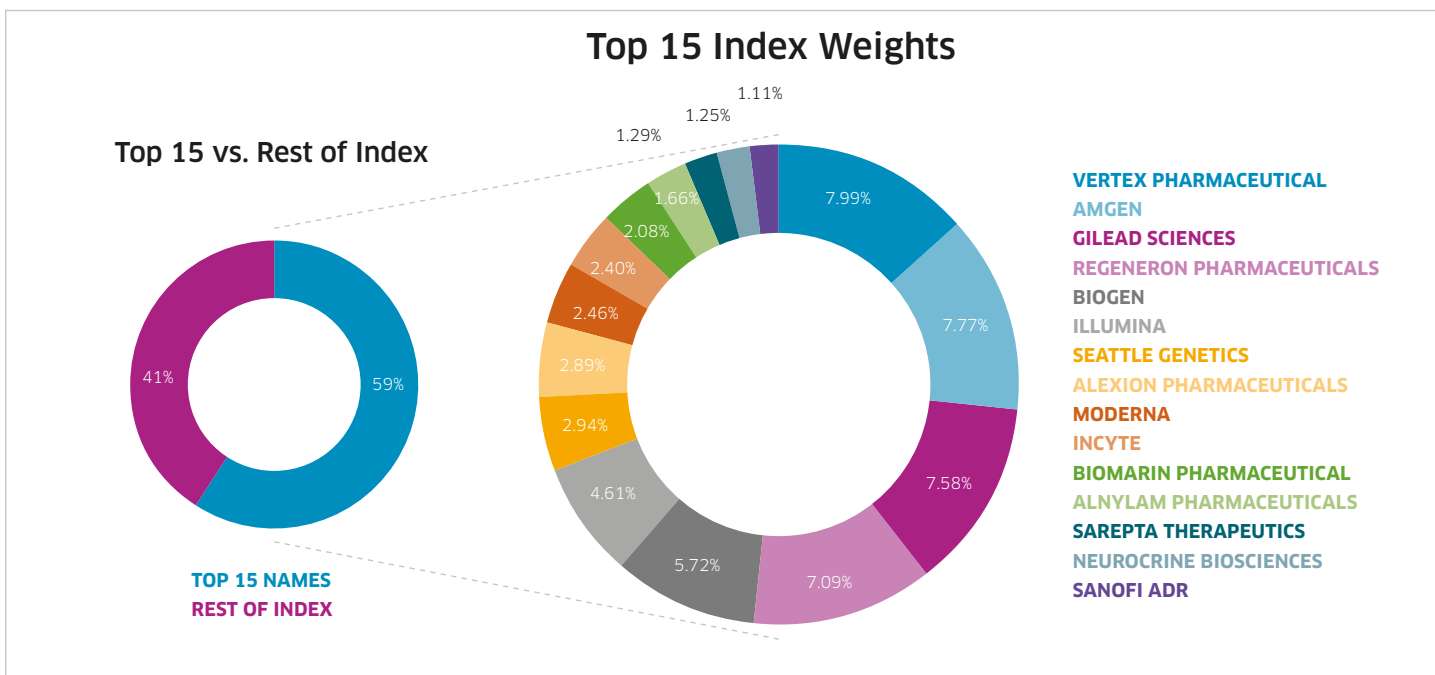


Biotech in the Age of Coronavirus

Mark Marex, Product Development Specialist

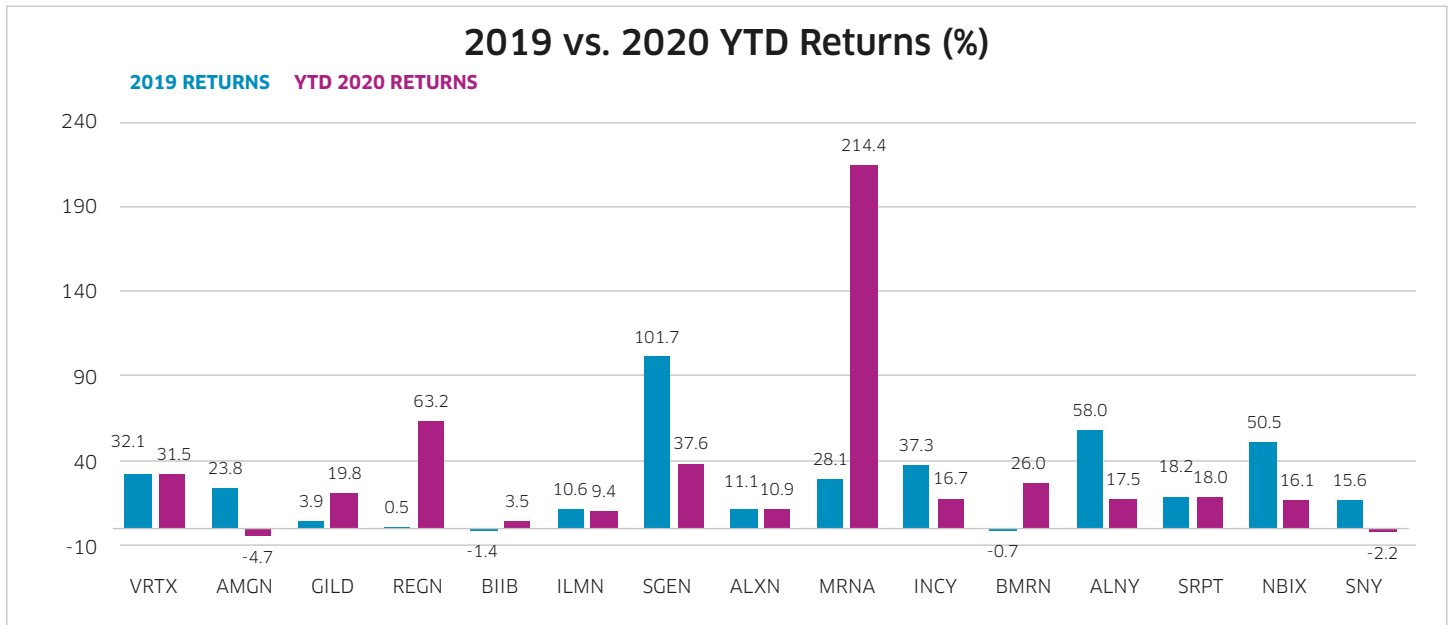
The Nasdaq Biotechnology Index (NBI) was launched on November 1, 1993, when the industry was still in the midst of the original “biotech revolution” ushered in by the discovery of recombinant DNA technology and Genentech’s IPO in 1980. The index zoomed almost 700% up to its peak in March of 2000, only to experience a dramatic fall along with the rest of the Internet-led equity bubble and a lost decade of subzero returns. NBI bounced back strongly during the 2010s, increasing 370% on a total return basis, trailing the Nasdaq-100 Index (426% TR) by only a few percentage points per year on average. Its constituent basket has swelled to over 200 components, with the following constraints: minimum market capitalization of \$200MM; average daily trading volume of at least 100,000 shares; classified as Biotechnology & Pharmaceuticals by ICB (Industry Classification Benchmark); and Nasdaq-listed. The index is modified market capitalization-weighted such that constituents are capped at 8% (for the top 5) and at 4% (for the remaining) at each quarterly index rebalance; the entire index is reviewed and reconstituted annually in December. Let’s examine how NBI has performed in the recent past and what its components look like today, followed by a consideration of the drivers of future performance – all in the context of the Coronavirus pandemic.

