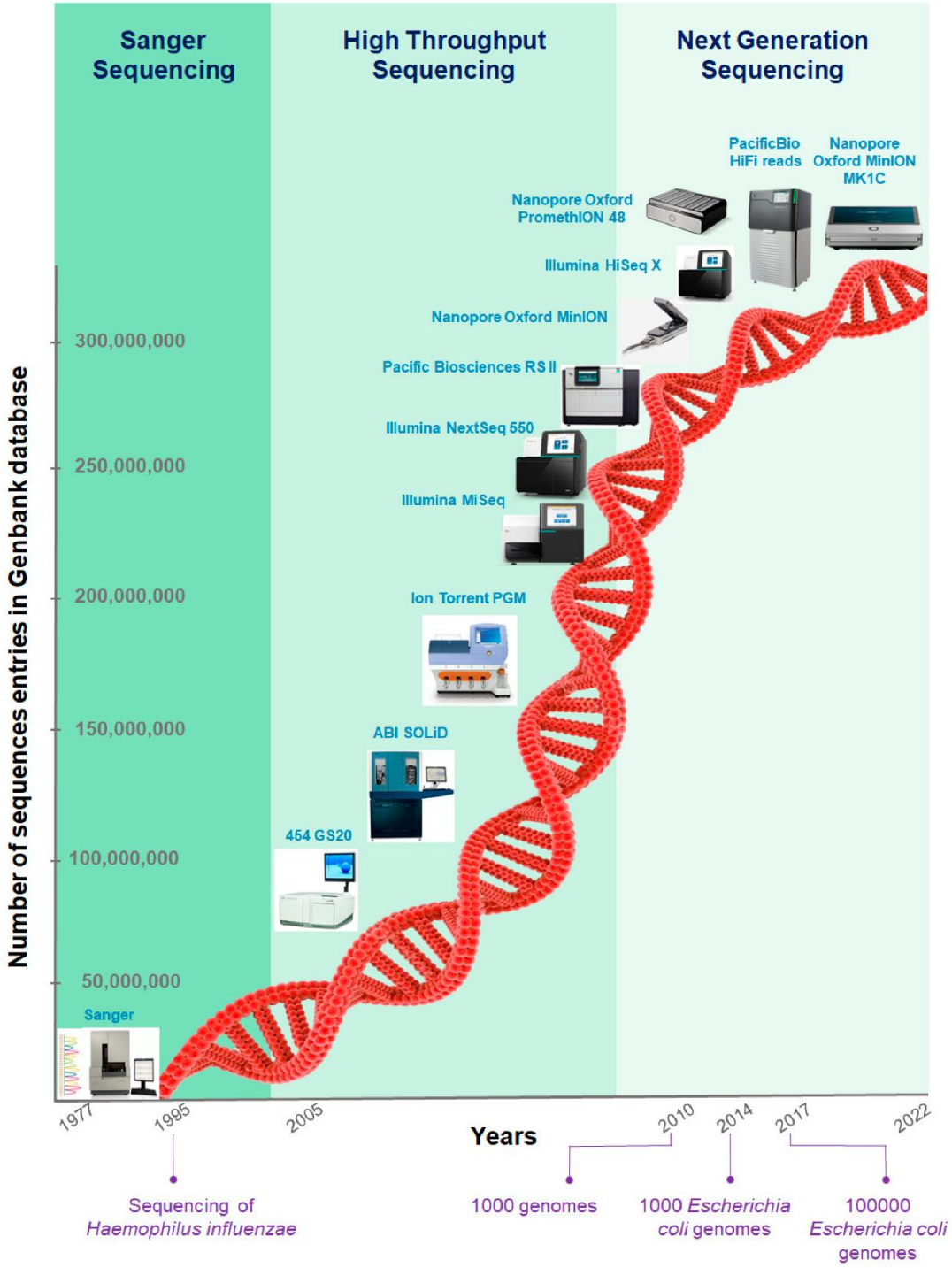
Now, the focus is increasingly turning to improving the interpretation of DNA sequence data.

This makes it possible to deliver genomics to broad populations.

Source: https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

Massive Increase in Number of Available Genetic Sequences: Example Bacterial Sequences

The total cost to sequence a complete bacterial genome has become affordable to many more people, which has contributed to opening the doors of genomics. A chronology that encompasses the various sequencing revolutions is highlighted in the chart at right.



Source: https://www.mdpi.com/1422-0067/23/3/1395

Pharma Adoption of ‘OMICS Technologies

In-House Genomic Database and Study	In-House Proteomic Database and Study	External Collaboration Model to Access Insights
AMGEN	AMGEN	abbvie
AstraZeneca	NOVARTIS	AstraZeneca
REGENERON		Biogen
		Bristol Myers Squibb
		GSK
		Johnson&Johnson
		MERCK
		Pfizer
		Roche
		Takeda

Example: Regeneron Genomics Center

REGENERON

Regeneron has made major investments in genomic discovery and can point to a series of drugs developed from in-house discoveries of disease-relevant genetic variations.

RGC™

Regeneron Genetics Center

RGC™ Regeneron Genetics Center

The Regeneron Genetics Center® (RGC™) is a uniquely integrated research initiative that seeks to improve patient care by using genomic approaches to speed drug discovery and development.

***CIDEB* & NASH**

Learn more about how RGC is cracking the genetic code to combat liver disease.

LEARN MORE >

Featured Perspective

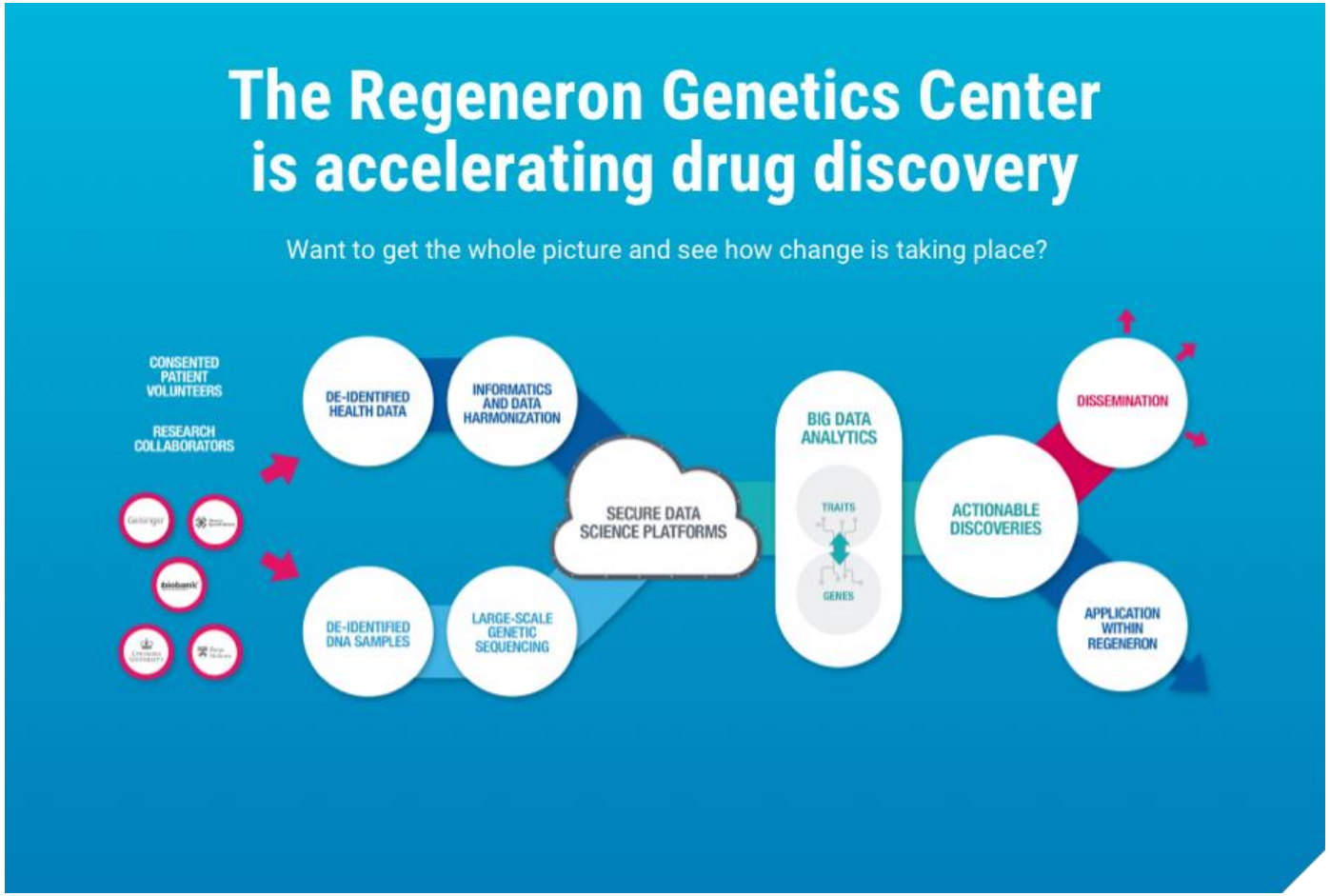
GOING "ALL IN" WITH LIVER DISEASE GENETICS >

By: Luca A. Lotta, MD, PhD

Vice President, Head of Cardiometabolic and Musculoskeletal Disease Genetics

One million exomes sequenced

Sequencing one million exomes and beyond to impact human health and novel drug discovery. This is just the beginning.



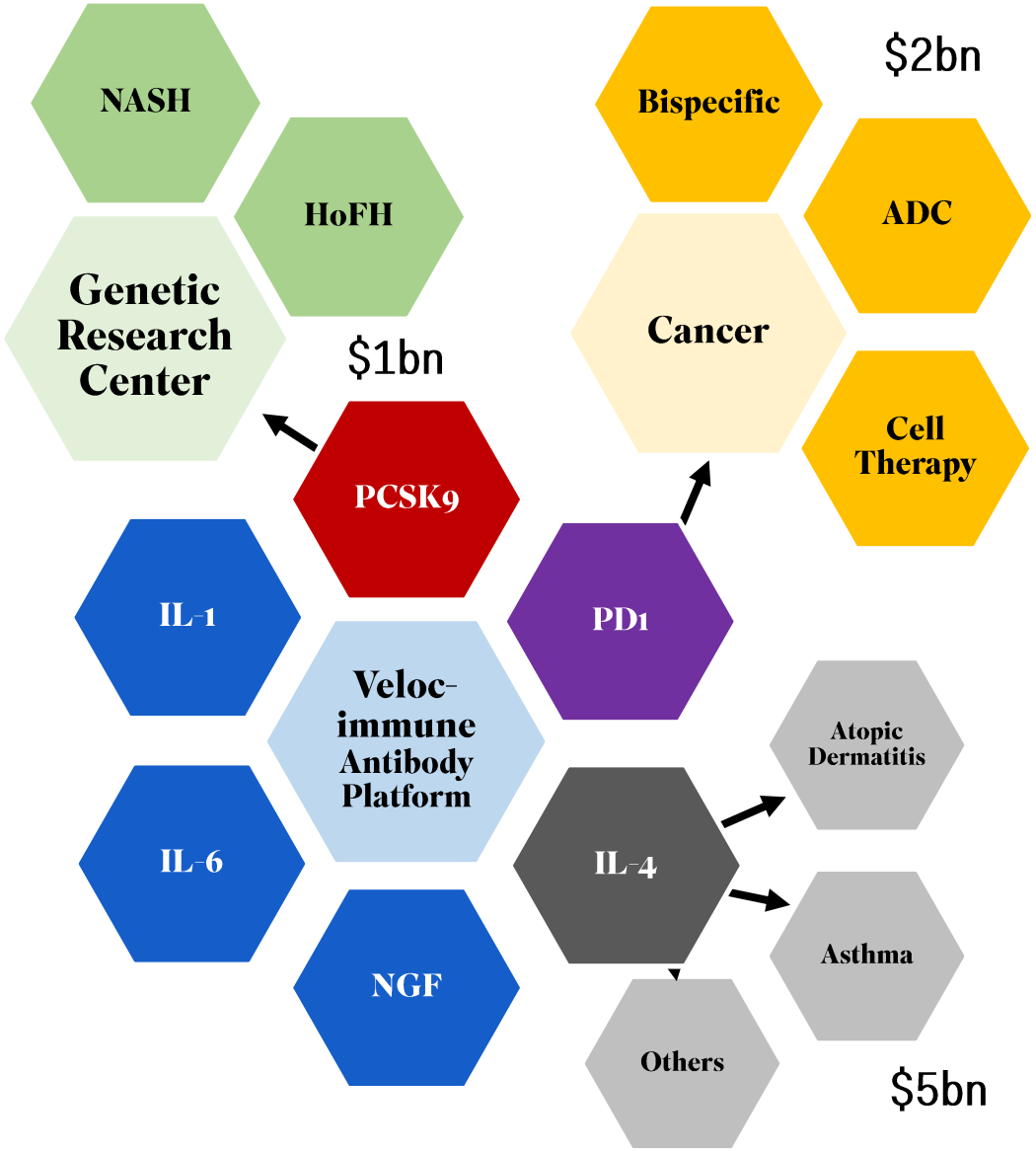
Source: https://www.regeneron.com/science/genetics-center

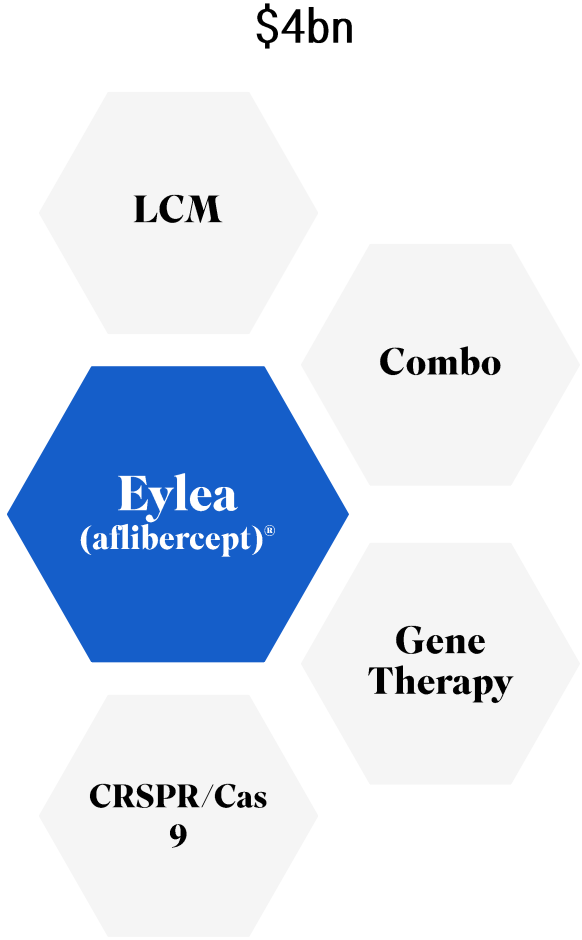
Starting with Eylea and Antibody Smarts Regeneron Has Leveraged Genetic Knowledge to Build a Pharma Giant

Regeneron's story is one of understanding disease through genetic insights, starting with the *Velocigene* platform in 2003 which permitted the study of genetic alterations in mice and disease.

This technology, coupled with Velocimmune in 2014 for making humanized antibodies, has led to many drug approvals, starting with rilonacept (IL-1 trap) and aflibercept (VEGF trap). A key development point was rollout of the Regeneron Genetics Center in 2014. This has facilitated a series of pathbreaking gene sequencing studies to find causes of serious human diseases.

We wish to note the importance of building proprietary technologies to find novel targets for disease and then exploiting these with the Velocimmune platform. Regeneron is a story of creating more than $10 billion in revenue by exploiting and combining technologies.





Recent *Tour de Force* Paper from Regeneron on Genomics

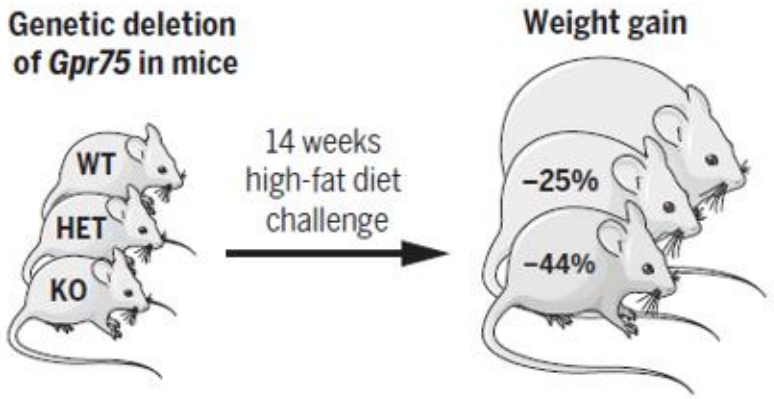
RESEARCH ARTICLE SUMMARY

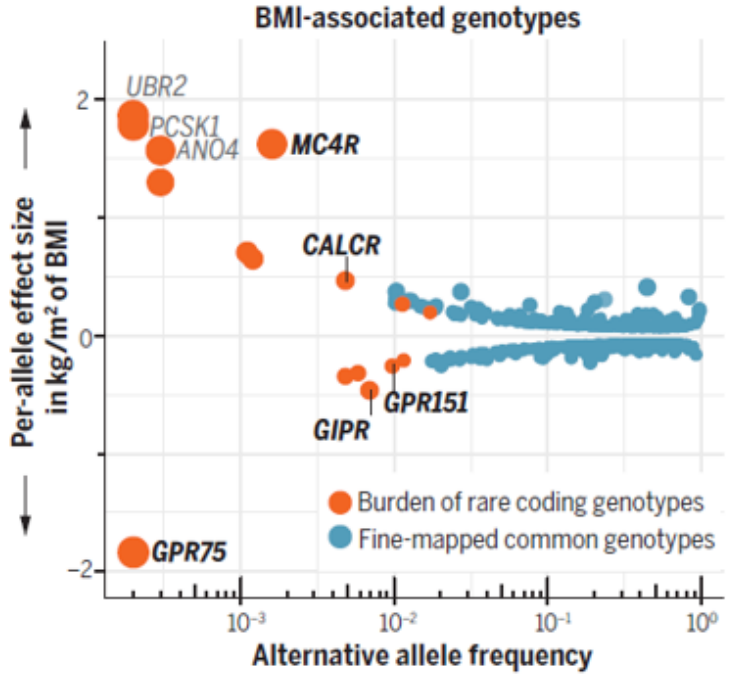
HUMAN GENOMICS

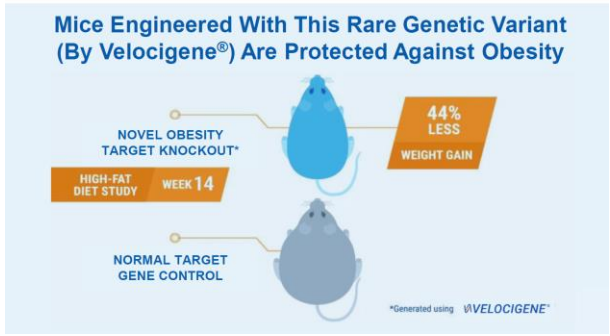
Science, July 2, 2021

Sequencing of 640,000 exomes identifies *GPR75* variants associated with protection from obesity

Parsa Akbari†, Ankit Gilani†, Olukayode Sosina†, Jack A. Kosmicki, Lori Khrimian, Yi-Ya Fang, Trikaldarshi Persaud, Victor Garcia, Dylan Sun, Alexander Li, Joelle Mbatchou, Adam E. Locke, Christian Benner, Niek Verweij, Nan Lin, Sakib Hossain, Kevin Agostinucci, Jonathan V. Pascale, Ercument Dirice, Michael Dunn, Regeneron Genetics Center, DiscovEHR Collaboration, William E. Kraus, Svati H. Shah, Yii-Der I. Chen, Jerome I. Rotter, Daniel J. Rader, Olle Melander, Christopher D. Still, Tooraj Mirshahi, David J. Carey, Jaime Berumen-Campos, Pablo Kuri-Morales, Jesus Alegre-Díaz, Jason M. Torres, Jonathan R. Emberson, Rory Collins, Suganthi Balasubramanian, Alicia Hawes, Marcus Jones, Brian Zambrowicz, Andrew J. Murphy, Charles Paulding, Giovanni Coppola, John D. Overton, Jeffrey G. Reid, Alan R. Shuldiner, Michael Cantor, Hyun M. Kang, Goncalo R. Abecasis, Katia Karalis, Aris N. Economides, Jonathan Marchini, George D. Yancopoulos, Mark W. Sleeman, Judith Altarejos, Giusy Della Gatta, Roberto Tapia-Conyer‡, Michal L. Schwartzman‡, Aris Baras‡*, Manuel A. R. Ferreira‡, Luca A. Lotta‡*







In this paper, Regeneron scientists looked at a stunningly large number of genomes and noticed that persons who were high expressors of GPR75 were less likely to become obese. To confirm that this target is active, Regeneron then did a mouse knockout study and showed that deleting this gene leads to massive weight gain in mice. Regeneron is now developing a drug against this target with AstraZeneca.

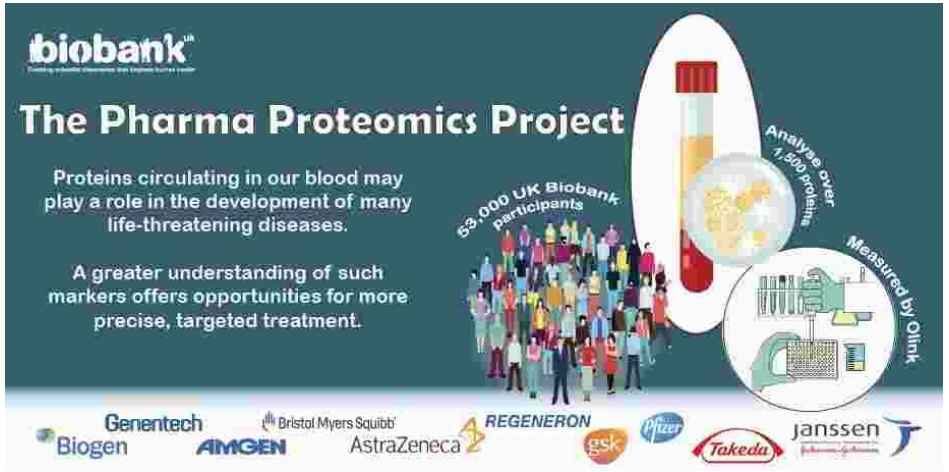
Source: https://pubmed.ncbi.nlm.nih.gov/34210852/

Example of a Collaboration Approach: Alliance for Genomic Discovery

SAN DIEGO, July 18, 2023 /PRNewswire/ -- Illumina Inc. (NASDAQ: ILMN), a global leader in DNA sequencing and array-based technologies, in collaboration with Nashville Biosciences, LLC, a leading clinical and genomic data company and wholly owned subsidiary of Vanderbilt University Medical Center (VUMC), today announced the five founding members of the Alliance for Genomic Discovery (AGD). The multiyear agreement aims to accelerate development of therapeutics through large-scale genomics and the establishment of a preeminent clinical genomic resource. Member organizations AbbVie, Amgen, AstraZeneca, Bayer, and Merck will co-fund the whole-genome sequencing (WGS) of 250,000 samples and have access to the resulting data for use in drug discovery and therapeutic development.

Source: https://news.vumc.org/2023/07/18/the-alliance-for-genomic-discovery-announces-founding-biopharma-members-abbvie-amgen-astrazeneca-bayer-and-merck/

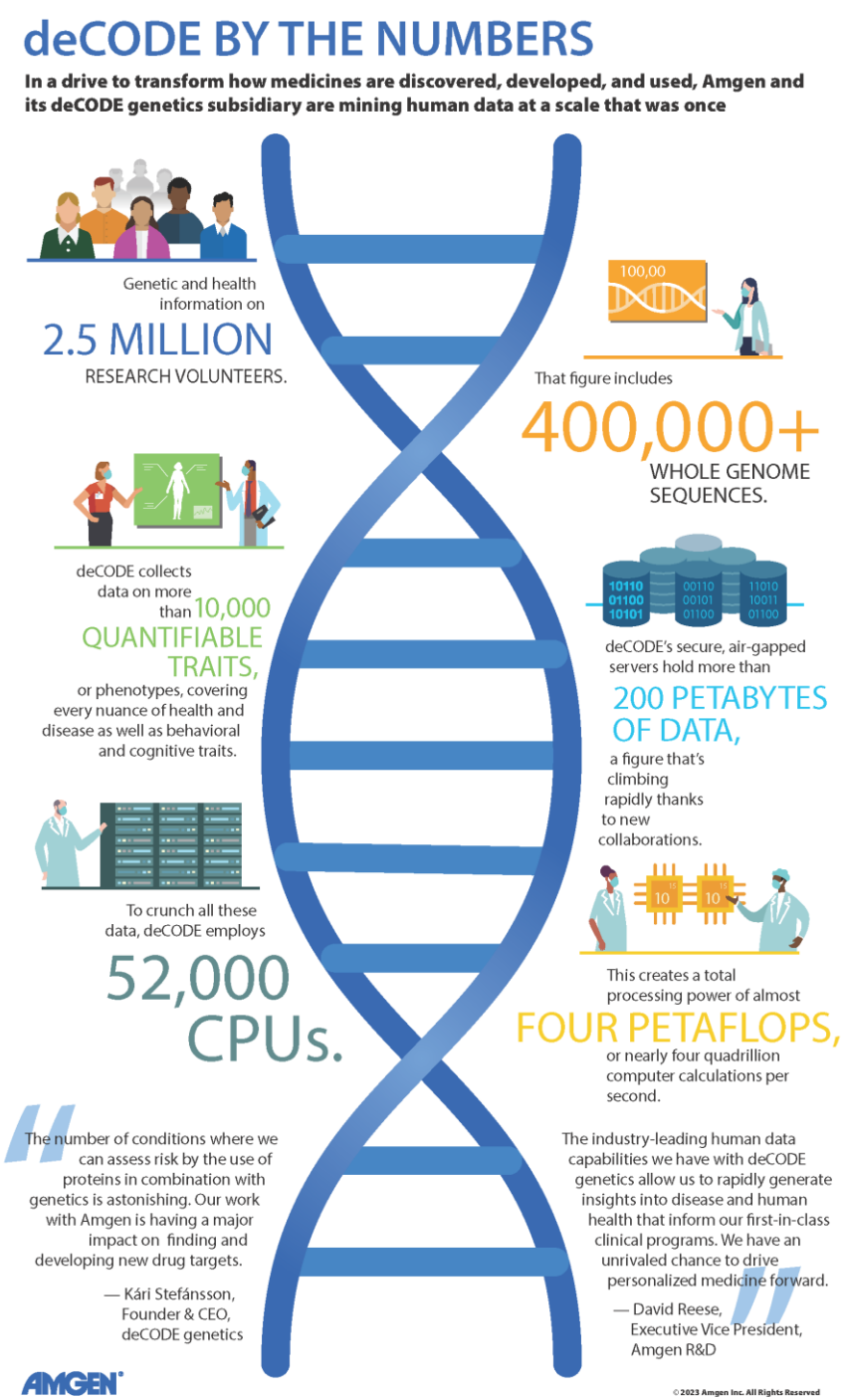
Example of a Collaboration Approach: UK Biobank & Olink



London, 7 Dec 2020 -- UK Biobank, one of the world's largest and most comprehensive biomedical databases and research resources, announces today that a consortium of ten biopharmaceutical companies will perform a study to measure circulating concentrations of almost 1,500 plasma proteins in approximately 53,000 UK Biobank participants. It will be one of the world's largest studies of blood protein concentrations conducted to date and aims to significantly enhance the field of 'proteomics', enabling better understanding of disease processes and supporting innovative drug development.

The study has been commissioned and funded by a consortium of leading biopharmaceutical companies including Amgen, AstraZeneca, Biogen, Bristol Myers Squibb, Genentech (a member of the Roche Group), GlaxoSmithKline (GSK), The Janssen Pharmaceutical Companies of Johnson & Johnson*, Pfizer Inc, Regeneron and Takeda Pharmaceutical Co. Ltd. The laboratory work to measure the proteins will be conducted by Olink, a leading Swedish proteomics company, using its proprietary technology, which combines high throughput and high-quality protein-level data from very small sample volumes.

Source: https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/news/uk-biobank-launches-one-of-the-largest-scientific-studies



Amgen's deCODE Investment

Amgen bought deCODE Genetics for $415 million in 2012

Since its founding in 1996, as shown at left, the company has worked with over 400,000 sequences.

A review of the GWAS era published in Nature Communications in 2019 quantified deCODE's outsized contribution to the field: Icelanders accounted for 12% of all participants in all published GWAS studies globally between 2007 and 2017, with each citizen participating on average to 19 published findings in that period alone.

Key outcomes from the deCODE collaboration include:

- Gene discoveries involving PCSK9
- GIP gene discoveries for AMG133
- Work for olpasiran, a SIRNA molecule for Lp(a)
- TREM2 role in Alzheimer's

https://www.amgen.com/stories/2022/06/decoding-disease

Amgen's AMG133 Has Profile of Best Obesity Drug in History

THOUSAND OAKS, Calif., Dec. 1, 2022 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced new Phase 1 data from AMG 133, a novel bispecific glucose-dependent insulinotropic polypeptide receptor (GIPR) antagonist and glucagon-like peptide-1 (GLP-1) receptor agonist molecule. This first-in-human study was designed to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic effects of AMG 133 in people with obesity and without diabetes (NCT04478708). These data will be presented as part of an oral presentation on Saturday, Dec. 3 at the 20th World Congress of Insulin Resistance, Diabetes and Cardiovascular Disease (WCIRDC) Hybrid Conference.

"AMG 133 was designed based on preclinical and human genetic data that strongly suggest GIPR inhibition as a strategy for weight loss, especially in combination with GLP-1 agonism," said David M. Reese, M.D., executive vice president of Research and Development at Amgen. "We are encouraged by these Phase 1 results with once-monthly dosing of AMG 133, specifically, the degree, rate and durability of the weight loss. We look forward to initiating the Phase 2 study early next year."

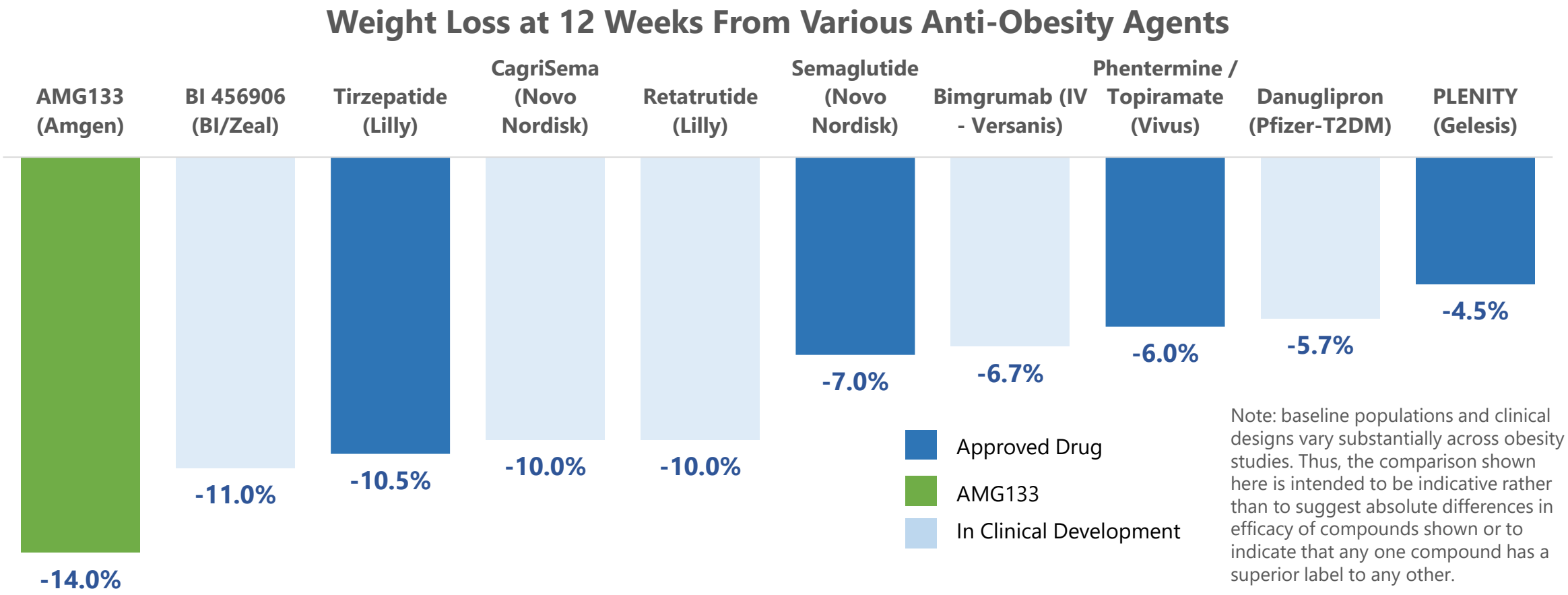
Participants were randomized (3:1) to receive subcutaneous AMG 133 or placebo either as a single ascending dose (SAD) or multiple ascending doses (MAD). The MAD cohorts showed mean percent changes in body weight (BW), ranging from -7.2% at the lowest dose (140mg Q4W), to -14.5% at the highest dose (420mg Q4W) by day 85. A substantial degree of weight loss was maintained beyond the treatment period, which will be shared as part of the oral presentation. Most treatment emergent adverse events (TEAEs) were mild and transient. The majority of the TEAEs were GI-related with the most common being nausea and vomiting, most events resolved within 48 hours. Based on these data, a Phase 2 trial will be initiated early next year to further study the attributes of this molecule.

Amgen was the first pharma company to achieve the effects of bariatric surgery with a drug called AMG133. Patients lost 14.5% of their body weight in a recent trial of this GLP1 agonist / GIPR antagonist. Amgen's genetic team noted the importance of GIPR variants in weight loss and then went on to create a GIPR antagonist. They found that this drug induced profound weight loss in weight. The next step was to create a drug (patent filed in 2018) and they are now in Phase 2 clinical studies with data slated for 2024.

Source: https://www.amgen.com/newsroom/press-releases/2022/12/amgen-presents-new-amg-133-phase-1-clinical-data-at-wcirdc-2022

How do the Phase 1 / 2 Challengers to Mounjaro® Weigh In? A Look at 12 Week Data

The emerging players in obesity have a good chance to beat Mounjaro® efficacy. These include AMG133 which is a GIPr antagonist combined with a GLP1 agonist. Stunningly, the weight loss seen with AMG133 matches that seen at 12 weeks with bariatric surgery.



Note: baseline populations and clinical designs vary substantially across obesity studies. Thus, the comparison shown here is intended to be indicative rather than to suggest absolute differences in efficacy of compounds shown or to indicate that any one compound has a superior label to any other.