Current Composition



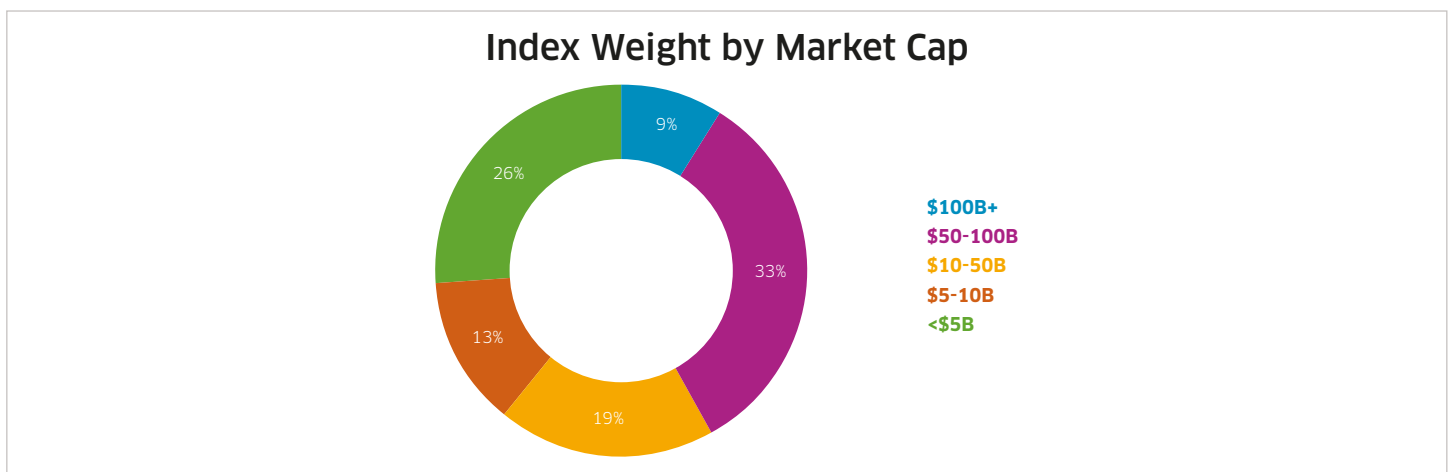
(As of May 29, 2020)

Of the 209 constituents in NBI, the top 15 represented 59% of the index weight as of the end of May 2020. The top 30 names represented approximately 71%, while the top 5 represented 36%. The latest of these was Vertex Pharmaceutical (VRTX), with a market cap of \$75bn, followed closely by Amgen (AMGN/\$135bn), Gilead Sciences (GILD/\$98bn), and Regeneron Pharmaceuticals (REGN/\$69bn). Most in the top 15 have seen positive YTD returns in the context of the Coronavirus pandemic, with an average YTD return of nearly 32%. Only Amgen (AMGN) and Sanofi (SNY) have registered negative YTD returns thus far, while the clear standout has been Moderna (MRNA, up over 200%) thanks to its leading efforts in developing a novel type of vaccine for COVID-19. Meanwhile, Gilead has made numerous headlines as its previously developed antiviral therapeutic – Remdesivir – has been repurposed to fight Covid-19 with modestly encouraging success; Regeneron, on the other hand, is developing an antibody-based therapeutic that will see clinical trials throughout the summer and hopefully approved for use sometime in the fall.



(As of May 29, 2020)

In terms of market capitalization for the overall group, the average was \$5.8bn, while the weighted average was \$40.9bn. The median was only \$1.4bn, however. This is reflective of the substantial representation of smaller stocks in the index, with 171 components under \$5bn of market cap comprising 26% of the index weight. 87 of these constituents measured at less than \$1bn.¹