Sources: https://www.amgen.com/newsroom/press-releases/2022/12/amgen-presents-new-amg-133-phase-1-clinical-data-at-wcirdc-2022; https://dom-pubs.onlinelibrary.wiley.com/doi/10.1111/dom.14948; https://www.nejm.org/doi/full/10.1056/NEJMoa2206038; https://www.novonordisk.com/content/dam/nncorp/global/en/investors/pdfs/capital-markets-day-2022/P5-obesity-care.pdf; https://www.biopharmadive.com/news/lilly-2023-guidance-diabetes-obesity/638733/; https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2796491; https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2774903; https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=40dd5602-53da-45ac-bb4b-15789a; https://s28.q4cdn.com/781576035/files/doc_presentation/2022/09/2022-EASD-IR_Presentation_FINAL.pdf; https://onlinelibrary.wiley.com/doi/full/10.1002/oby.22347

Cool Private Biotechs Leveraging ‘OMICS Technologies

ASIMOV

Web: https://asimov.com

Headquartered in Boston, Asimov’s mission is to advance humanity’s ability to design living systems, enabling biotechnologies with outsized societal benefit. The company is developing a synthetic biology platform – from cells to software – to design and manufacture next-generation therapeutics, including biologics, cell/gene therapies, and RNA. Founded by bioengineers from MIT and Boston University, the company has raised over $200 million from top institutional investors including Andreessen Horowitz, CPP Investments, Horizons Ventures, and Fidelity Management & Research Company.

cerevance

Web: https://cerevance.com

Cerevance is focused on the development of treatments for central nervous system (CNS) disorders, prioritizing chronic neurodegenerative conditions such as Alzheimer's disease and Parkinson's diseaseUtilizing a large and growing collection of over 14,000 human brain tissue samples, Cerevance is generating an unprecedented level of expression and epigenetic data thereby enabling the company to identify the most promising targets for the next generation of treatments for CNS disorders. The company utilizes its proprietary NETSseq platform and advanced machine learning techniques to uncover the gene expression profiles of select cell types to identify novel targets.

Web: https://www.eikontx.com/

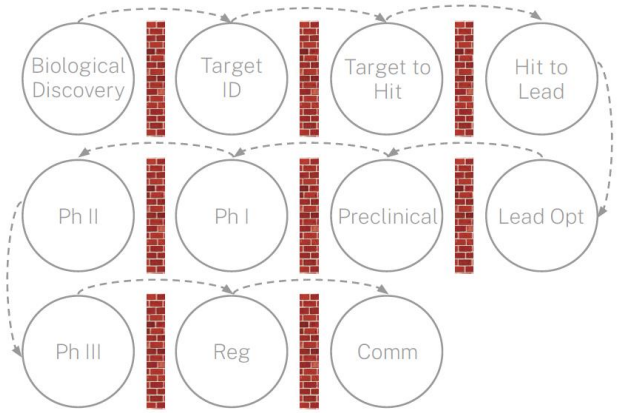
Eikon Therapeutics seeks to advance breakthrough therapeutics through the purposeful integration of engineering and science. Our proprietary discovery technologies leverage Nobel Prize-winning super-resolution microscopy, advanced engineering, and high-performance computing to visualize and measure the real-time movement of proteins in living cells, with the goal of bringing important new medicines to people suffering from grievous illness.

Integrating OMICs with AI: Valo Health

Valo

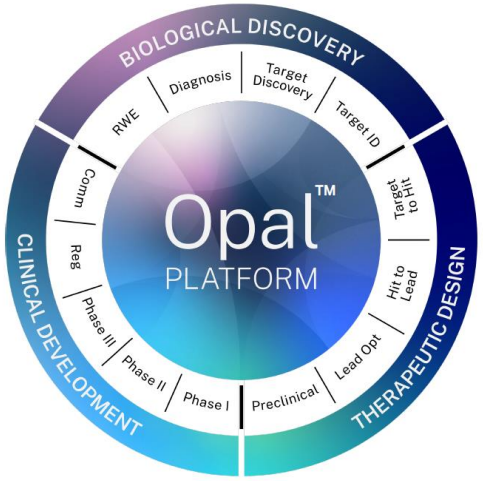
Valo Health is a technology company built to transform the drug discovery and development process using human-centric data and artificial intelligence-driven computation. Valo aims to fully integrate human-centric data across the entire drug development life cycle into a single unified architecture, thereby accelerating the discovery and development of life-changing drugs while simultaneously reducing costs, time, and failure rates. The company's Opal Computational Platform™ is an integrated set of capabilities designed to transform data into valuable insights that may accelerate discoveries and enable Valo to advance a robust pipeline of programs across cardiovascular metabolic renal, oncology, and neurodegenerative disease.

LEGACY BIOPHARMA MODEL[1,2]



LOCALIZED[3] | DISINTEGRATED[3]
SURROGATE-DEPENDENT[4] | SERIAL[1]

VALO DRUG ACCELERATION MODEL



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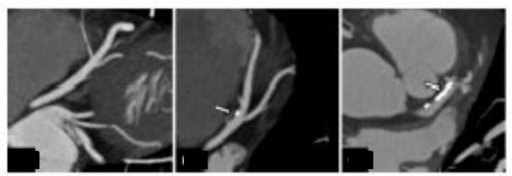
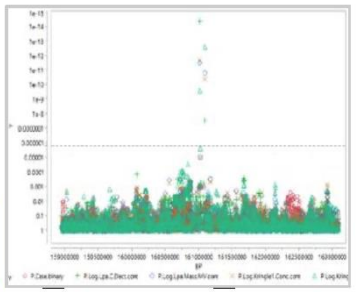
HUMAN-CENTRIC | PARALLEL

Multidimensional -'omics

Exclusive access to one of the largest prospective studies spanning pan-omics, imaging, and medical records

>22.5T	>210M	>21M	>320K
Whole genome sequencing data points	mRNA sequencing data points	Metabolomic and/or proteomic data points	Blood sample aliquots



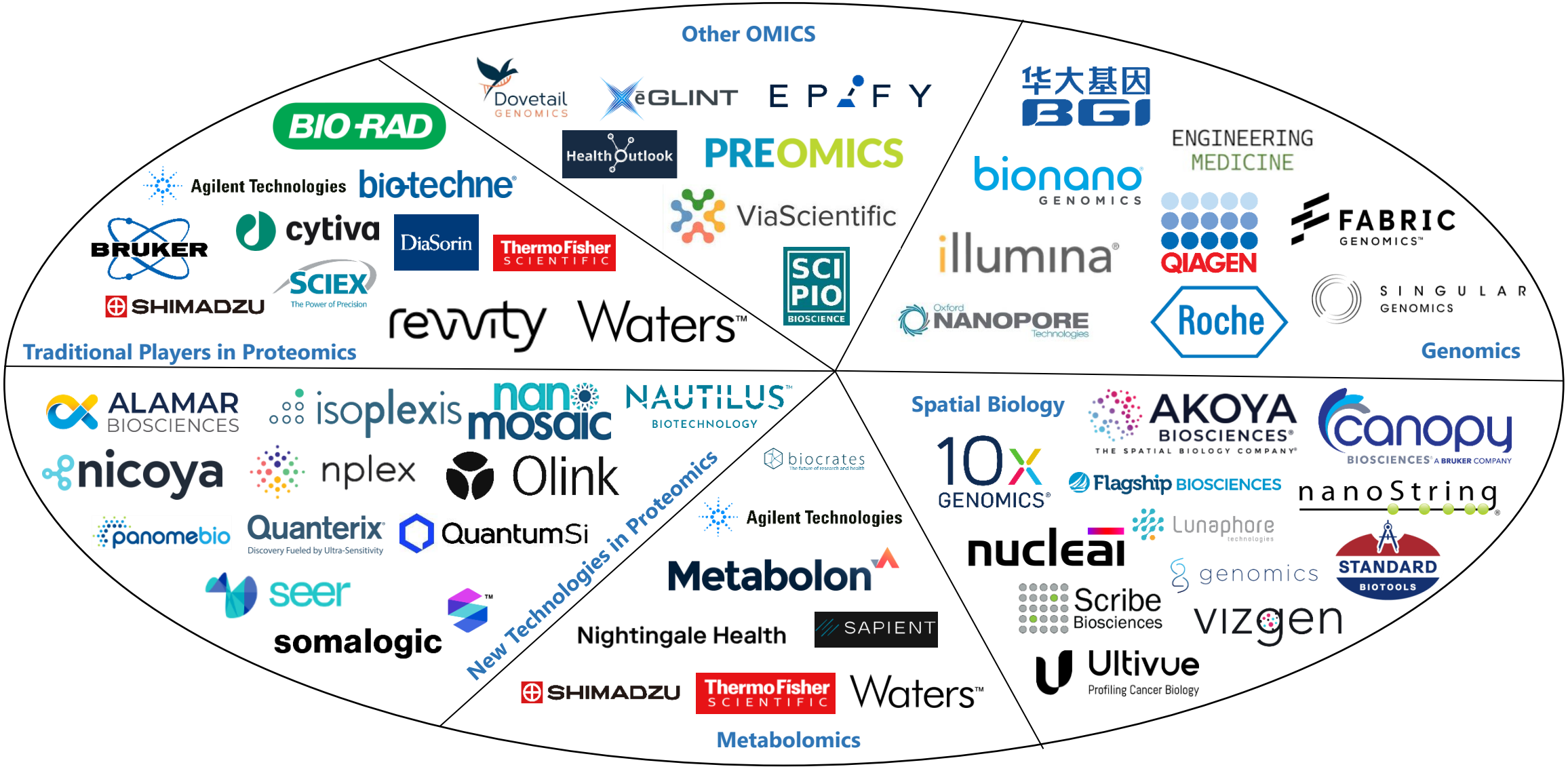


>13K images
paired with related scoring data

Target ID = Target Identification; RWE = Real World Evidence; Lead Opt = Lead Optimization; Reg = Regulatory; Comm = Commercial; AI = Artificial Intelligence
[1] Paul, Steven M., et al. "How to improve R&D productivity: the pharmaceutical industry's grand challenge." Nat Rev Drug Discov 9, 203–214 (Mar 2010). [2]Hughes, James P., et al. "Principles of Early Drug Discovery." *British Journal of Pharmacology* 162.6, 1239-1249 (Mar 2011). [3] Konersmann, Todd., et al. "Innovating R&D with the Cloud: Business Transformation Could Require Cloud-Enabled Ecosystems, and Services." Deloitte

Source: https://valohealth.com

Key OMICS Life Science Tools Players



PacBio, Once Slated to be Acquired by Illumina, is Taking on the DNA Giant

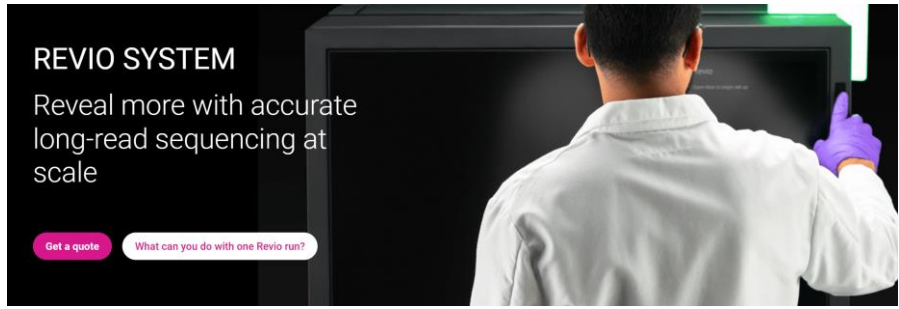
Jared Whitlock, Endpoints News, Aug 29, 2023

Pacific Biosciences, a company that Illumina once tried to buy, is coming for its former suitor. More than three years ago, the companies called off their $1.2 billion merger after antitrust opposition. Back then, Pacific Biosciences, known as PacBio, was in a financially precarious position but is now posing a competitive threat to Illumina.

PacBio is capitalizing on the demand for reading longer pieces of DNA, while expanding into a market dominated by Illumina. At the same time, Illumina finds itself with slowing sales, an interim CEO and another acquisition that could be torpedoed because of antitrust regulators.

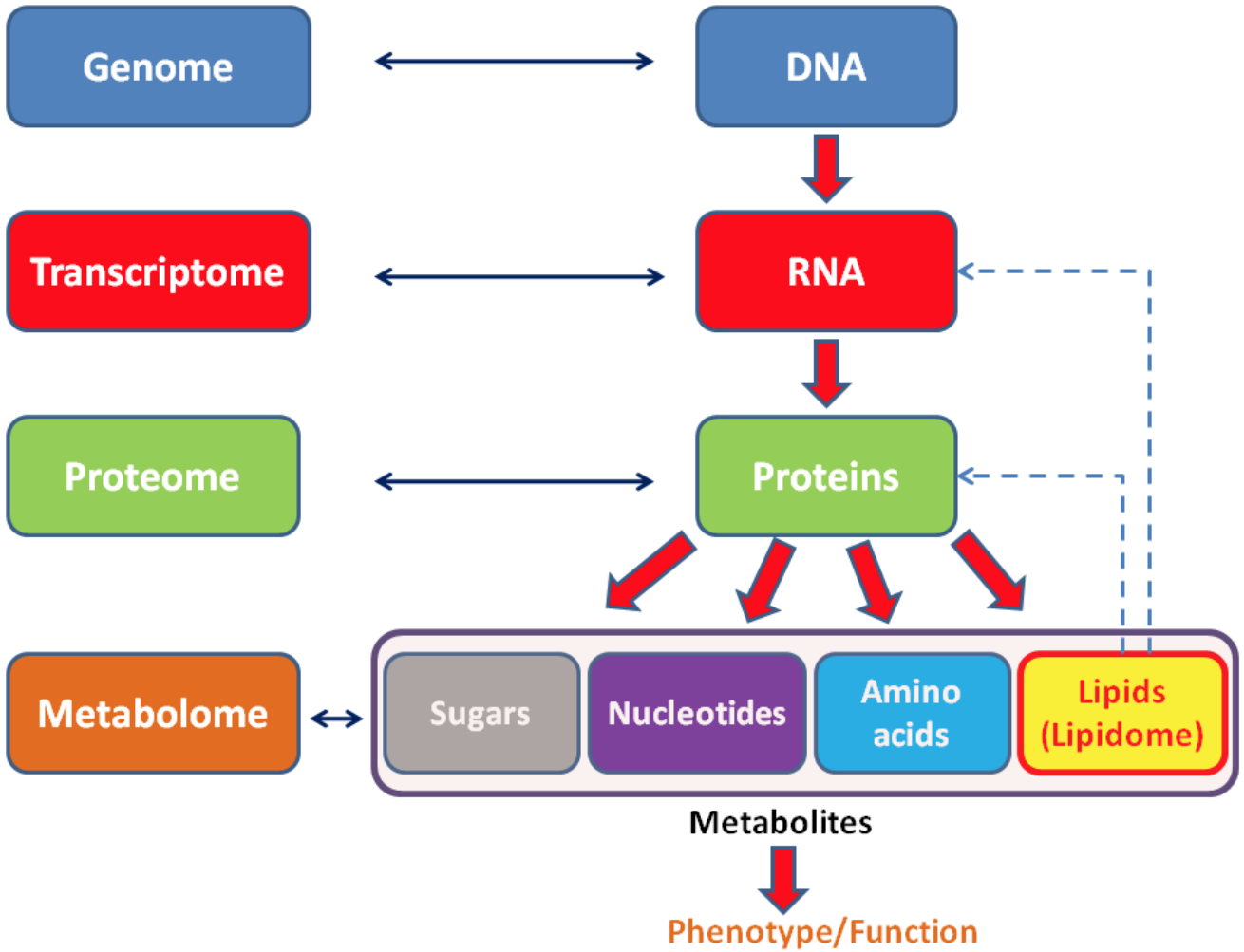
Illumina, a $25 billion company, is roughly 10 times as big as PacBio. But PacBio has something the sequencing giant doesn't: momentum. "We came in and built a new team and have a new big vision. And we're well-funded and financed, so we're ready to go," PacBio CEO Christian Henry said in an interview with Endpoints News.

Using PacBio's DNA sequencer, called Revio, researchers are deciphering previously undecipherable parts of the genome, including to find rare disease diagnoses.



Source: https://endpts.com/pacbio-once-slated-to-be-acquired-by-illumina-is-taking-on-the-dna-giant/

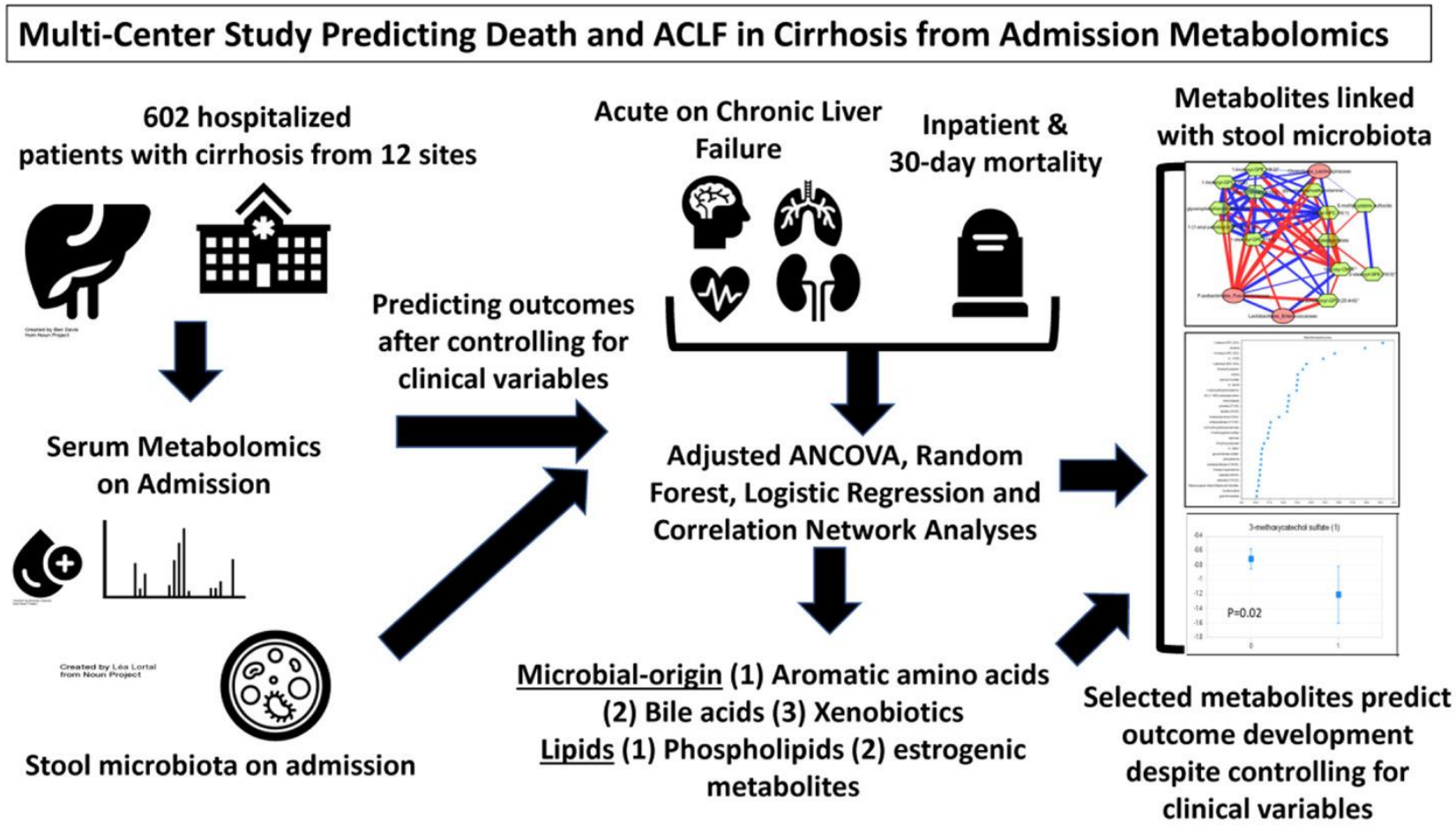
Background on Metabolomics



Metabolomics is defined as the comprehensive analysis of metabolites in a biological specimen. Metabolomics is an emerging technology that holds promise to inform the practice of precision medicine. Historically, small numbers of metabolites have been used to diagnose complex metabolic diseases as well as monogenic disorders such as inborn errors of metabolism. Current metabolomic technologies go well beyond the scope of standard clinical chemistry techniques and are capable of precise analyses of hundreds to thousands of metabolites. Consequently, metabolomics affords detailed characterization of metabolic phenotypes and can enable precision medicine at a number of levels, including the characterization of metabolic derangements that underlie disease, discovery of new therapeutic targets, and discovery of biomarkers that may be used to either diagnose disease or monitor activity of therapeutics.

Source: Clish CB. Metabolomics: an emerging but powerful tool for precision medicine. *Cold Spring Harb Mol Case Stud*. 2015;1(1):a000588.

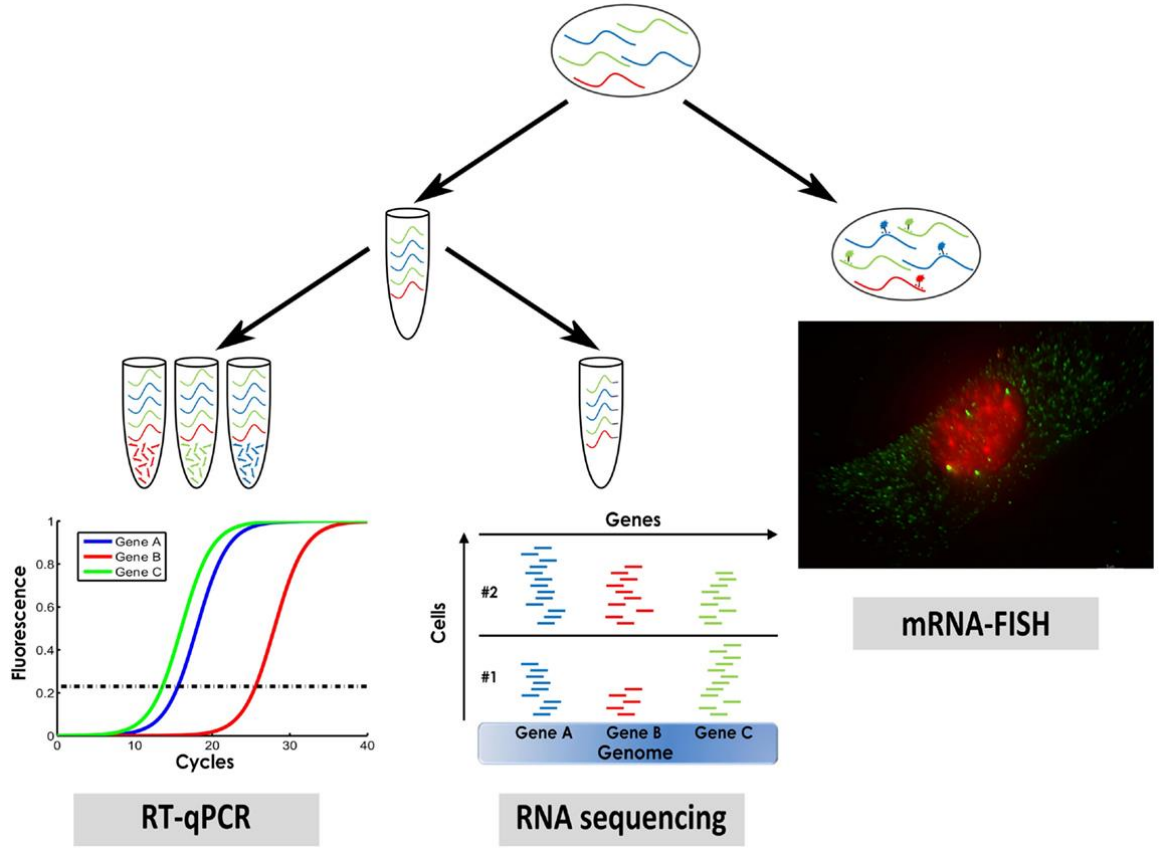
Illustrative Metabolomics Study in Cirrhosis



Gastroenterology

Source: Bajaj JS, Reddy KR, O'Leary JG, Vargas HE, Lai JC, Kamath PS, Tandon P, Wong F, Subramanian RM, Thuluvath P, Fagan A, White MB, Gavis EA, Sehrawat T, de la Rosa Rodriguez R, Thacker LR, Sikaroodi M, Garcia-Tsao G, Gillevet PM. Serum Levels of Metabolites Produced by Intestinal Microbes and Lipid Moieties Independently Associated With Acute-on-Chronic Liver Failure and Death in Patients With Cirrhosis. Gastroenterology. 2020 Nov;159(5):1715-1730.e12.

Transcriptomics: The Study of RNA Levels in Biological Samples



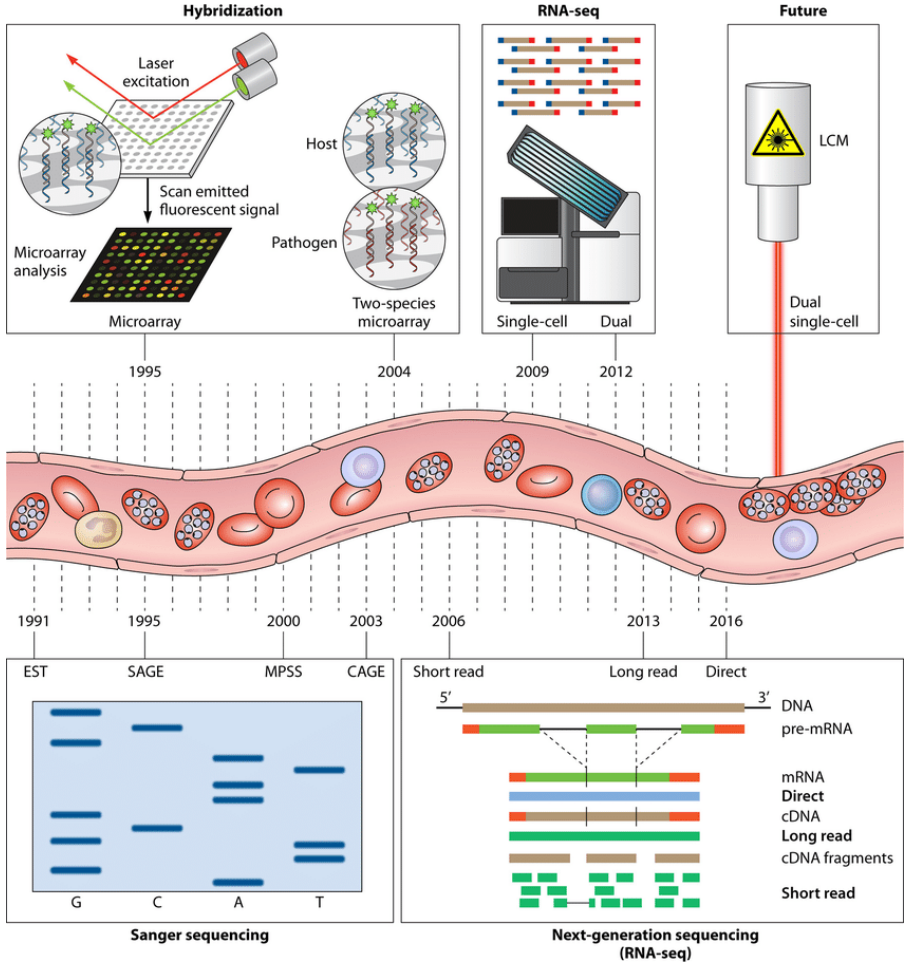
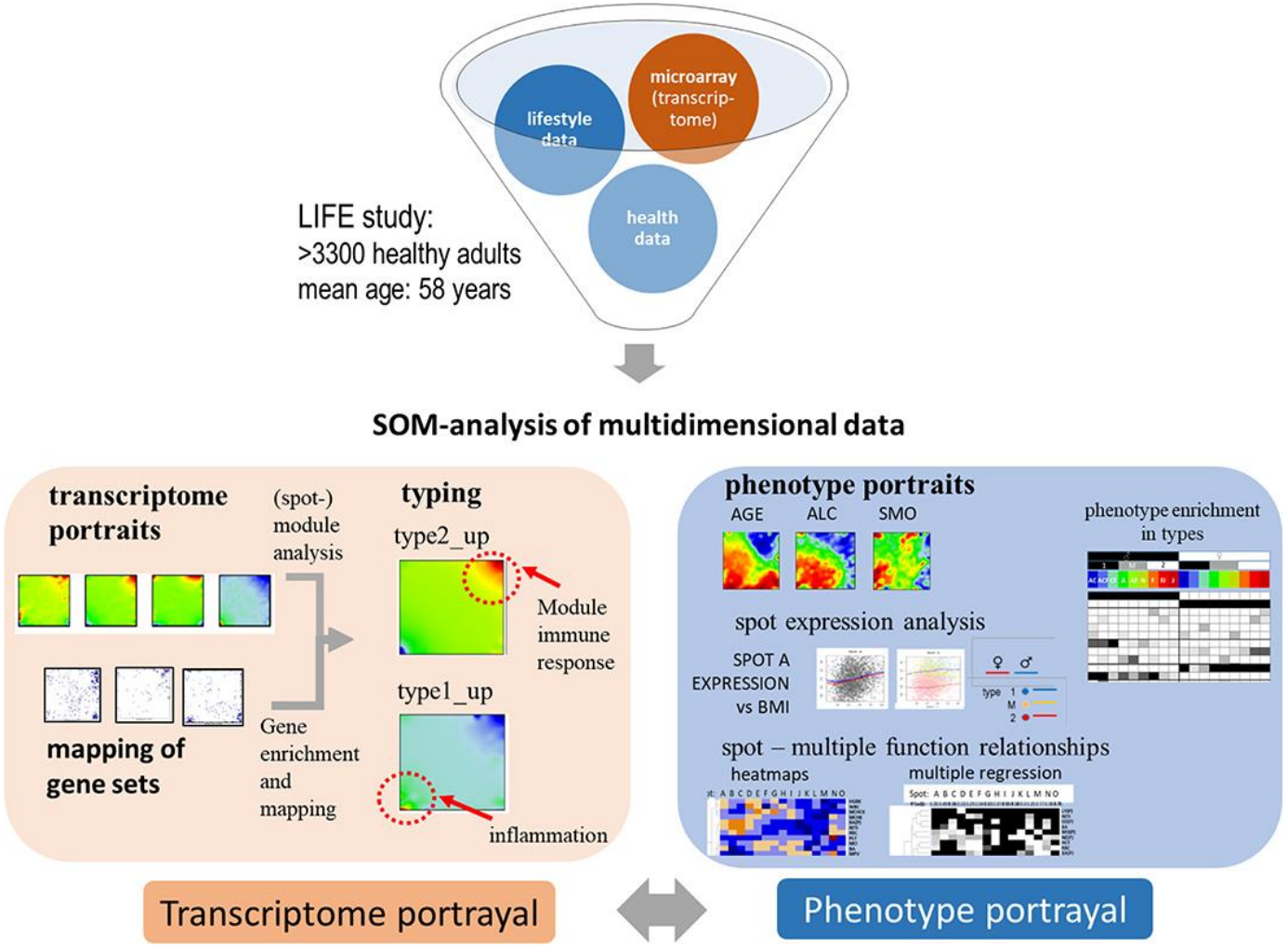


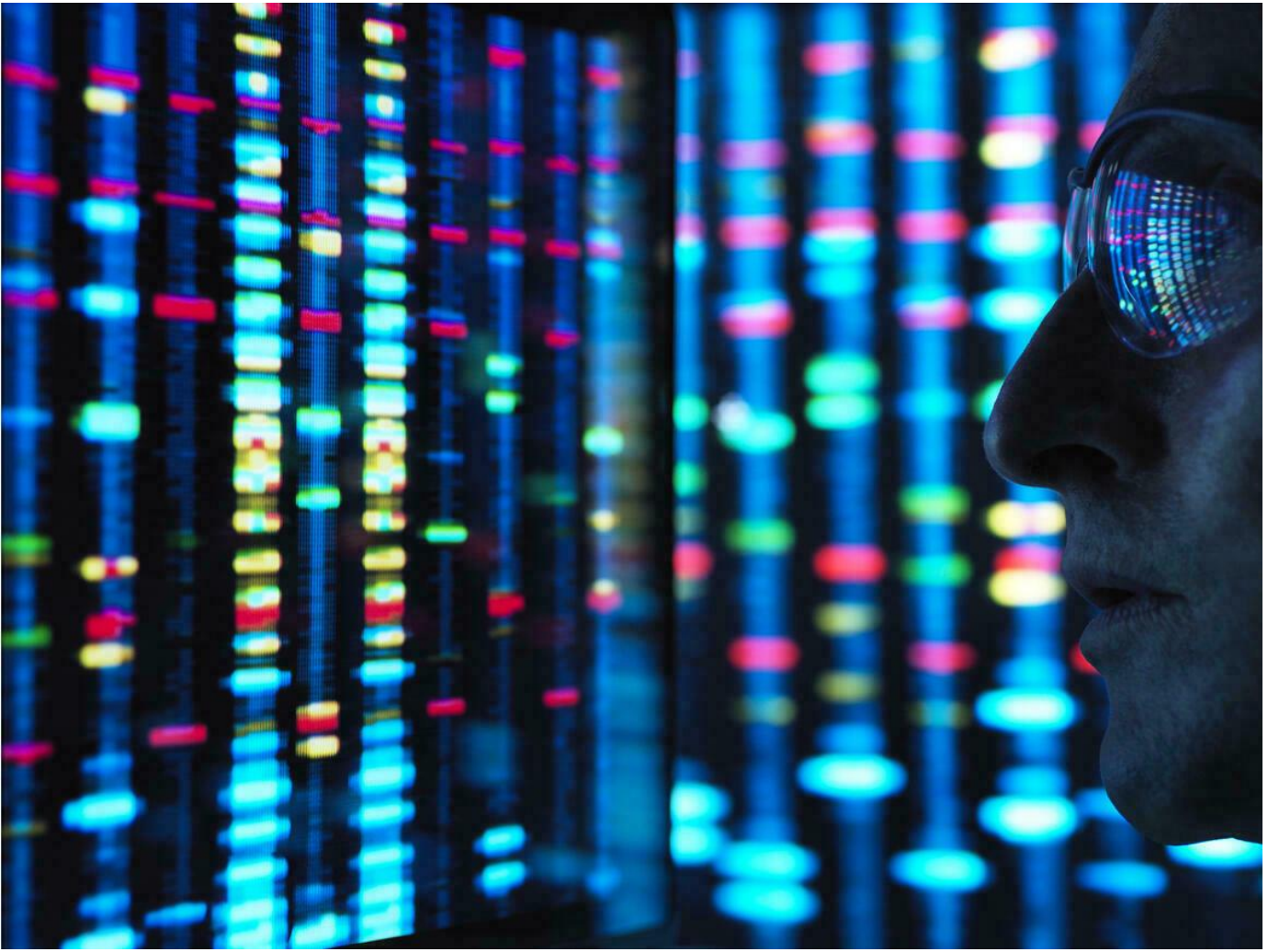
Chart at right from: ulia dilulio, Istvan Bartha, Roberto Spreafico, Herbert W. Virgin, Amalio Telenti, Transfer transcriptomic signatures for infectious diseases, *PNAS* June 1, 2021 118 (22) e2022486118

Illustration of Transcriptomic / Phenotype Association Study



Source: Schmidt M, Hopp L, Arakelyan A, Kirsten H, Engel C, Wirkner K, Krohn K, Burkhardt R, Thiery J, Loeffler M, Loeffler-Wirth H, Binder H. The Human Blood Transcriptome in a Large Population Cohort and Its Relation to Aging and Health. *Front Big Data*. 2020 Oct 30;3:548873.