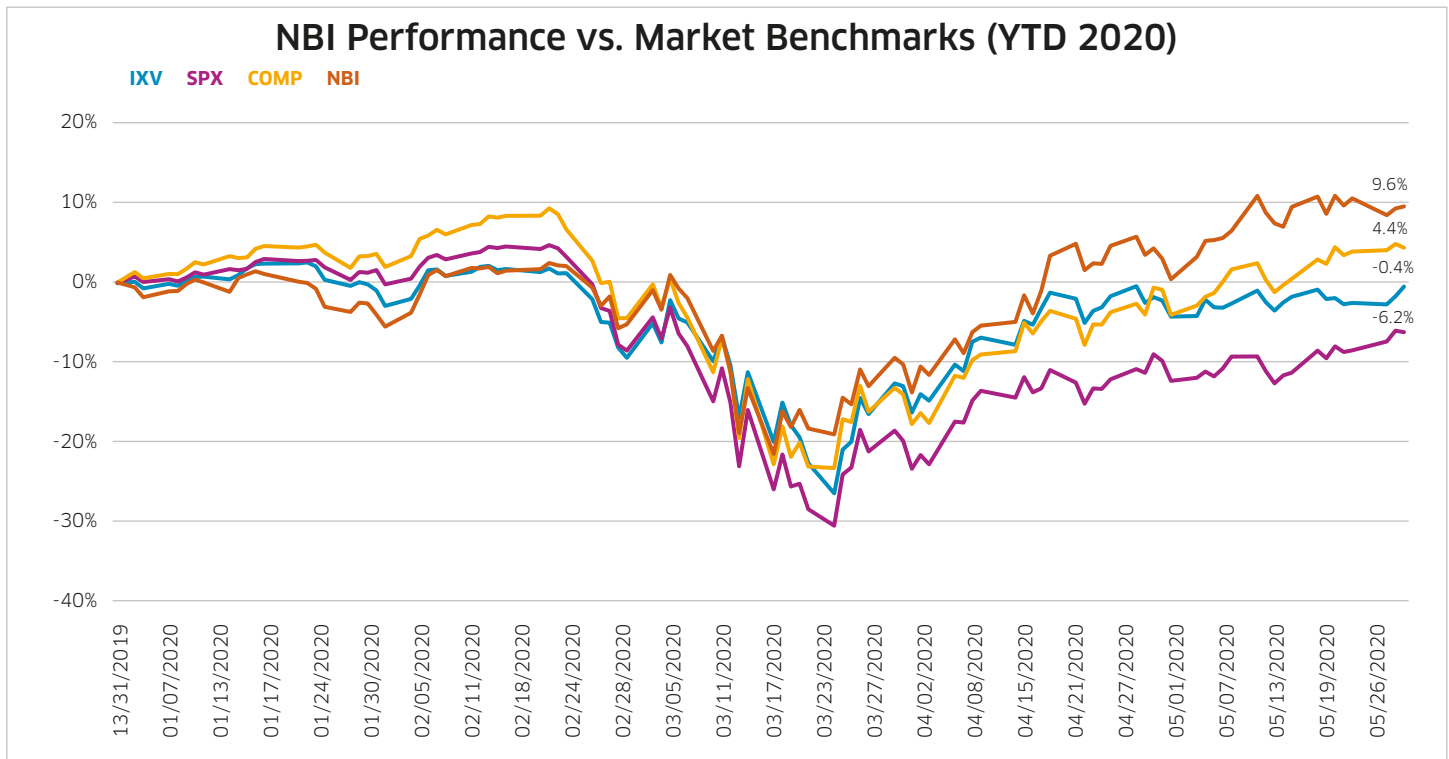


(As of May 29, 2020)

1. This market cap dynamic is what led Nasdaq to launch the Nasdaq Junior Biotechnology Index (NBIJR) on April 30, 2020. NBIJR utilizes the same rules and process as the Nasdaq Biotechnology Index, but with a max market capitalization of \$5bn as of the reference date.

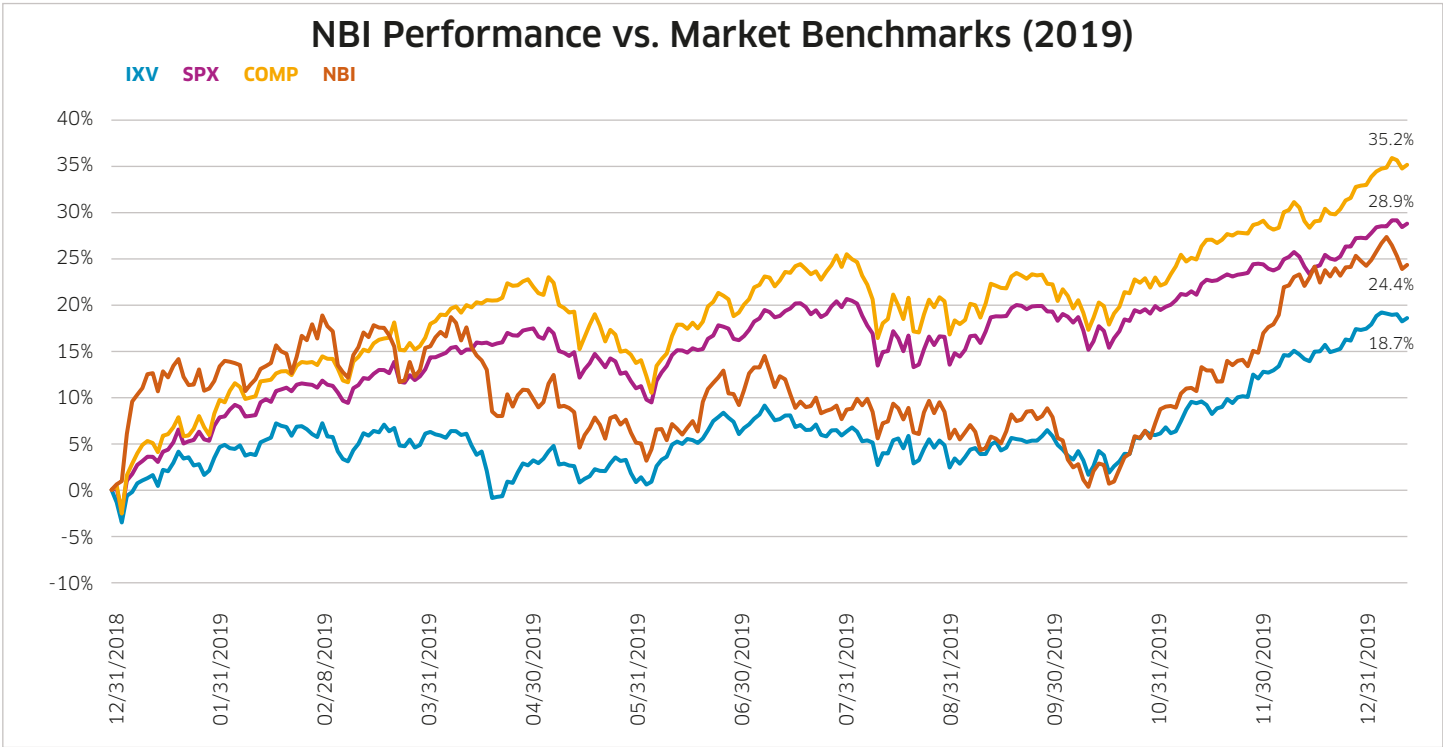
Recent Performance

NBI has been a relative outperformer in 2020 thus far, as one might expect given an abundance of healthcare-driven macroeconomic developments. It has not only meaningfully outperformed the Nasdaq Composite (COMP) and dominated the S&P 500 (SPX), but has also substantially outpaced the S&P Health Care Select Sector Index (IXV), which struggled to reach positive territory even following the powerful market rally from late March through the end of May. With only marginally positive YTD returns when the broader market peaked on February 19, NBI has proceeded to outperform during both the subsequent bear market period and the sharp recovery, accelerating ahead of IXV in mid-April and again in early May.