Proteomics



The proteome is the full set of proteins produced by a cell in its lifetime.

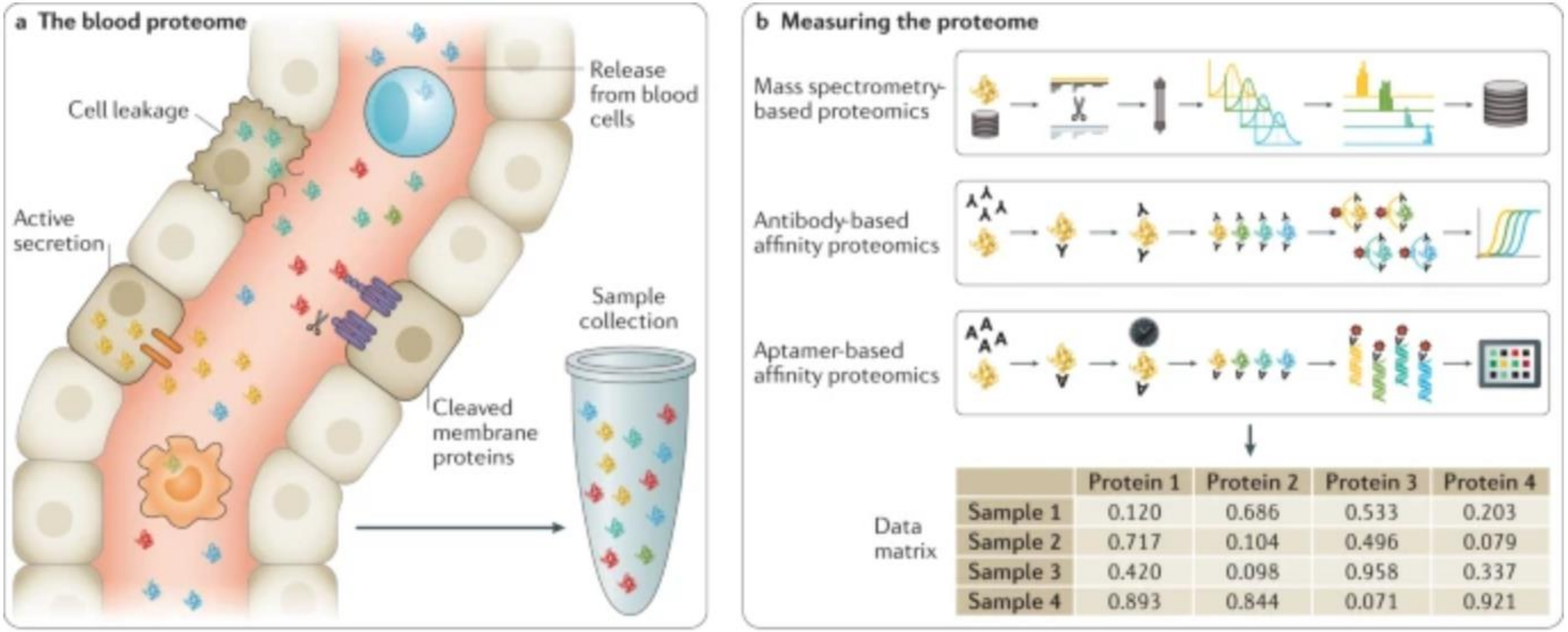
Proteomics is the study of the proteome.

The presence of proteins and protein interactions tell you a **tremendous amount about what is happening in an organism.**

In general, our body works through proteins which can be measured using an immuno-analyzer. We also have many chemicals such as salt or potassium. These can be measured using a chemical analyzer.

Technologies for Measuring Protein Expression in Blood

Available approaches include mass spectrometry (e.g., Seer), Antibody approaches (e.g,. ELISA, Olink) & Aptamer Affinity (e.g., Somalogic).



	Protein 1	Protein 2	Protein 3	Protein 4
Sample 1	0.120	0.686	0.533	0.203
Sample 2	0.717	0.104	0.496	0.079
Sample 3	0.420	0.098	0.958	0.337
Sample 4	0.893	0.844	0.071	0.921

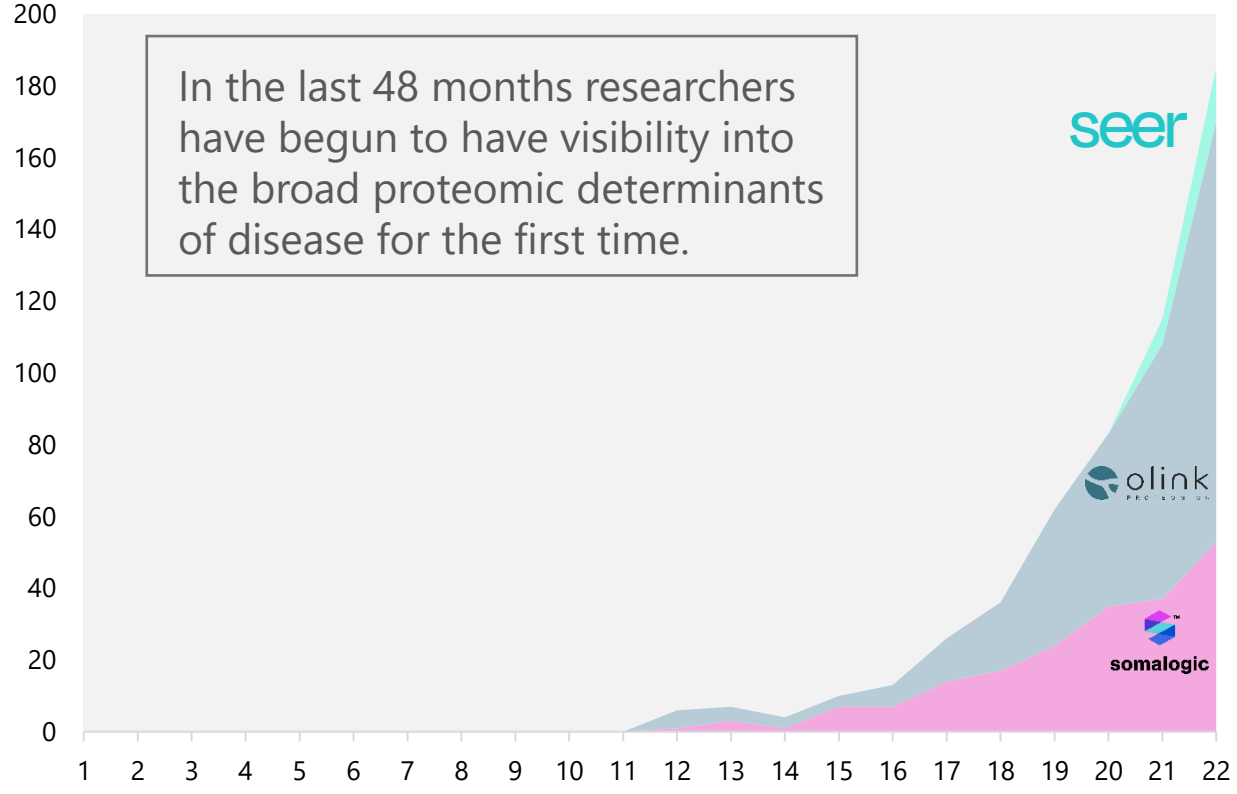
Source: Suhre K, McCarthy MI, Schwenk JM. Genetics meets proteomics: perspectives for large population-based studies. Nat Rev Genet. 2021 Jan;22(1):19-37.

Rapid Adoption of High Throughput Proteomic Research Platforms

The three new technologies identified at right allow scientists to measure thousands of proteins from small samples without great difficulty. These technologies have been in widespread use in the research context for less than a decade.

Activity has exploded. In the last five years the publication count using these technologies is up over 400%.

Number of Articles on Pubmed / Manufacturer Sites Mentioning Three Leading Large Scale Protein Detection Platforms



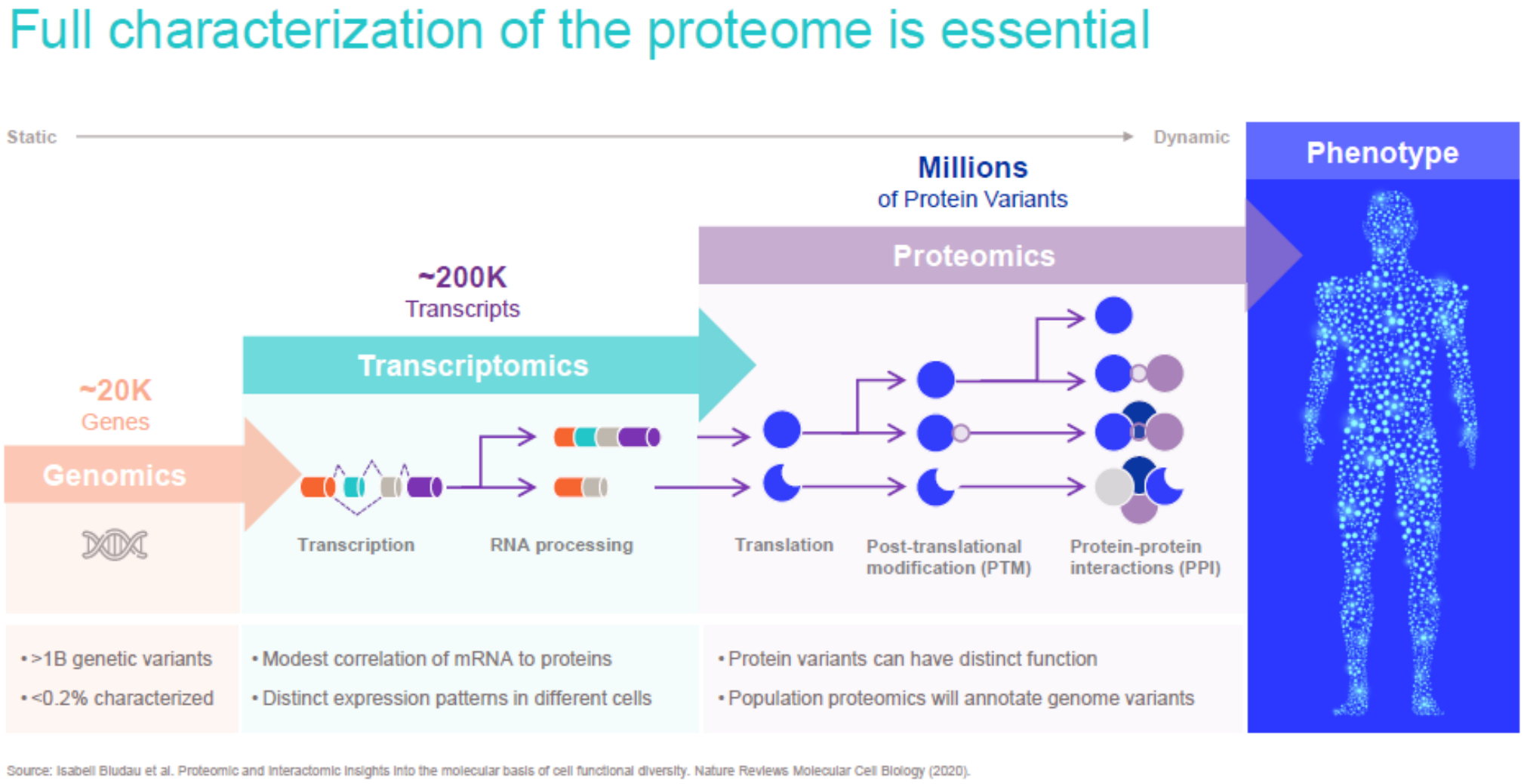
Proteomics Platform Comparison

Newer machines allow access to much more of the proteome than has been available from conventional machines from groups like Beckman. Newer machines are costly on a per sample basis and designed for the research market.

	Beckman Coulter	Luminex	Millipore Sigma	olink Proteomics	Quanterix	seer	somalogic
Technology	Electro-chemiluminescence	Multiplex ELISA	ELISA	Proximity Extension Assay on Illumina Sequencer	SIMOA	Nanoparticles on mass spectrometer	Aptamer binding and fluorescence
Key Strength	Mature technology. Widely available	Mature technology. Easy to make beads.	Highly accurate quantitative assays	Large number of proteins can be interrogated	Can detect proteins with low concentration well	Can find any known protein. Unbiased.	Most mature high throughput platform
Key Weakness	Very limited set of proteins measurable	Many assays require validation. Cross reactivity.	Very expensive and laborious for multiplexing.	Many of their assays are not accurate. Not validated.	Fairly limited set of assays available today.	Most complex process of all platforms	Some of their assays are not accurate. Not validated.
Analytes / Sample	< 5 proteins	25 proteins	1 protein	3000+ proteins	5 proteins	10,000+ proteins	7,000+ proteins
Commercial Use Possible	Yes	Yes	Yes	Research Only (working on it)	Yes	Research Only	Research Only (working on it)
Cost / Sample*	$35	$50	$15	$750	$100	$1,250	$750

* Estimated based on discussions with industry participants and research reports.

The Proteome is Invaluable in Biology Research



Source: Seer investor presentation, Sep 2023 (https://investor.seer.bio/news-and-events/presentations)

We Are Just Beginning to Understand Relationship Between Protein Variations and Disease

Functional understanding of protein variants across the population is key

UK Biobank study highlights the unmet need to understand how variation affects function

Population (~455,000 individuals)

All protein genetic variants	8,868,971
Potential deleterious variants	6,345,457
Protein loss of function	915,289
Change protein structure/binding	> 3 million

Single individual (~20,000 genes)

Protein variants per participant	9,506
Potential deleterious variants	2,945
Protein loss of function	214
Alternative splice forms	95% of genes

We have a lot more work to do and we are only at the beginning.

Source: Backman, J.D. et al. Exome sequencing and analysis of 454,787 UK Biobank participants. Nature 599, 628–634 (2021).

seer

Source: Seer investor presentation, Sep 2023 (https://investor.seer.bio/news-and-events/presentations)

Proteomic Platforms Revolutionizing Epidemiology

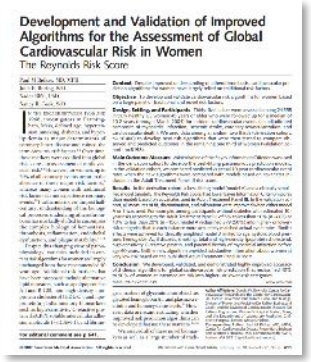
Less than 75 years ago we did not measure blood analytes in epidemiology. By 1959, Kannel and colleagues measured two analytes in Framingham. By 2019 it was 88 blood analytes. By 2021 it was 4,907 analytes in a 33,000+ person study to predict over 300 disease states. Somewhere around 2018 we surpassed the ability to quickly relate findings to known epidemiology. Today, with studies like DeCODE's, there is almost an unmanageable amount of post-study metadata. We are in a completely different world of epidemiology today.


BRITISH MEDICAL JOURNAL

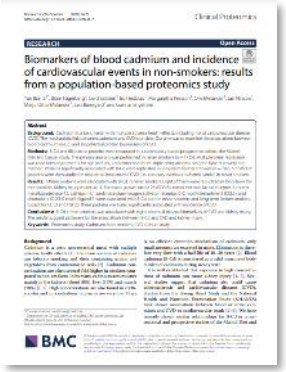
SMOKING AND CARCINOMA OF THE LUNG


SOME FACTORS ASSOCIATED WITH THE DEVELOPMENT OF CORONARY HEART DISEASE

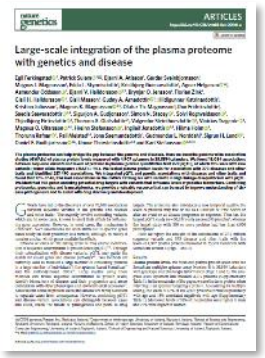
SIX YEARS' FOLLOW-UP EXPERIENCE IN THE FRAMINGHAM STUDY


Development and Validation of Improved Algorithms for the Assessment of Global Cardiovascular Risk in Women

The Reynolds Risk Score


Biomarkers of blood cadmium and incidence of cardiovascular events in non-smokers: results from a population-based proteomics study

BMC


ARTICLES

Large-scale integration of the plasma proteome with genetics and disease

1950

Doll and Hill show that lung cancer closely linked to smoking. No proteins used in the paper. Main dataset was based on interviews of over 1,000 people with cancer in London hospitals.

1959

Dawber, Kannel and colleagues identify several key variables which predict heart disease from the Framingham Study. A total of two blood analytes were included.No immuno-analyzers existed.

2007

Ridker, Cook and colleagues estimate the Reynolds Risk score to predict heart disease. They consider 35 factors among 24,558 initially healthy women. They had full access to ELISA's for immunoassays.

2018

Jennifer Ho and colleagues revisit Framingham but this time use 85 biomarkers in 3,523 persons. They used Luminex to do immuno-assays.

2019

Borne and colleagues use OLINK to measure 88 proteins in a study of 1725 individuals in the Malmo Heart study. The OLINK technology allowed significant expansion of the proteins considered.

2021

DeCODE publishes a paper which measures 4,907 proteins in 33,559 Icelanders across 300+ disease states. They did full DNA / protein association analysis facilitated by Somalogic.

In 70 years, we have seen epidemiology transformed by proteomic tools.

We went from interviews to ELISA and now Somalogic and OLINK.

Biogen Releases Proteomics Paper Last Week Using Olink and UK Biobank

Biogen scientists teamed up with colleagues at Cambridge University to interrogate UK Biobank data based on the Olink platform. They found that a ten variable protein model has excellent power to predict if a person will get Alzheimer's. This has obvious value in a world where Leqembi® is approved.

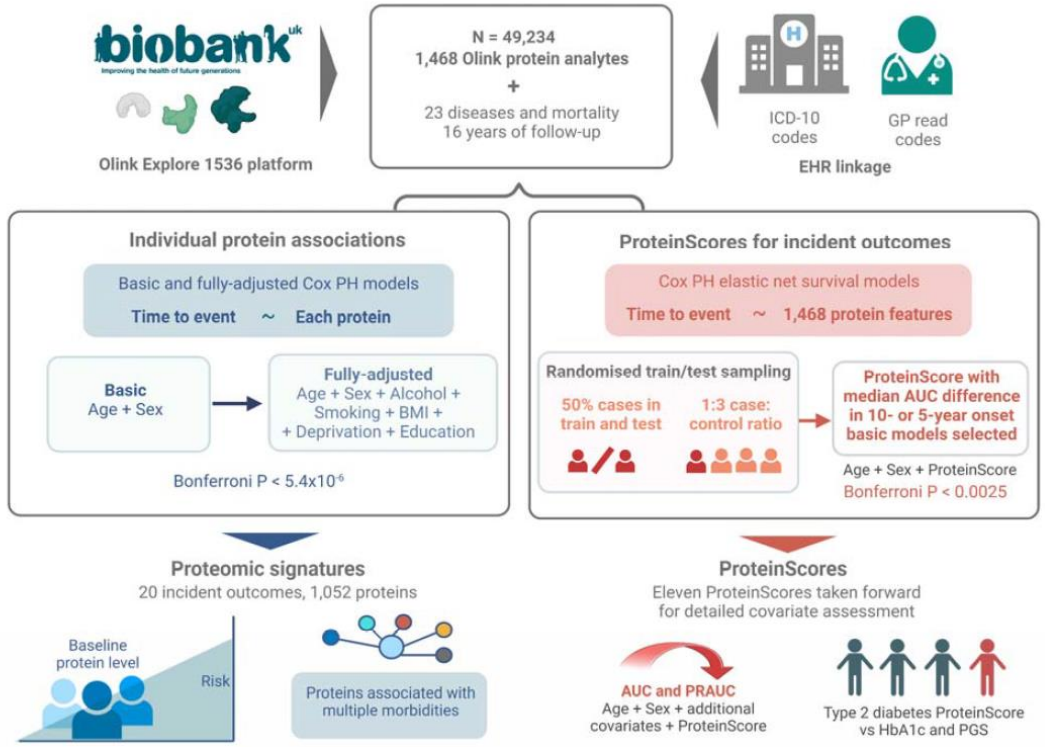


Figure 1. Proteomic assessment of 23 incident diseases and mortality in the UK Biobank (N=49,234). First, individual Cox proportional hazards (PH) models were used to profile relationships between baseline protein analytes and incident diseases or death. Associations that had PBonferroni < 5.4x10-6 in both basic and fully-adjusted models were retained. Proteins associated with multiple morbidities were identified. Next, proteomic predictors (ProteinScores) were trained using Cox PH elastic net regression for 20 of the time-to-event outcomes that had a minimum of 150 cases.

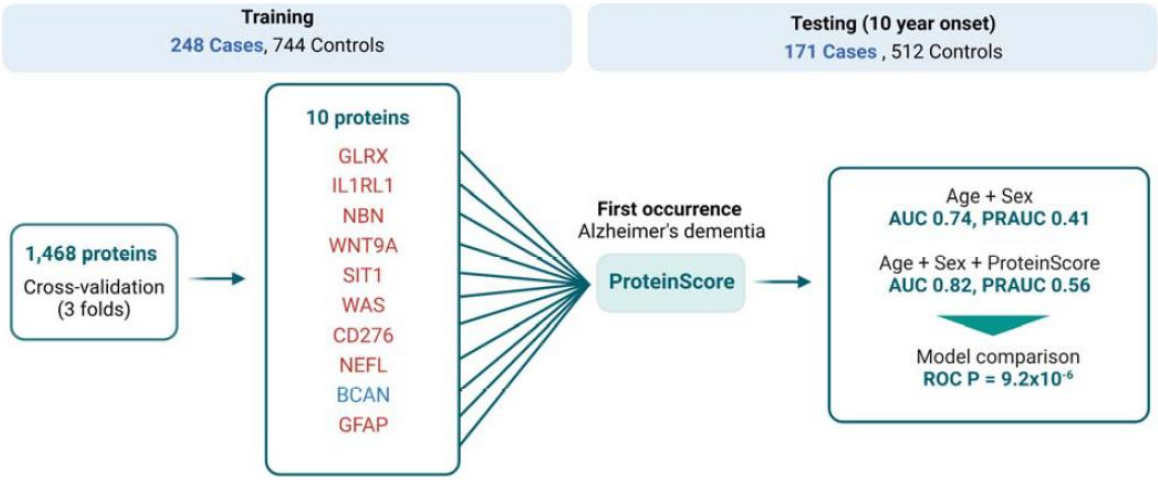
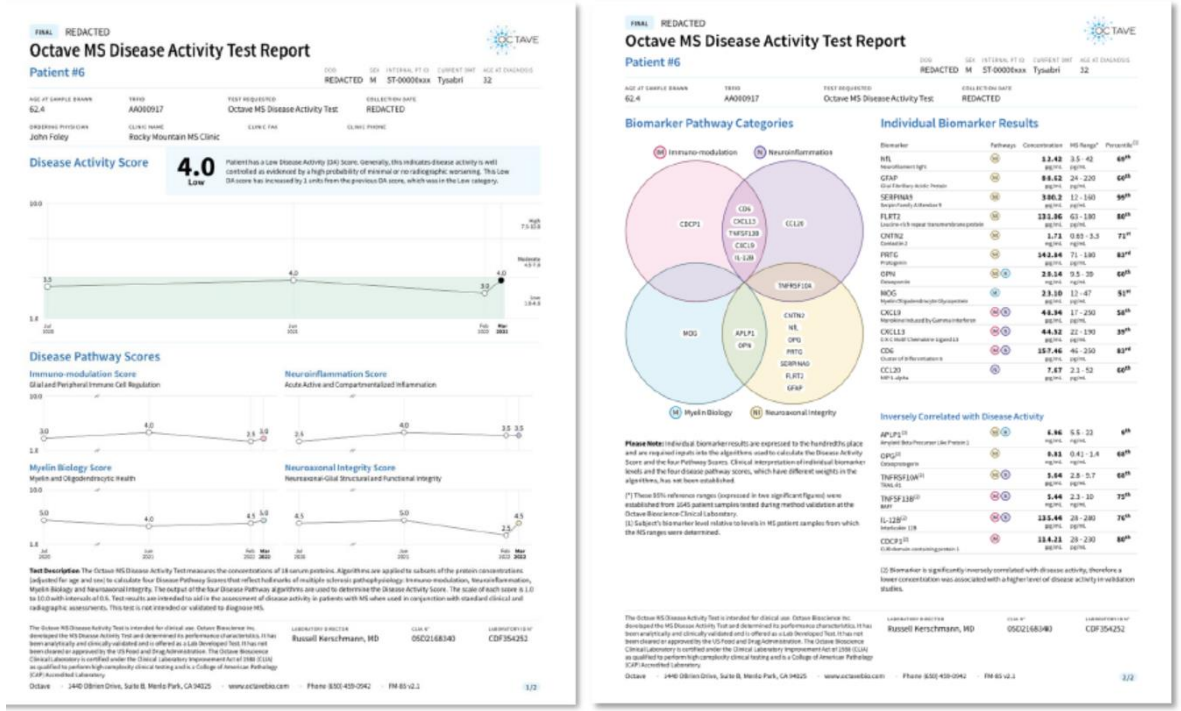


Figure 3. Example of feature selection and basic model evaluation for the Alzheimer's dementia ProteinScore. Of the 1,468 proteins considered, ten were selected and assigned weighting coefficients (positive = red, negative = blue) via Cox PH elastic net regression with 3-fold cross-validation (Ncases < 500) in the training sample. Weighting coefficients from this step were used to derive the ProteinScore in the test set. A model comparison between 10-year first occurrence of Alzheimer's dementia in the test sample with and without the ProteinScore yielded ROC P = 9.2x10-6, beyond adjustments for age and sex.

Source: https://www.medrxiv.org/content/10.1101/2023.05.01.23288879v2

Octave Bio: Uses Serum Proteomics from Olink to Describe Operative Pathways in Multiple Sclerosis and Then Impute Responsiveness to Drug Treatment

Figure 4: Octave MSDA Patient Report



Octave MS Disease Activity Test Report

Patient #6

Disease Activity Score 4.0 Low

Disease Pathway Scores

Immuno-modulation Score

Neuroinflammation Score

Myelin Biology Score

Neuroaxonal Integrity Score

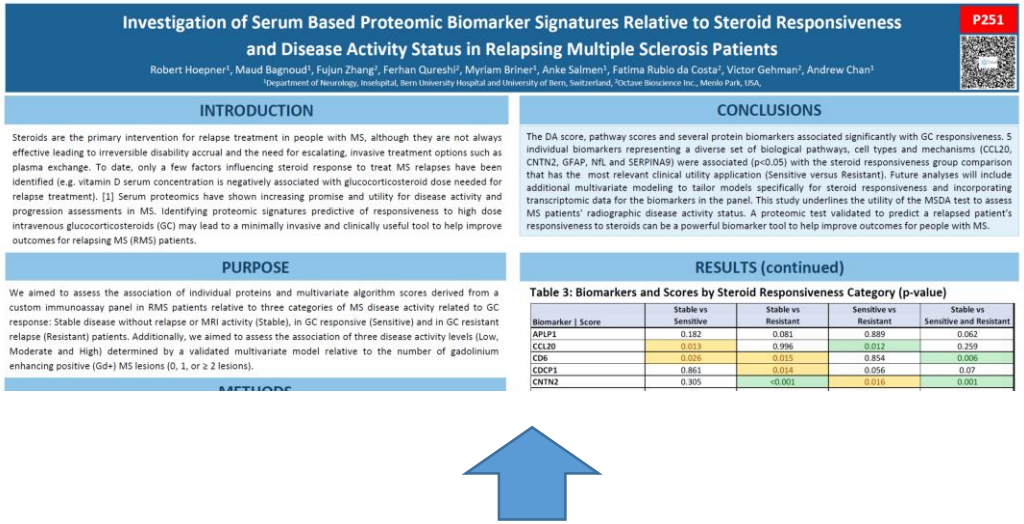
Octave MS Disease Activity Test Report

Patient #6

Biomarker Pathway Categories

Individual Biomarker Results

Inversely Correlated with Disease Activity



Investigation of Serum Based Proteomic Biomarker Signatures Relative to Steroid Responsiveness and Disease Activity Status in Relapsing Multiple Sclerosis Patients

P251

INTRODUCTION

Steroids are the primary intervention for relapse treatment in people with MS, although they are not always effective leading to irreversible disability accrual and the need for escalating, invasive treatment options such as plasma exchange. To date, only a few factors influencing steroid response to treat MS relapses have been identified (e.g. vitamin D serum concentration is negatively associated with glucocorticosteroid dose needed for relapse treatment). [1] Serum proteomics have shown increasing promise and utility for disease activity and progression assessments in MS. Identifying proteomic signatures predictive of responsiveness to high dose intravenous glucocorticosteroids (GC) may lead to a minimally invasive and clinically useful tool to help improve outcomes for relapsing MS (RMS) patients.

PURPOSE

We aimed to assess the association of individual proteins and multivariate algorithm scores derived from a custom immunoassay panel in RMS patients relative to three categories of MS disease activity related to GC response: Stable disease without relapse or MRI activity (Stable), in GC responsive (Sensitive) and in GC resistant relapse (Resistant) patients. Additionally, we aimed to assess the association of three disease activity levels (Low, Moderate and High) determined by a validated multivariate model relative to the number of gadolinium enhancing positive (Gd+) MS lesions (0, 1, or ≥ 2 lesions).

CONCLUSIONS

The DA score, pathway scores and several protein biomarkers associated significantly with GC responsiveness. 5 individual biomarkers representing a diverse set of biological pathways, cell types and mechanisms (CCL20, CNTN2, GFAP, NfL and SERPINA9) were associated ($p<0.05$) with the steroid responsiveness group comparison that has the most relevant clinical utility application (Sensitive versus Resistant). Future analyses will include additional multivariate modeling to tailor models specifically for steroid responsiveness and incorporating transcriptomic data for the biomarkers in the panel. This study underlines the utility of the MSDA test to assess MS patients' radiographic disease activity status. A proteomic test validated to predict a relapsed patient's responsiveness to steroids can be a powerful biomarker tool to help improve outcomes for people with MS.

RESULTS (continued)

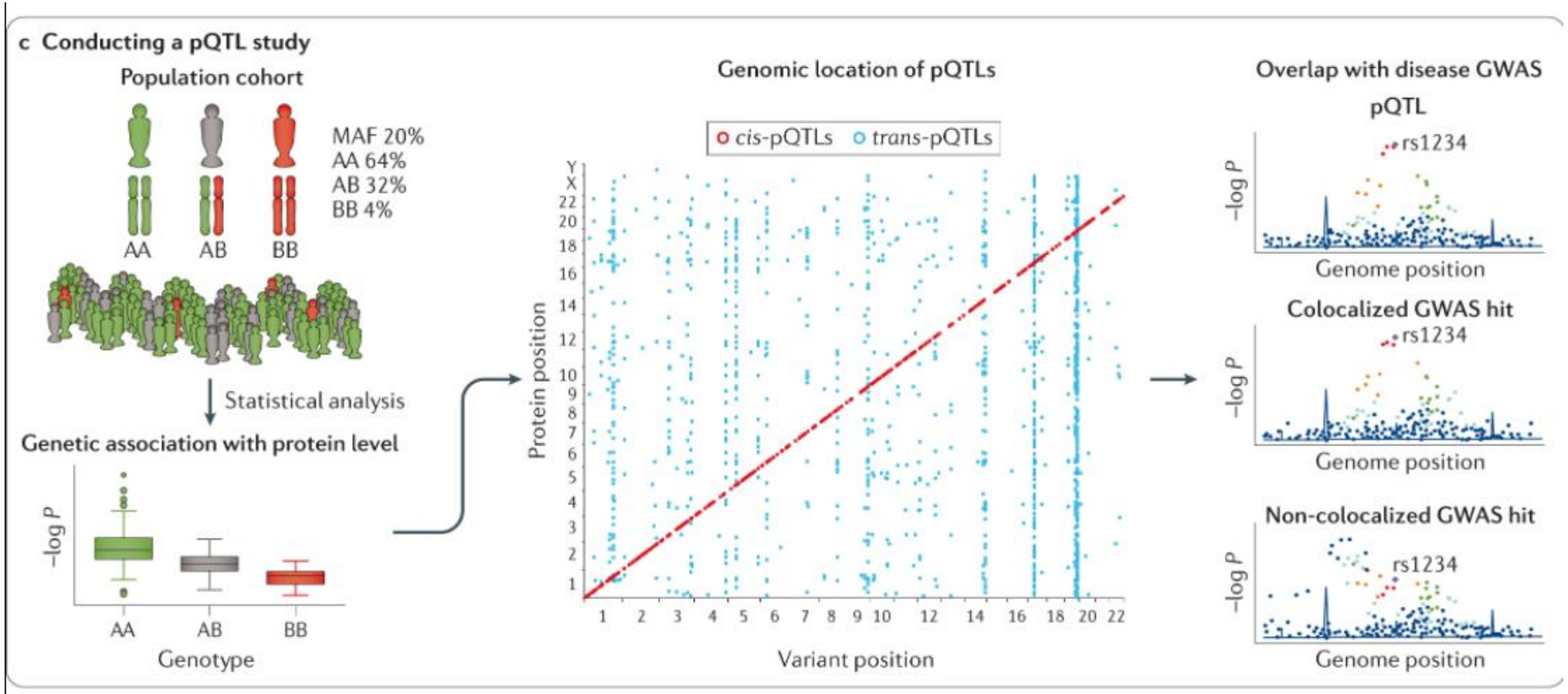
Table 3: Biomarkers and Scores by Steroid Responsiveness Category (p-value)

Biomarker | Score	Stable vs Sensitive	Stable vs Resistant	Sensitive vs Resistant	Stable vs Sensitive and Resistant
APLP1	0.182	0.081	0.889	0.062
CCL20	0.013	0.996	0.012	0.259
CD6	0.026	0.015	0.854	0.006
CDCP1	0.861	0.014	0.056	0.07
CNTN2	0.305	<0.001	0.016	0.001

Steroids are, by far, the least expensive option to treat MS. Octave is able to use biomarkers to provide physicians with information on which patients will respond to steroids.

Source: https://www.octavebio.com/our-science/

Genetic Polymorphisms Can be Associated with Proteins. A Statistically Significant Association in a Large Sample is Termed a pQTL (Protein Quantitative Trait Loci)



Source: Suhre K, McCarthy MI, Schwenk JM. Genetics meets proteomics: perspectives for large population-based studies. Nat Rev Genet. 2021 Jan;22(1):19-37.