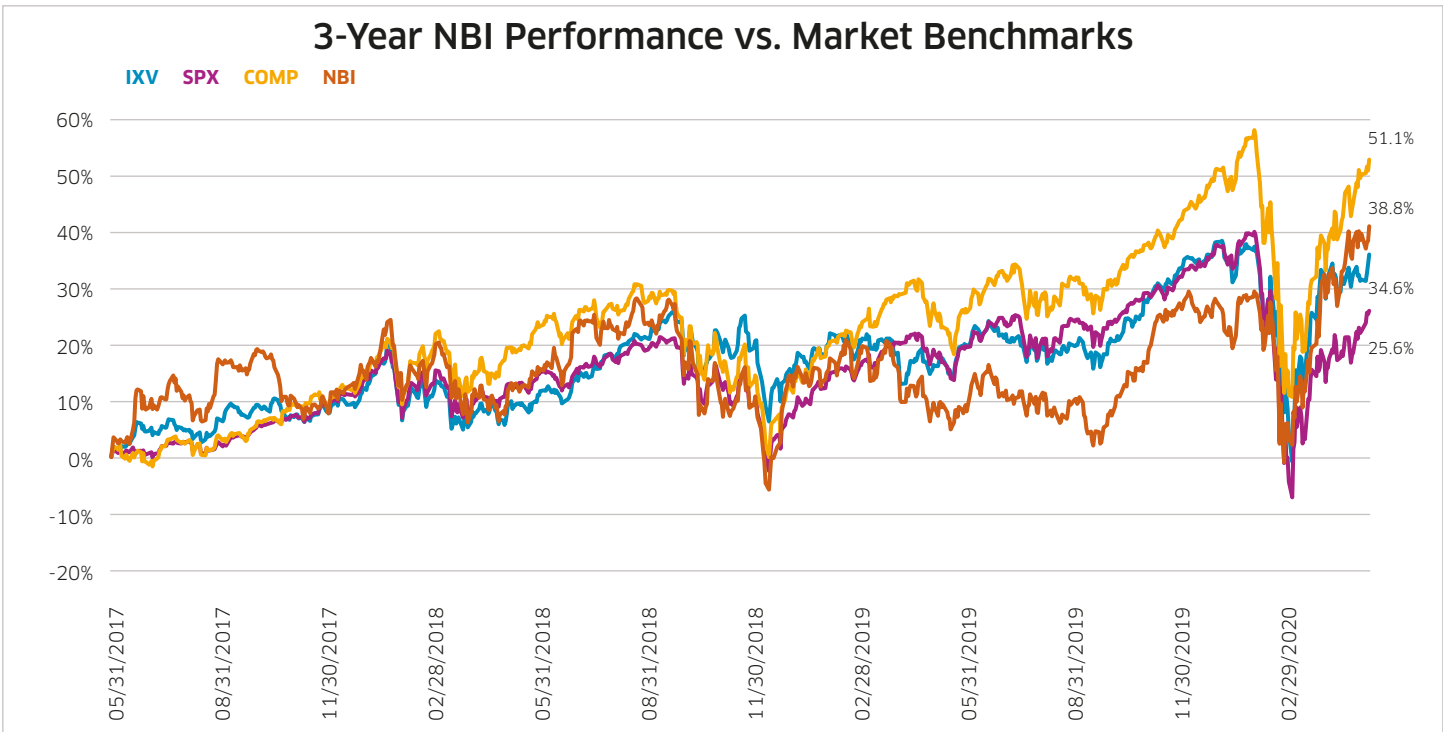
(Data through May 29, 2020)

In 2019, NBI also meaningfully outperformed IXV, while failing to keep pace with an exceptional year of performance for both the broader S&P 500 and the Nasdaq Composite.



(Data through May 29, 2020)

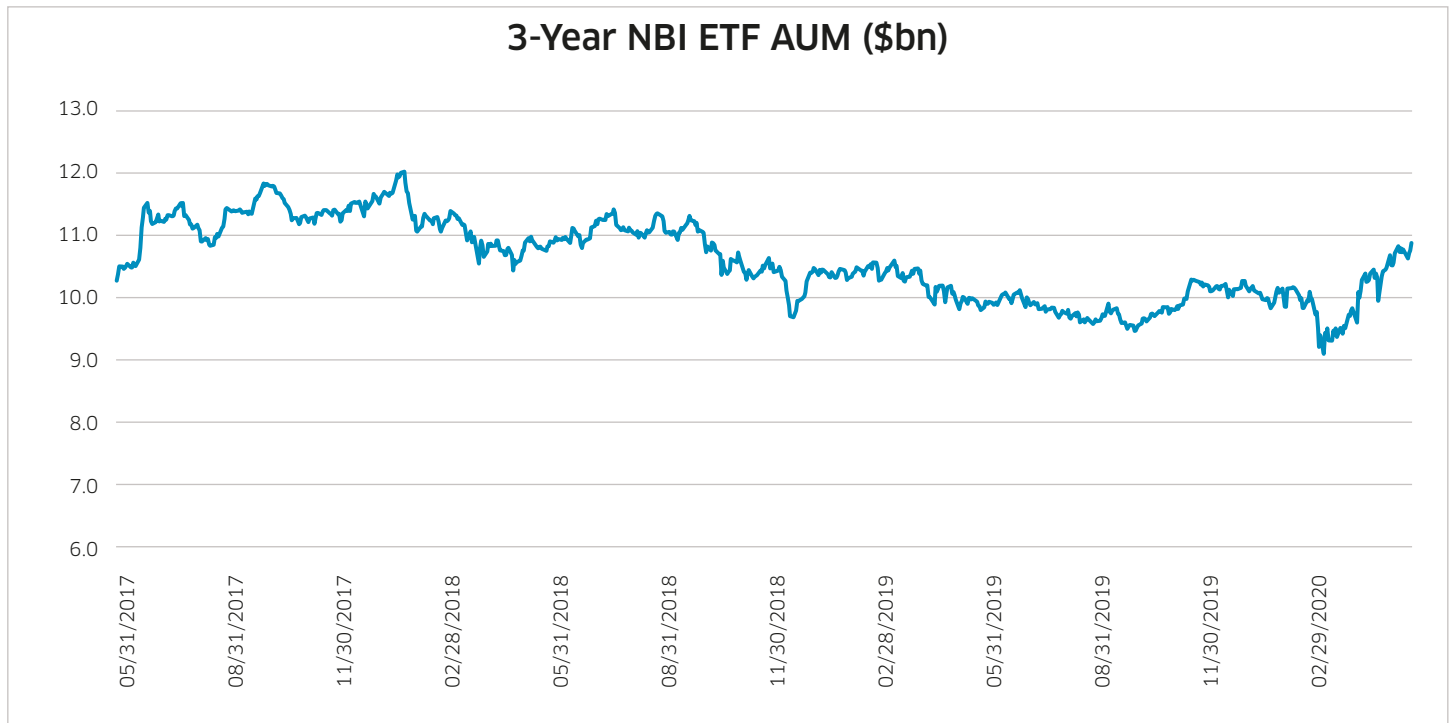
On a trailing three-year basis, NBI has outperformed both SPX and IXV, while the Nasdaq Composite has endured as the clear outperformer.