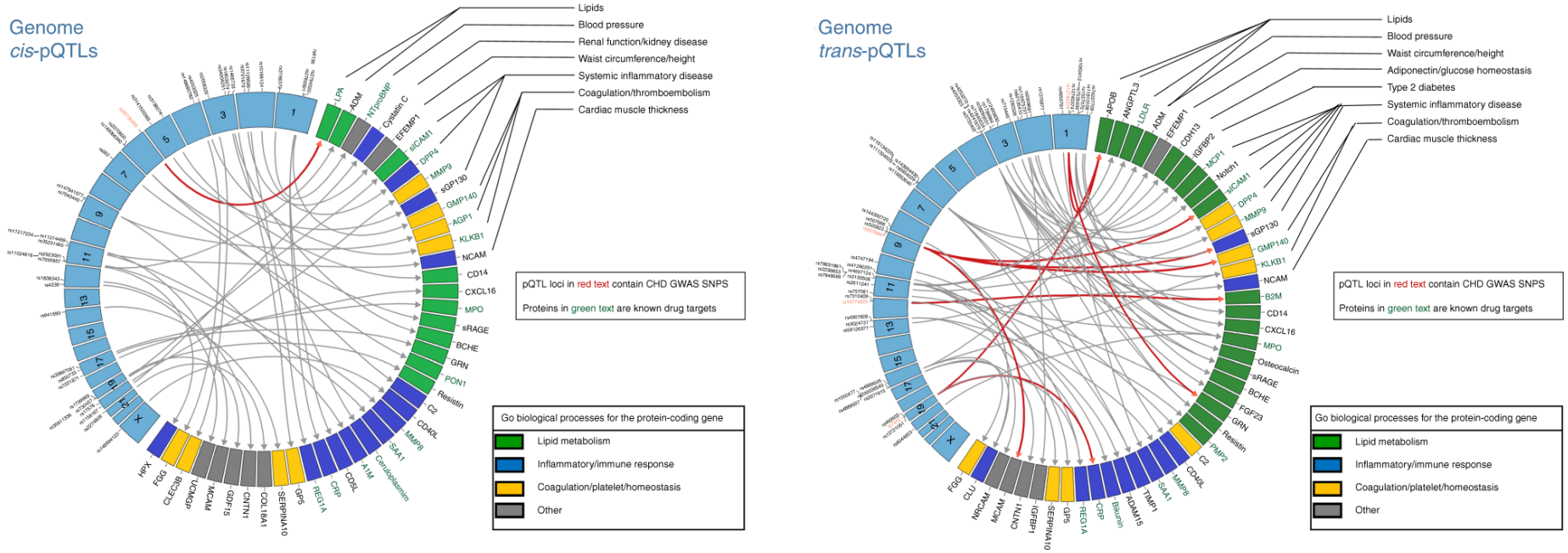
It's Possible to Go From the Study of pQTLs to Identification of Disease-Causing Genes and Pathways

Yao C, Chen G, Song C, Keefe J, Mendelson M, Huan T, Sun BB, Laser A, Maranville JC, Wu H, Ho JE, Courchesne P, Lyass A, Larson MG, Gieger C, Graumann J, Johnson AD, Danesh J, Runz H, Hwang SJ, Liu C, Butterworth AS, Suhre K, Levy D. Genome-wide mapping of plasma protein QTLs identifies putatively causal genes and pathways for cardiovascular disease. *Nat Commun*. 2018 Aug 15;9(1):3268.

"Identifying genetic variants associated with circulating protein concentrations (protein quantitative trait loci; pQTLs) and integrating them with variants from genome-wide association studies (GWAS) may illuminate the proteome's causal role in disease and bridge a knowledge gap regarding SNP-disease associations. We provide the results of GWAS of 71 high-value cardiovascular disease proteins in 6861 Framingham Heart Study participants and independent external replication. We report the mapping of over 16,000 pQTL variants and their functional relevance. We provide an integrated plasma protein-QTL database. Thirteen proteins harbor pQTL variants that match coronary disease-risk variants from GWAS or test causal for coronary disease by Mendelian randomization. Eight of these proteins predict new-onset cardiovascular disease events in Framingham participants. We demonstrate that identifying pQTLs, integrating them with GWAS results, employing Mendelian randomization, and prospectively testing protein-trait associations holds potential for elucidating causal genes, proteins, and pathways for cardiovascular disease and may identify targets for its prevention and treatment."

Source: https://www.nature.com/articles/s41467-018-05512-x

Illustration From Cardio Disease Study that Shows How pQTL Variants Link to Specific Proteins and Disease

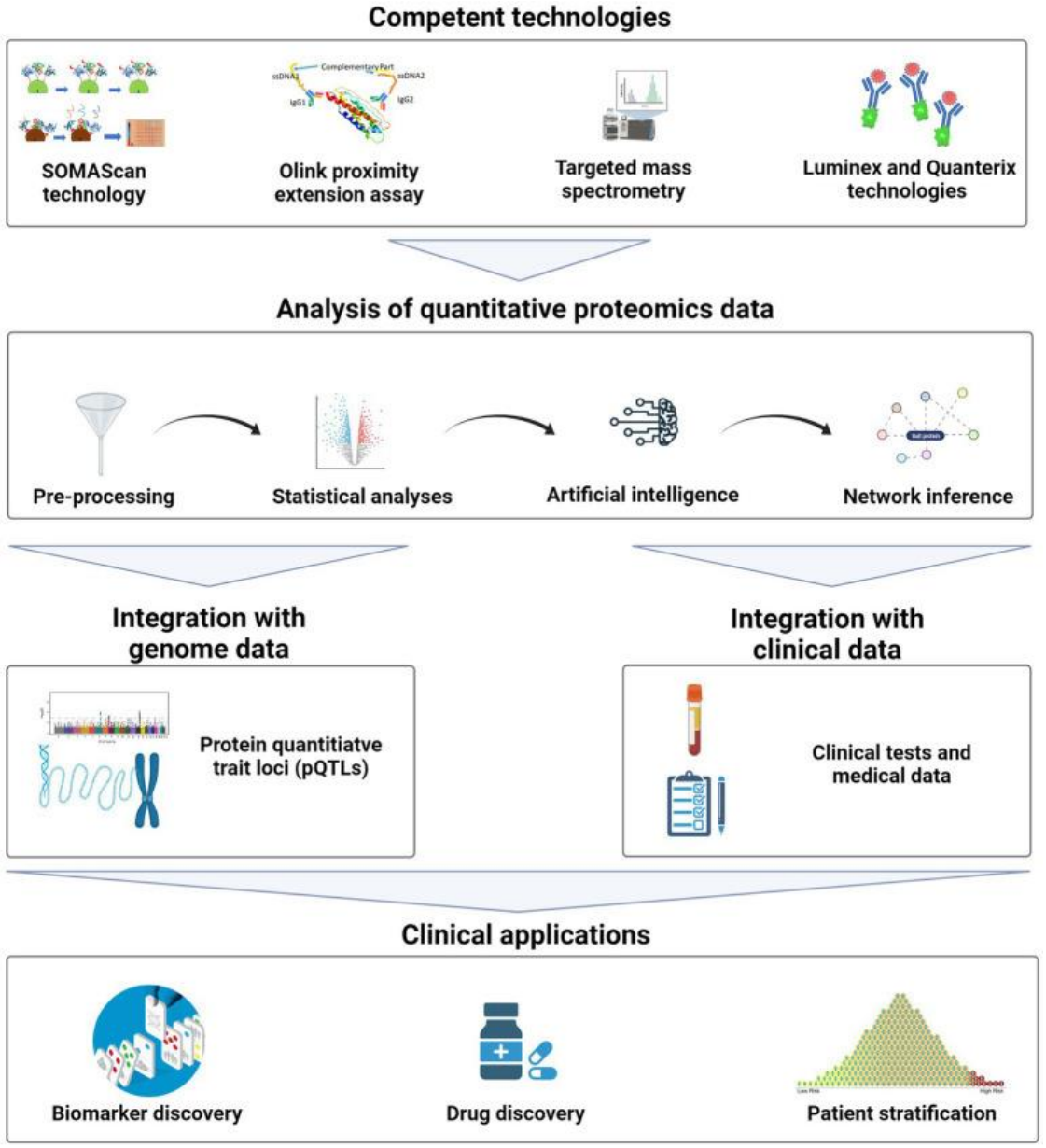


Sentinel *cis*- and *trans*-pQTLs and their associated proteins. Circos plots of sentinel *cis*- (left panel) and *trans*-pQTL variants (right panel). Sentinel pQTL variants are listed in order of chromosomal locations (blue boxes in the left semicircle). pQTL variants previously identified in GWAS to be associated with CHD appear in red text. Proteins with genome-wide significant pQTLs are listed in the right semicircle. The following two conditions are summarized for each protein: (1) The corresponding protein-coding gene is a known drug target (green text). (2) GO biological processes for the protein-coding gene (green box denotes lipid metabolism pathways, blue box denotes inflammatory/immune response pathways, yellow box denotes coagulation/platelet/hemostasis pathways, and gray box denotes other pathways not included in the three most common, previously listed pathways). A single primary GO process was chosen when the protein-coding gene was included in multiple pathways. *CHD* coronary heart disease, *GO* Gene Ontology, *GWAS* genome-wide association study, *pQTL* protein quantitative trait locus, *SNP* single-nucleotide polymorphism

Source: Yao C, Chen G, Song C, Keefe J, Mendelson M, Huan T, Sun BB, Laser A, Maranville JC, Wu H, Ho JE, Courchesne P, Lyass A, Larson MG, Gieger C, Graumann J, Johnson AD, Danesh J, Runz H, Hwang SJ, Liu C, Butterworth AS, Suhre K, Levy D. Genome-wide mapping of plasma protein QTLs identifies putatively causal genes and pathways for cardiovascular disease. *Nat Commun.* 2018 Aug 15;9(1):3268. doi: 10.1038/s41467-018-05512-x.

Typical Workflow Used to Integrate Proteomic Data with Genetic and Phenotype Data for Insights

General workflow for quantitative proteomics. The figure describes the different types of targeted technologies, and the common methodologies to analyse quantitative proteomics data. These analyses potentially provide clinical applications in biomarker and drug discovery and patient stratification.



Source: Correa Rojo A, Heylen D, Aerts J, Thas O, Hooyberghs J, Ertaylan G, Valkenborg D. Towards Building a Quantitative Proteomics Toolbox in Precision Medicine: A Mini-Review. *Front Physiol.* 2021 Aug 26;12:723510.

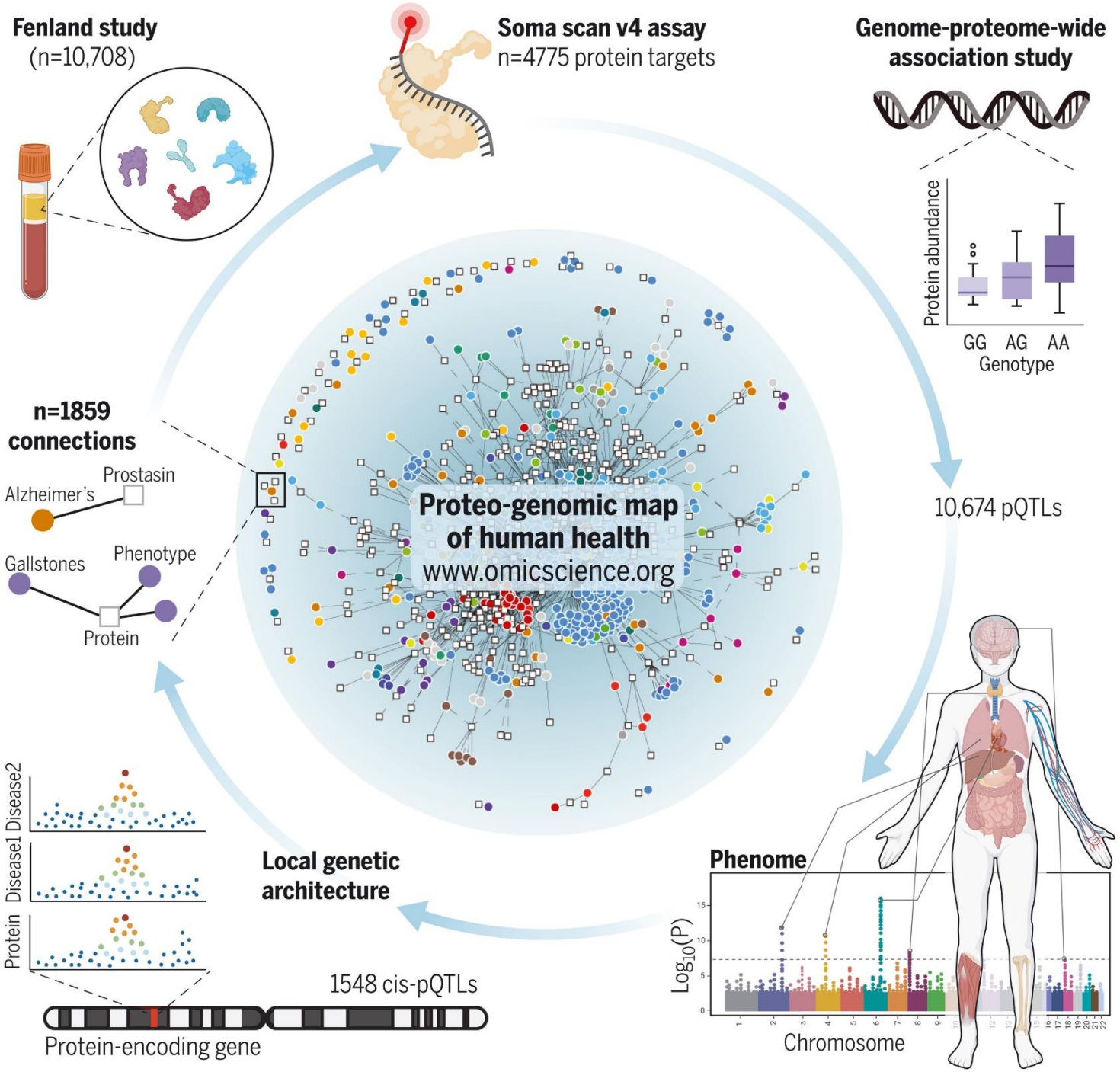
What is Happening Now:

High Throughput Studies of pQTL's, Proteins and Phenotype (Pietzner Paper)

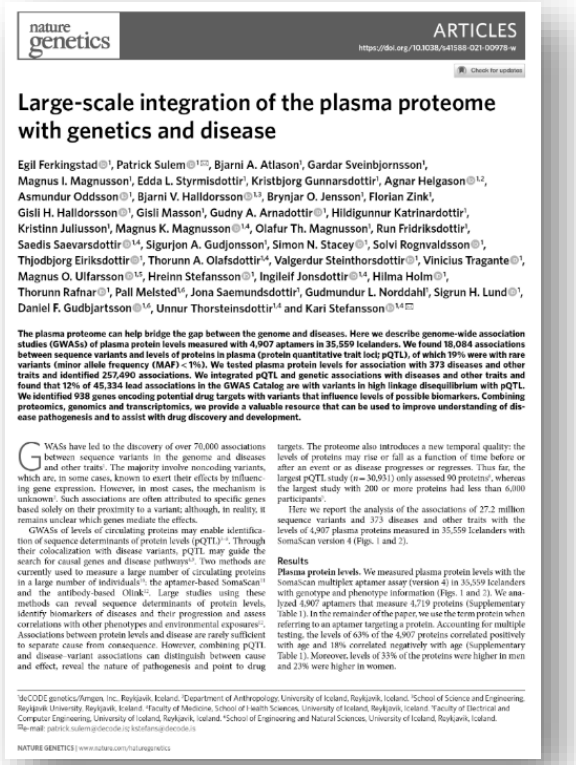
"Many diseases are at least partially due to genetic causes that are not always understood or targetable with specific treatments. To provide insight into the biology of various human diseases as well as potential leads for therapeutic development, Pietzner *et al*. undertook detailed, genome-wide proteogenomic mapping. The authors analyzed thousands of connections between potential disease-associated mutations, specific proteins, and medical conditions, thereby providing a detailed map for use by future researchers.

They also supplied some examples in which they applied their approach to medical contexts as varied as connective tissue disorders, gallstones, and COVID-19 infections, sometimes even identifying single genes that play roles in multiple clinical scenarios."

Source: Pietzner M, Wheeler E, Carrasco-Zanini J, Cortes A, Koprulu M, Wörheide MA, Oerton E, Cook J, Stewart ID, Kerrison ND, Luan J, Raffler J, Arnold M, Arlt W, O'Rahilly S, Kastenmüller G, Gamazon ER, Hingorani AD, Scott RA, Wareham NJ, Langenberg C. Mapping the proteo-genomic convergence of human diseases. Science. 2021 Nov 12;374(6569):eabj1541. doi: 10.1126/science.abj1541. Epub 2021 Nov 12



deCODE Paper: A Blood Draw Can Give a Very Good Read of the Presence of Prevalent Disease and Causes



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Check for updates

Large-scale integration of the plasma proteome with genetics and disease

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The plasma proteome can help bridge the gap between the genome and diseases. Here we describe genome-wide association studies (GWASs) of plasma protein levels measured with 4,907 aptamers in 35,559 Icelanders. We found 18,084 associations between sequence variants and levels of proteins in plasma (protein quantitative trait loci; pQTL), of which 19% were with rare variants (minor allele frequency (MAF) < 1%). We tested plasma protein levels for association with 373 diseases and other traits and identified 257,490 associations. We integrated pQTL and genetic associations with diseases and other traits and found that 12% of 45,334 lead associations in the GWAS Catalog are with variants in high linkage disequilibrium with pQTL. We identified 938 genes encoding potential drug targets with variants that influence levels of possible biomarkers. Combining proteomics, genomics and transcriptomics, we provide a valuable resource that can be used to improve understanding of disease pathogenesis and to assist with drug discovery and development.