(Data through May 29, 2020)

NBI ETP Assets

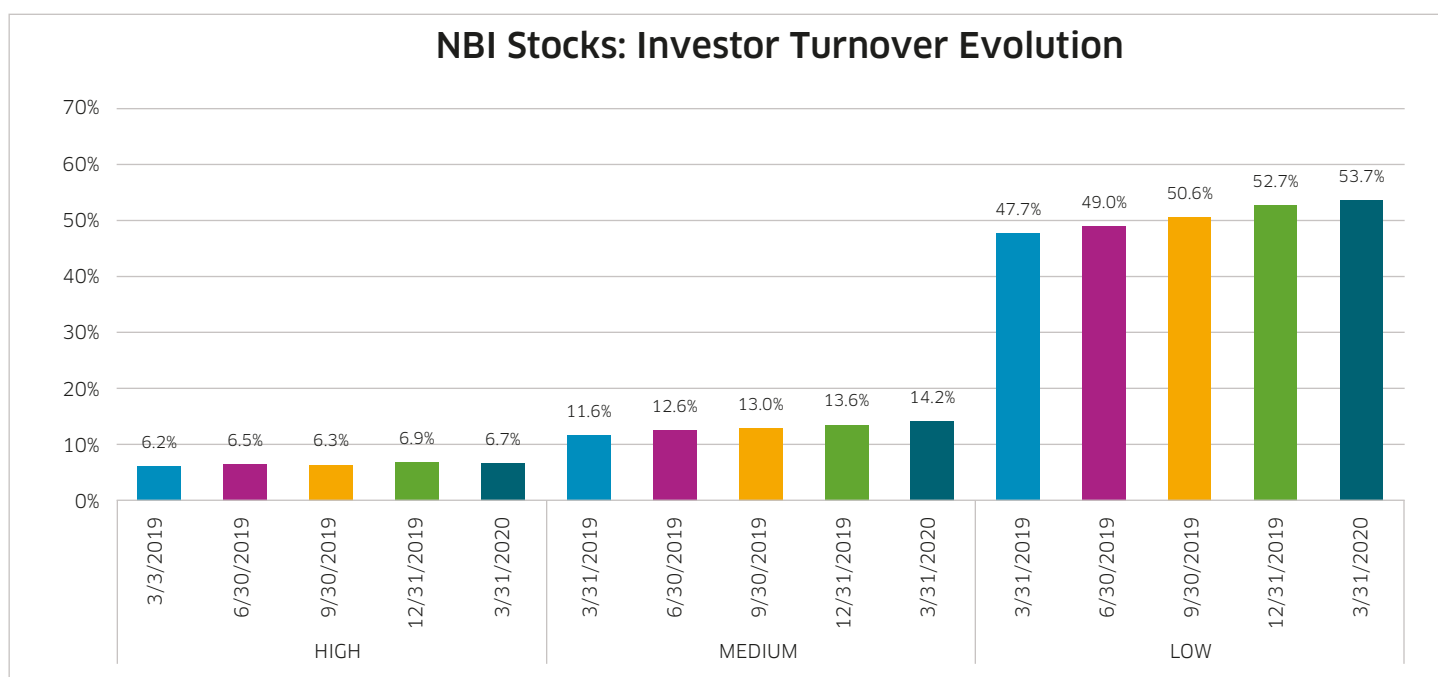
Having looked at performance, we can also gauge the impact of Coronavirus on investor appetite for Biotech by tracing how assets under management (AUM) have changed over the past few years within the largest exchange-traded product tracking NBI – the iShares Nasdaq Biotechnology ETF (IBB) – in addition to a few smaller products listed at the end of this piece. AUM has staged an impressive comeback in 2020, up from a multiyear low of \$6.2bn on March 16 to almost \$10bn by the end of May. With no clear end in sight for the pandemic, allocations have cause to remain elevated.



(Data through May 29, 2020)

Investor Style & Turnover Trends

By segmenting the investor base across all of NBI's constituents, one can also get a sense of just how speculative the trading activity in this space is. High-turnover investors have remained fairly constant at 6-7% on average, while low-turnover investors have increased the most, from approximately 48% in March 2019 to almost 54% in March 2020. Medium-turnover investors have increased somewhat as well, from 11.6% to 14.2%. This likely indicates that more investors are viewing the companies in the index as long-term, stable investments – not as speculative in nature as during the 1990s.



Biotech IPOs in the Last 18 Months

Nasdaq has demonstrated its leadership with respect to company listings in the Biotech space over many years, and recent history has only further affirmed its dominance. Through the end of May, there have been 15 IPOs of Biotechnology firms in the US in 2020, of which 13 listed with Nasdaq. Over the course of the last 18 months, there were a total of 74 IPOs, only three of which did not list with Nasdaq. Collectively, these listings raised nearly \$11.5bn.

On average, these firms have generated returns of 64%, with 48 of them achieving positive returns versus their IPO prices, and 16 firms more than doubling their IPO price; as of May 29, 2020, their combined market caps totaled \$126bn. The four largest firms - Moderna, Avantor, Genmab ADR, and BioNTech ADR - comprised \$65bn.

TICKER	COMPANY NAME	FIRST TRADE DATE	EXCHANGE	IPO PRICE \$	PRICE 5/29/20	PERFORMANCE
ADCT	ADC Therapeutics Ltd	5/15/20	NYSE	19.00	36.95	94%
AYLA	Ayala Pharmaceuticals, Inc.	5/8/20	Nasdaq	15.00	15.08	1%
LYRA	Lyra Therapeutics, Inc.	5/1/20	Nasdaq	16.00	15.87	-1%
ORIC	ORIC Pharmaceuticals, Inc.	4/24/20	Nasdaq	16.00	29.02	81%
KROS	Keros Therapeutics, Inc.	4/8/20	Nasdaq	16.00	28.74	80%
ZNTL	Zentalis Pharmaceuticals, Inc.	4/3/20	Nasdaq	18.00	52.22	190%
IMRA	IMARA, Inc.	3/12/20	Nasdaq	16.00	33.49	109%
PASG	Passage Bio, Inc.	2/28/20	Nasdaq	18.00	22.03	22%
RVMD	Revolution Medicines, Inc.	2/13/20	Nasdaq	17.00	30.72	81%
BEAM	Beam Therapeutics, Inc.	2/6/20	Nasdaq	17.00	25.55	50%
ARQT	Arcutis Biotherapeutics, Inc.	1/31/20	Nasdaq	17.00	33.55	97%
BDTX	Black Diamond Therapeutics, Inc.	1/30/20	Nasdaq	19.00	39.05	106%

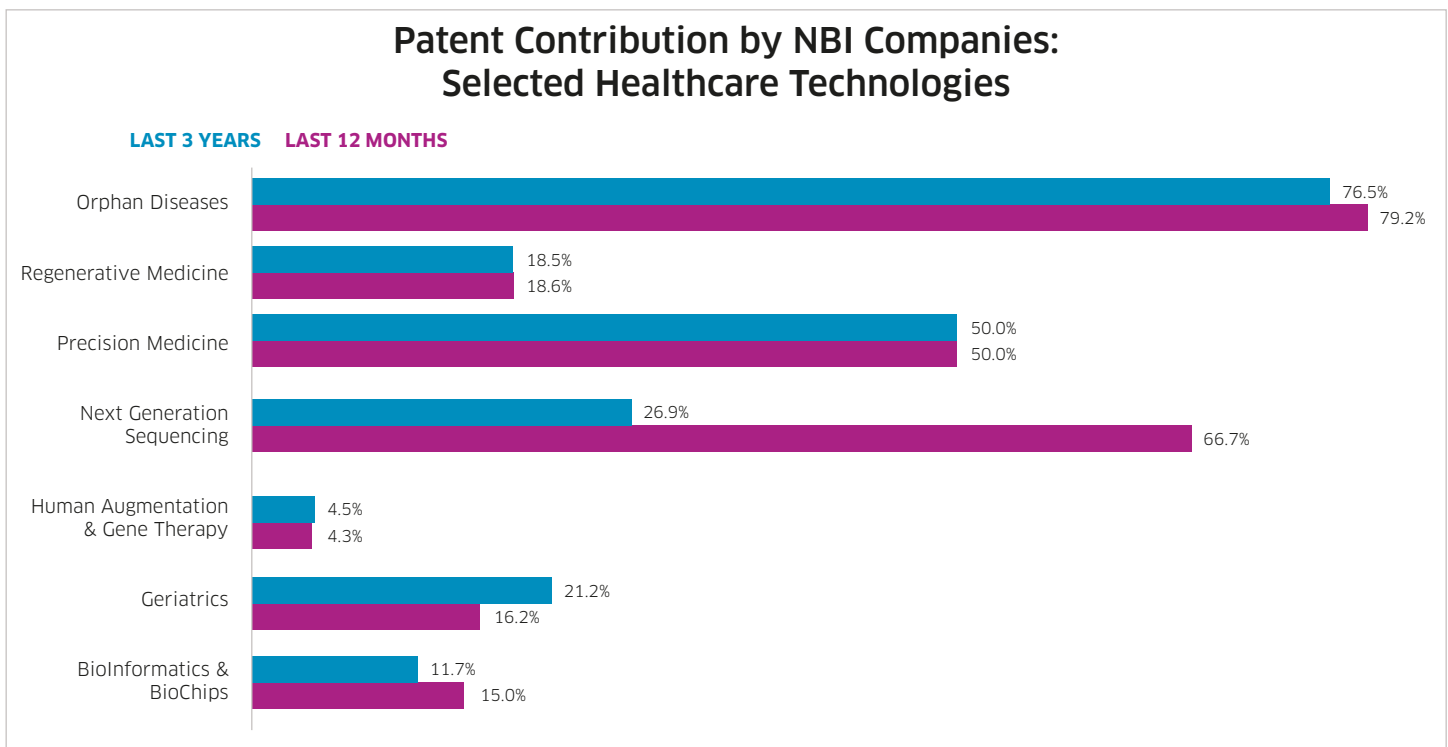
TICKER	COMPANY NAME	FIRST TRADE DATE	EXCHANGE	IPO PRICE \$	PRICE 5/29/20	PERFORMANCE
ANPC	AnPac Bio-Medical Science Co. Ltd. Sponsored ADR Class A	1/30/20	Nasdaq	12.00	7.70	-36%
ANVS	Annovis Bio, Inc.	1/29/20	NYSE AMEX	6.00	4.44	-26%
IMAB	I-MAB Sponsored ADR	1/17/20	Nasdaq	14.00	24.93	78%
MNPR	Monopar Therapeutics, Inc.	12/19/19	Nasdaq	8.00	7.70	-4%
ETNB	89bio, Inc.	11/11/19	Nasdaq	16.00	25.76	61%
CNSP	CNS Pharmaceuticals, Inc.	11/8/19	Nasdaq	4.00	2.66	-34%
GRTX	Galera Therapeutics, Inc.	11/7/19	Nasdaq	12.00	10.46	-13%
OYST	Oyster Point Pharma, Inc.	10/31/19	Nasdaq	16.00	28.46	78%
RAPT	RAPT Therapeutics, Inc.	10/31/19	Nasdaq	12.00	18.28	52%
TFFP	TFF Pharmaceuticals, Inc.	10/25/19	Nasdaq	5.63	5.33	-5%
CABA	Cabaletta Bio, Inc.	10/25/19	Nasdaq	11.00	8.55	-22%
PHAT	Phathom Pharmaceuticals, Inc.	10/25/19	Nasdaq	19.00	42.28	123%
IPHA	Innate Pharma SA Sponsored ADR	10/17/19	Nasdaq	5.50	6.50	18%
VIR	Vir Biotechnology, Inc.	10/11/19	Nasdaq	20.00	34.18	71%
BNTX	BioNTech SE Sponsored ADR	10/10/19	Nasdaq	15.00	49.53	230%
APRE	Apra Therapeutics, Inc.	10/3/19	Nasdaq	15.00	26.86	79%
FREQ	Frequency Therapeutics, Inc.	10/3/19	Nasdaq	14.00	18.56	33%
VIE	Viela Bio, Inc.	10/3/19	Nasdaq	19.00	46.90	147%
IGMS	IGM Biosciences, Inc.	9/18/19	Nasdaq	16.00	64.78	305%
SWTX	Springworks Therapeutics, Inc.	9/13/19	Nasdaq	5.61	38.07	578%
STSA	Satsuma Pharmaceuticals, Inc.	9/13/19	Nasdaq	15.00	26.20	75%
BLU	BELLUS Health, Inc.	9/5/19	Nasdaq	7.10	10.49	48%
CSTL	Castle Biosciences, Inc.	7/25/19	Nasdaq	16.00	38.43	140%
GMAB	Genmab A/S Sponsored ADR	7/18/19	Nasdaq	17.75	30.47	72%
MIRM	Mirum Pharmaceuticals, Inc.	7/18/19	Nasdaq	30.74	16.85	-45%
FULC	Fulcrum Therapeutics, Inc.	7/18/19	Nasdaq	16.00	19.91	24%
KRTX	Karuna Therapeutics, Inc.	6/28/19	Nasdaq	16.00	93.86	487%
BBIO	BridgeBio Pharma, Inc.	6/27/19	Nasdaq	17.00	29.33	73%
MORF	Morphic Holding, Inc.	6/27/19	Nasdaq	15.00	20.78	39%