GWASs have led to the discovery of over 70,000 associations between sequence variants in the genome and diseases and other traits[1]. The majority involve noncoding variants, which are, in some cases, known to exert their effects by influencing gene expression. However, in most cases, the mechanism is unknown[2]. Such associations are often attributed to specific genes based solely on their proximity to a variant; although, in reality, it remains unclear which genes mediate the effects.

GWASs of levels of circulating proteins may enable identification of sequence determinants of protein levels (pQTL)[3–9]. Through their colocalization with disease variants, pQTL may guide the search for causal genes and disease pathways[10]. Two methods are currently used to measure a large number of circulating proteins in a large number of individuals[11]: the aptamer-based SomaScan[12] and the antibody-based Olink[13]. Large studies using these methods can reveal sequence determinants of protein levels, identify biomarkers of diseases and their progression and assess correlations with other phenotypes and environmental exposures[14]. Associations between protein levels and disease are rarely sufficient to separate cause from consequence. However, combining pQTL and disease–variant associations can distinguish between cause and effect, reveal the nature of pathogenesis and point to drug targets. The proteome also introduces a new temporal quality: the levels of proteins may rise or fall as a function of time before or after an event or as disease progresses or regresses. Thus far, the largest pQTL study ($n = 30,931$) only assessed 90 proteins[9], whereas the largest study with 200 or more proteins had less than 6,000 participants[3].

Here we report the analysis of the associations of 27.2 million sequence variants and 373 diseases and other traits with the levels of 4,907 plasma proteins measured in 35,559 Icelanders with SomaScan version 4 (Figs. 1 and 2).

Results

Plasma protein levels. We measured plasma protein levels with the SomaScan multiplex aptamer assay (version 4) in 35,559 Icelanders with genotype and phenotype information (Figs. 1 and 2). We analyzed 4,907 aptamers that measure 4,719 proteins (Supplementary Table 1). In the remainder of the paper, we use the term protein when referring to an aptamer targeting a protein. Accounting for multiple testing, the levels of 63% of the 4,907 proteins correlated positively with age and 18% correlated negatively with age (Supplementary Table 1). Moreover, levels of 33% of the proteins were higher in men and 23% were higher in women.

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- In a Dec 2021 paper, researchers at deCODE studied associations between nearly 5000 proteins, underlying genetics and over 100 prevalent diseases.
- They found that protein expression levels can usually discriminate well between those with and without prevalent disease.
- In many cases, they showed that disease associations were attributable to underlying genetic polymorphisms using pQTL analysis.
- That is, many associational pathways are also causative and can, in theory, be druggable.
- Many of the proteins proxy for underlying pathologies including cellular stress, extracellular matrix formation and inflammation.

Source: https://pubmed.ncbi.nlm.nih.gov/34857953/

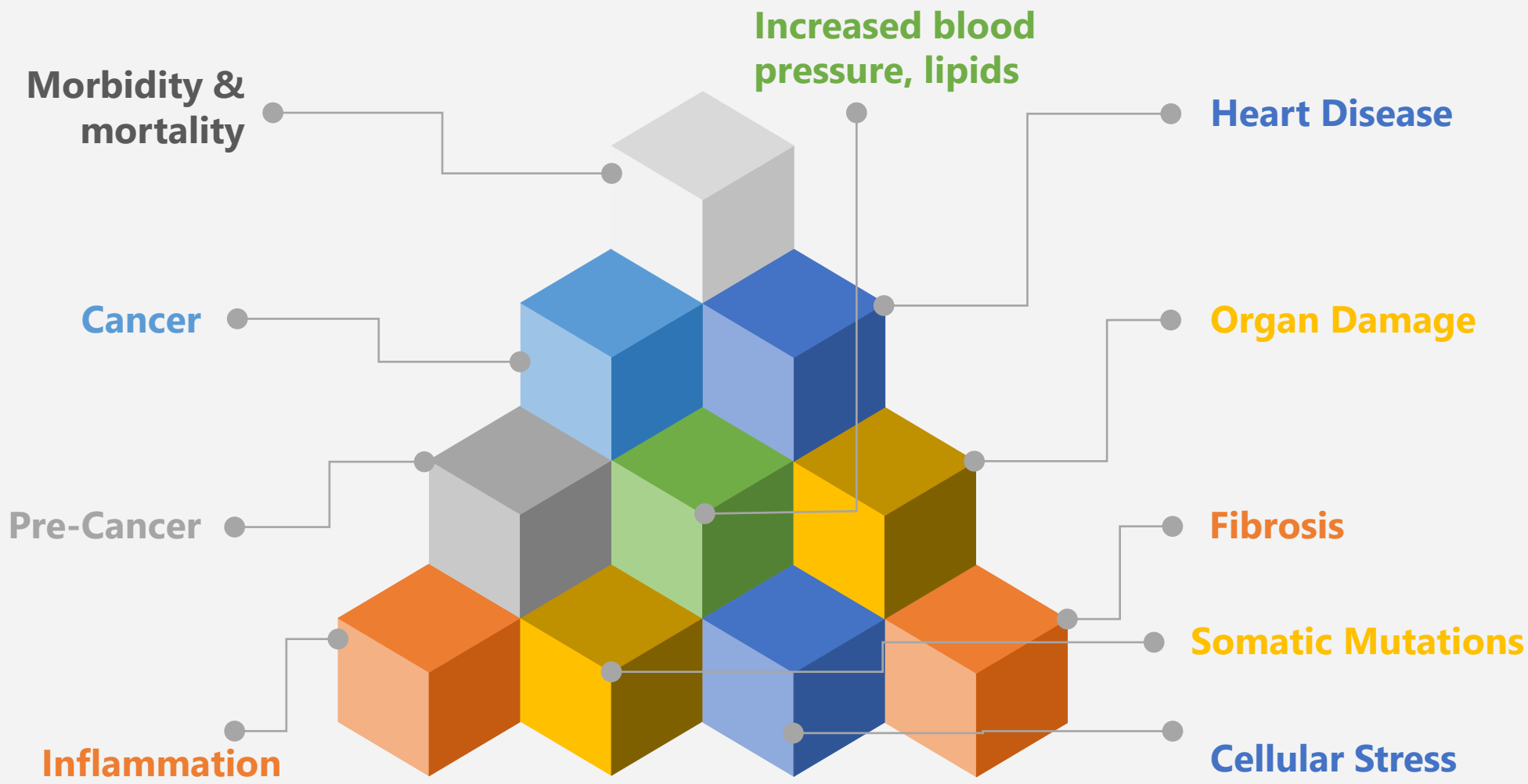
Disease Typically Starts with Subclinical Pathologies

Traditional medicine spends little time analyzing the underlying causes of disease including inflammation, cellular stress, fibrosis and somatic mutation. A key insight from the deCODE Dec 2021 paper is that most disease causes are subclinical involving areas such as extracellular matrix, inflammation, cellular stress, the IGF1 system and the like.

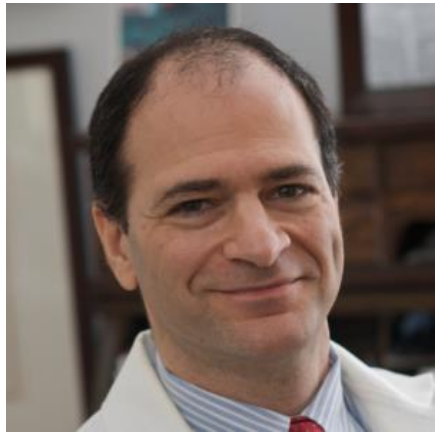
Consequences

Overt disease
Mid-stage phenotypic disease

Underlying Causes of Overt Disease
Subclinical disease



Working Through pQTL Findings in deCODE Study (or Related Studies) a Daunting Task



Paul Ridker
Director of the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston

Ridker PM. Proteomics for the prediction and prevention of atherosclerotic disease. Eur Heart J. 2022 Apr 19;43(16):1578-1581.

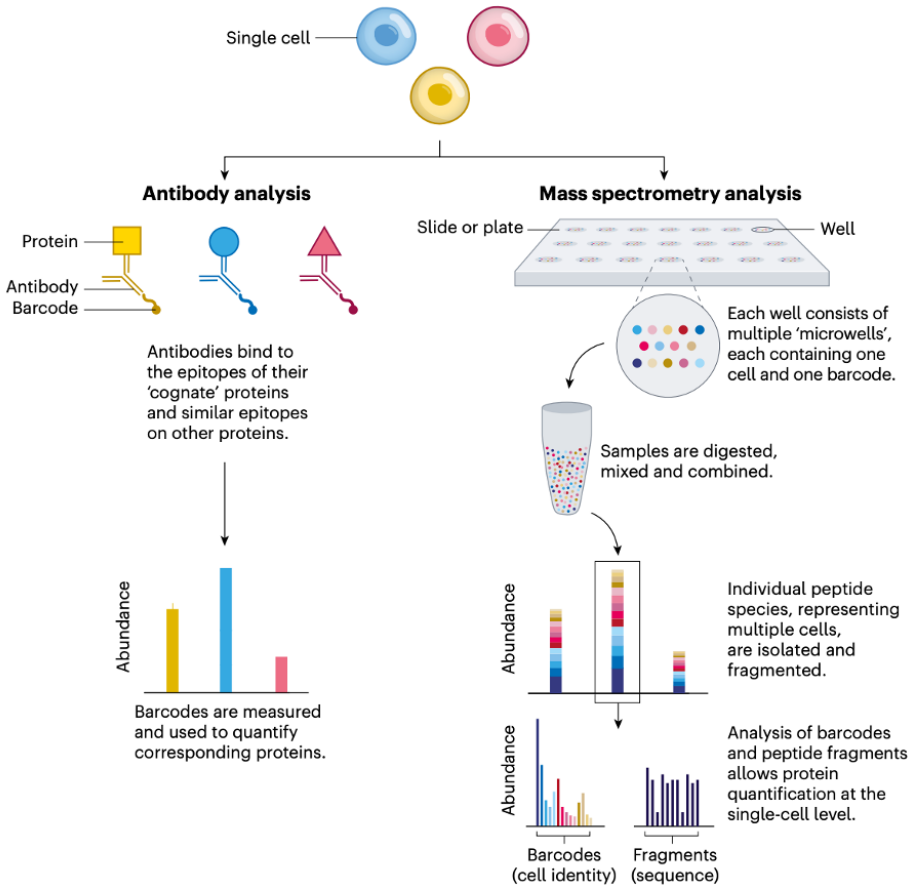
"Despite considerable bioinformatic advances, clinical translation will be slow simply due to the diversity of protein effects with potential pathological relevance. In a recent genomic and proteomic evaluation of 71 selected proteins among 6861 participants in the Framingham Heart Study, 13 proteins were considered likely to be causal, eight of which were found that predicted new-onset cardiovascular disease.14 In a comparable assessment of genomic and proteomic data inclusive of 90 proteins in 30,000 individuals, 11 new proteins with causal evidence of involvement in disease are described that have not been previously targeted.

Once investigators move beyond a single disorder such as atherosclerotic disease, the multiplicity issue becomes exponentially more complicated. In perhaps the largest study to date of its type, a current publication from deCODE Genetics evaluated 4907 aptamers in 35 559 Icelanders and identified 250 000 associations across 373 disease states. The daunting task of working through this emerging novel biology is further underscored by recognition that only a fraction of the proteins secreted by human cells (the 'secretome') are captured in evaluations of blood and other body fluids, whereas a large number of potentially crucial proteins are retained intracellularly.

We thus are at the end of the beginning for proteomic science as it relates to atherosclerotic and related metabolic disorders. The critical questions moving forward are many, with profound implications for cardiovascular medicine. How do environmental interactions and behaviours such as diet, nutrition, exercise, and smoking work at the protein level to initiate and promote atherosclerosis? What crucial intracellular and secreted proteins can be exploited both as biomarkers and as targets for therapy? And ultimately, how will proteomics and downstream metabolomics address future intervention strategies of primordial, primary, and secondary prevention?"

Source: https://pubmed.ncbi.nlm.nih.gov/35165698/

A Key Recent Technology is the Ability to Conduct Proteomic Analysis at the Single-Cell Level



At a single-cell level, there are two main approaches available for analyzing the proteome. These are antibody-based methods and mass spectrometry-based methods. Flow cytometry is a traditional method for measuring proteins in a single cell suspension and commonly uses fluorescent-tagged antibodies that bind to the protein of interest on the surface of cells.

Mass cytometry is an advancement of flow cytometry, which also combines elemental mass spectrometry.

Mass spectrometry provides a sensitive, nontargeted, method for the analysis of the whole proteome by identifying molecules based on their mass-to-charge ration (m/z). Typically, mass spectrometry methods are optimized for bulk analysis of cells.

Source: https://www.nature.com/articles/d41586-021-02530-6

Can Take Proteomic, Genomic and Transcriptomic Single Cell Data and Create a Spatial Map of What's Going in to Glean Biology Insights

Single-cell analysis enters the multiomics age

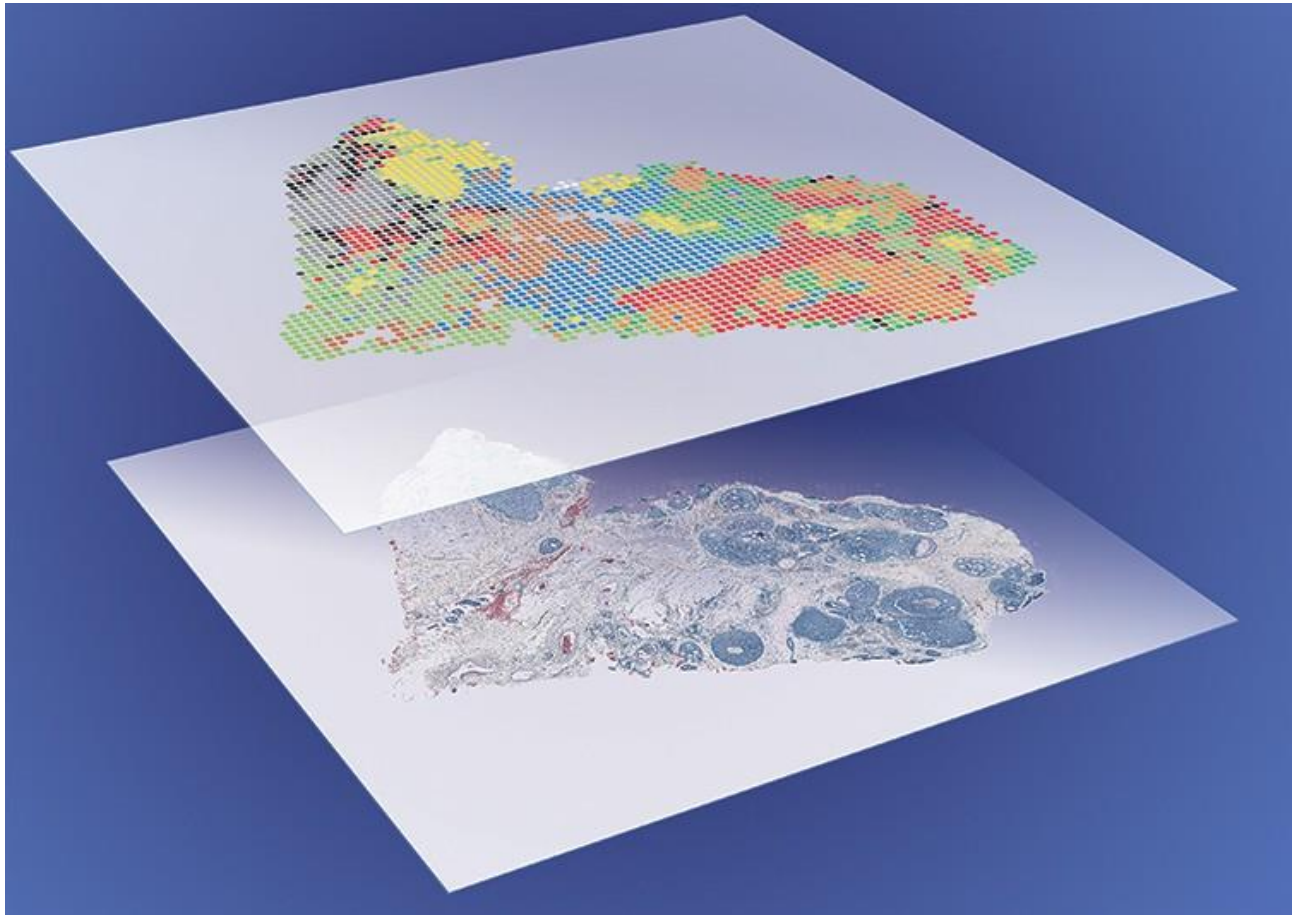
A rapidly growing collection of software tools is helping researchers to analyse multiple huge '-omics' data sets.

Jeffrey Perkel, *Nature*, July 19, 2021

"The past decade has witnessed an explosion in single-cell genomics. Single-cell RNA sequencing (RNA-seq), which profiles gene expression, is the most common technique. Other methods detail processes such as methylation, genetic variation, protein abundance and chromatin accessibility.

Now, researchers are increasingly combining these methods — and the resulting layers of data — in 'multiomics' experiments. Argelaguet, for instance, combined gene-expression profiling, methylation and chromatin accessibility in a technique called scNMT-seq. Another technique, CITE-seq, profiles both transcription and protein abundance. And G&T-seq captures both genomic DNA and RNA.

Whatever the acronym, all these techniques aim to glean complex biological insights that might be undetectable using any single method. But the task is computationally challenging, and making sense of the resulting data even more so. A fast-growing suite of software tools can help."



Illustrative Multi-omic Spatial Analysis Using 10X Genomics Technology

Source: https://www.nature.com/articles/d41586-021-01994-w

Disclosure

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