TICKER	COMPANY NAME	FIRST TRADE DATE	EXCHANGE	IPO PRICE \$	PRICE 5/29/20	PERFORMANCE
ADPT	Adaptive Biotechnologies Corp.	6/27/19	Nasdaq	20.00	38.70	94%
AKRO	Akero Therapeutics, Inc.	6/20/19	Nasdaq	16.00	25.42	59%
BCEL	Atreca, Inc. Class A	6/20/19	Nasdaq	17.00	18.47	9%
PRVL	Prevail Therapeutics, Inc.	6/20/19	Nasdaq	17.00	16.68	-2%
PSNL	Personalis, Inc.	6/20/19	Nasdaq	17.00	11.84	-30%
STOK	Stoke Therapeutics, Inc.	6/19/19	Nasdaq	18.00	27.66	54%
IDYA	IDEAYA Biosciences, Inc.	5/23/19	Nasdaq	10.00	9.79	-2%
BCYC	Bicycle Therapeutics Plc Sponsored ADR	5/23/19	Nasdaq	14.00	17.87	28%
AVTR	Avantor, Inc.	5/17/19	NYSE	14.00	18.97	36%
APLT	Applied Therapeutics, Inc.	5/14/19	Nasdaq	10.00	45.52	355%
CRTX	Cortexyme, Inc.	5/9/19	Nasdaq	17.00	46.09	171%
NXTC	NextCure, Inc.	5/9/19	Nasdaq	15.00	31.21	108%
AXLA	Axcella Health, Inc.	5/9/19	Nasdaq	20.00	6.00	-70%
MIST	Milestone Pharmaceuticals, Inc.	5/9/19	Nasdaq	15.00	3.16	-79%
TRVI	Trevi Therapeutics, Inc.	5/7/19	Nasdaq	10.00	2.74	-73%
HOOK	Hookipa Pharma, Inc.	4/18/19	Nasdaq	14.00	10.91	-22%
TPTX	Turning Point Therapeutics, Inc.	4/17/19	Nasdaq	18.00	69.25	285%
NGM	NGM Biopharmaceuticals, Inc.	4/4/19	Nasdaq	16.00	19.73	23%
DTIL	Precision BioSciences, Inc.	3/28/19	Nasdaq	16.00	7.01	-56%
GNFT	Genfit SA Sponsored ADR	3/27/19	Nasdaq	20.32	5.22	-74%
KLDO	Kaleido Biosciences, Inc.	2/28/19	Nasdaq	15.00	7.22	-52%
MITO	Stealth Biotherapeutics Corp Sponsored ADR	2/15/19	Nasdaq	12.00	1.96	-84%
TCRR	TCR2 Therapeutics, Inc.	2/14/19	Nasdaq	15.00	10.10	-33%
AVDR	Avedro, Inc.	2/14/19	Nasdaq	14.00	22.99	64%
ANCN	Anchiano Therapeutics Ltd. Sponsored ADR	2/12/19	Nasdaq	11.50	1.10	-90%
GOSS	Gossamer Bio, Inc.	2/8/19	Nasdaq	16.00	12.15	-24%
HARP	Harpoon Therapeutics, Inc.	2/8/19	Nasdaq	14.00	21.76	55%
ALEC	Alector, Inc.	2/7/19	Nasdaq	19.00	32.70	72%
INMB	Inmune Bio, Inc.	2/4/19	Nasdaq	8.00	5.70	-29%
SXTC	China Sxt Pharmaceuticals, Inc.	1/4/19	Nasdaq	4.00	0.40	-90%
APM	Aptorum Group Limited Class A	12/18/18	Nasdaq	15.80	3.08	-81%
MRNA	Moderna, Inc.	12/7/18	Nasdaq	23.00	61.50	167%
THOR	Synthorx, Inc.	12/7/18	Nasdaq	11.00	67.99	518%

The Current Landscape and Future Prospects of Biotech R&D

As one might reasonably expect, constituents of NBI tend to engage in above-average levels of Research & Development. For the group as a whole, R&D expense totaled \$55bn in 2019, a stunning 30% of these companies' total revenues. (As a reference point, weighted average R&D expense as a percentage of total sales was 10.5% for the Nasdaq-100, and 4.8% for the S&P 500 in 2019.) To some extent, this is a distorted measure to consider given that nearly 20% (37) of these firms recorded no revenues whatsoever in 2019; approximately 20% (42) of NBI constituents IPO'ed in 2018 or 2019, contributing to roughly half of this population of zero-revenue companies. Even for those that did report some level of sales, 81 (more than one-third of the constituent count of the index, totaling nearly 22% of the index weights) of them recorded R&D expense that exceeded their revenues – clearly an indicator of the unique business models at play in the space. Moderna is a useful example, though, of the tradeoffs investors accept with Biotech. R&D expense in 2019 totaled \$465MM, far exceeding revenues of \$60MM. Yet that wager on future revenue has already paid off handsomely, to the tune of almost \$23bn in market capitalization as of May 29, 2020. Its differentiated, m-RNA vaccine technology has positioned Moderna as one of the leading candidates for an eventual Covid-19 vaccine, and perhaps the fastest-ever-to-market.

Another way to contextualize the intensity of R&D across NBI is to look at patent activity in distinct healthcare applications. Leveraging datasets from Yewno – a trusted Nasdaq partner in various Thematic Tech indexes – we can observe, for example, that on both trailing-twelve-month and trailing-three-year timeframes, NBI companies contributed 50% of all patents in the Precision Medicine space. For Orphan Diseases, the contributions exceeded 75%. And for a handful of others, contributions remained significant, in spite of the index's exclusion of major pharmaceutical players like Johnson & Johnson, Pfizer, Merck, and Bristol-Myers Squibb. Sanofi represents an interesting exception to this rule, owing to its ADR being listed with Nasdaq. With 100,000 employees and well north of \$100bn in market capitalization, Sanofi is one of France's premier pharmaceutical giants and was founded almost half a century ago. Along with GlaxoSmithKline, it too is developing a unique, promising vaccine candidate to treat Covid-19. Unlike Moderna's genetics-fueled m-RNA vaccine, Sanofi's will use engineered viruses grown inside insect cells to produce viral proteins that, in theory, should stimulate the same kind of protective, immunological response in human beings that traditional vaccines do.



(Source: Yewno Data)

More broadly speaking, bio innovations in the fight against Covid-19 have developed across a range of five sub-disciplines: Identification, Diagnosis, Vaccines, Treatment, and Epidemiology. In terms of Identification, the full genome of SARS-CoV-2 was sequenced and published within weeks, considerably faster than the SARS-CoV-1 virus that caused the SARS outbreak in 2002-2004. Diagnosis - while uneven and error-prone initially - has been ultimately aided by advances in nucleic acid-based diagnostic methods, and by the machines that process test samples becoming smaller, more affordable, and more widely available; numerous commercialized testing approaches now exist providing reliable, safe, and discrete results in a fraction of the time versus only a few months ago. Vaccine candidates have entered clinical trials faster than ever before, leveraging a range of previously unavailable approaches. Treatment has been aided by, among other things, genetically engineered animals specifically developed to test potential avenues for encouraging monoclonal and polyclonal antibody production. And in Epidemiology, genomics has helped uncover population-level insights thanks to regular sequencing of the virus across different areas of the world, while also discovering the various mutations that explain transmission dynamics. These achievements all exist somewhere on the spectrum of Biotech, and our current advantages in fighting a new, deadly pandemic stem from decades of costly, intensive R&D.

In terms of what the longer-term future holds for Biotech R&D, there are numerous reasons to feel excited. Biological sciences are driving innovation today in four key arenas: Biomolecules, Biosystems, Biomachine Interfaces, and Biocomputing. Each of these encompasses distinct revolutions in both Mapping and Engineering processes, aided greatly by recent advancements in technologies such as machine learning and artificial intelligence. In other words, a true fusion of Biology and Technology is taking place right now, and the dividends it yields should be far-reaching, impactful, and in some cases, even transformative.

McKinsey Global Institute estimates that up to 60% of the world's physical inputs could be made using biological means, while up to 45% of the world's disease burden could be addressed, leading to \$2-4tn of annual direct economic potential globally by 2030-40.² In practical terms, this means for example, shifting some meat and plant production from traditional, resource-intensive agricultural methods to lab-grown, while increasing yields in the former thanks to precision mapping of a plant or soil's microbiome and subsequent genetic engineering; repurposing fermentation (and other existing, natural processes) to create sustainable, biodegradable (and in some cases, even self-repairing) fabrics; truly personalized medicine and nutrition plans stemming from increasingly cost-effective human genomics and direct-to-consumer testing; leveraging biofuels to more efficiently store energy while initiating biosequestration processes to capture carbon emissions; even using DNA to store near-limitless quantities of data. McKinsey analyzed approximately 400 such applications and use cases that could be plausibly commercialized by 2050, with more than half of the impact from the currently visible pipeline existing outside the realm of healthcare itself. This is a function of the considerable overlap in the previously separate spheres of Biology & Computing R&D, as well as from all of the anticipated diffuse spillovers to upstream, downstream, and ancillary sectors.

In terms of biotech R&D monetization, analysts at ARK Financial are also thinking big - to the tune of trillions of dollars. Their recent research focuses on how artificial intelligence, combined with advances in Next Generation Sequencing (NGS) and CRISPR Gene-Editing, will drastically boost the efficiency of the pharmaceutical drug development process. By leveraging NGS to match up prospective patients more precisely for clinical trials of new drugs, the failure rate can be reduced by anywhere from 10% to as much as 45%.³ Fewer failures means less money spent developing drugs that don't ultimately make it to market. Additionally, they forecast a reduction in the length of clinical trials themselves, potentially by more than 50%, thanks to increasing usage of AI. All told, they forecast these improvements to R&D efficiency may add up to \$9tn to the market capitalization of therapeutics companies (currently estimated at closer to \$2tn) as soon as 2024, assuming only a 10% failure rate reduction and a 25% time-to-market reduction across the industry. And while gene therapies are still in their infancy and more expensive than traditionally-developed therapeutics, they have already proven to be more cost-effective per life-year gained in the three initial examples of their usage to target cancer. Taken together, the returns to pharmaceutical R&D are projected to increase dramatically after stalling out during the last two decades.

2. <https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/the-bio-revolution-innovations-transforming-economies-societies-and-our-lives>

3. <https://ark-invest.com/analyst-research/big-ideas-2020-report>

Summary

While the Coronavirus pandemic continues to pose significant risks to both the macroeconomic and physical health of the entire planet, the Nasdaq Biotechnology Index offers a unique lens through which to view human society's scientific and technological advancements in fighting the virus. There are multiple efforts by established and upstart players alike seeking to treat, prevent, and outright eradicate this deadly pathogen, whose short-term impacts are far-ranging and obvious. Longer-term, there remains much uncertainty about how starkly human behavior will change and what the knock-on effects on the economy will be. What is undisputed, however, is how much better positioned we are to cope and ultimately defeat the virus, largely thanks to decades of advancement already made within the biotech space. When one considers the ongoing innovations and seemingly limitless potential for new kinds of advancements, the future does seem brighter indeed. As investors, we must also consider the lasting psychological impact from biotech leading us through and out of a global crisis. Perhaps a higher level of public approval, coupled with more proactive – as opposed to reactive, constraint-imposing – regulatory structures will help lead the industry into a truly sustainable, rewarding new age.

ETFs currently tracking NBI include the iShares Nasdaq Biotechnology ETF (Nasdaq: IBB), ProShares Ultra Nasdaq Biotechnology ETF (Nasdaq: BIB), ProShares UltraShort Nasdaq Biotechnology ETF (Nasdaq: BIS), Invesco Nasdaq Biotech UCITS ETF (London: SBIO), iShares Nasdaq US Biotechnology UCITS ETF (London: BTEC), Tachlit Nasdaq Biotechnology ILS (Tel Aviv: TCBI105), Capital Nasdaq Biotechnology Index ETF (Taiwan: 00678), and Mirae Asset TIGER Nasdaq BIO ETF (Korea: 203780).

Sources: Nasdaq Global Indexes, FactSet, Bloomberg, McKinsey Global Institute, ARK Invest, World Health Organization.

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