# The Nasdaq Biotechnology Index

## A True Benchmark for Technology-Driven Healthcare Innovation

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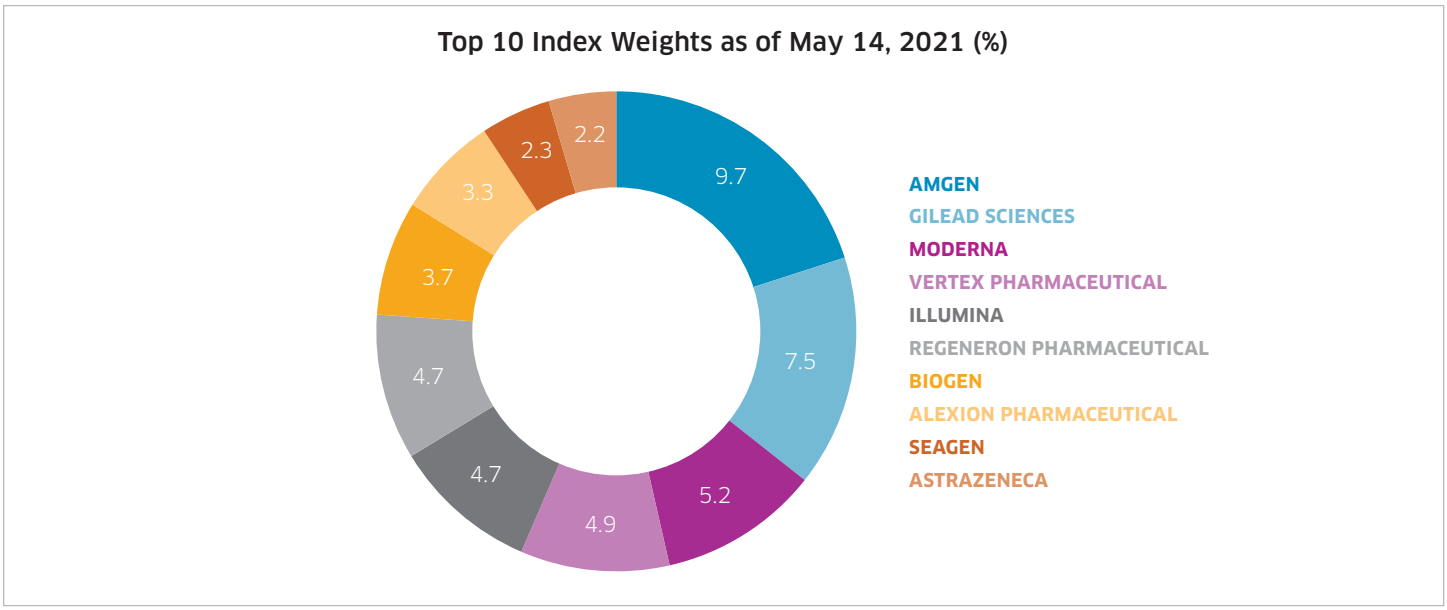
**The Nasdaq Biotechnology Index (NBI) was launched on November 1, 1993, when the industry was still in the midst of the original "biotech revolution" ushered in by the discovery of recombinant DNA technology and Genentech's IPO in 1980. The Index zoomed almost 700% up to its peak in March of 2000, only to experience a dramatic fall along with the rest of the Tech/Internet 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 fewer than two percentage points per year on average. Its constituent basket has swelled from 100 companies at the beginning of 2010 to 274 components today, reflecting the tremendous growth in the sector taking place within the small cap space – the overwhelming majority of which has stemmed from IPOs on the Nasdaq Stock Exchange.**

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.

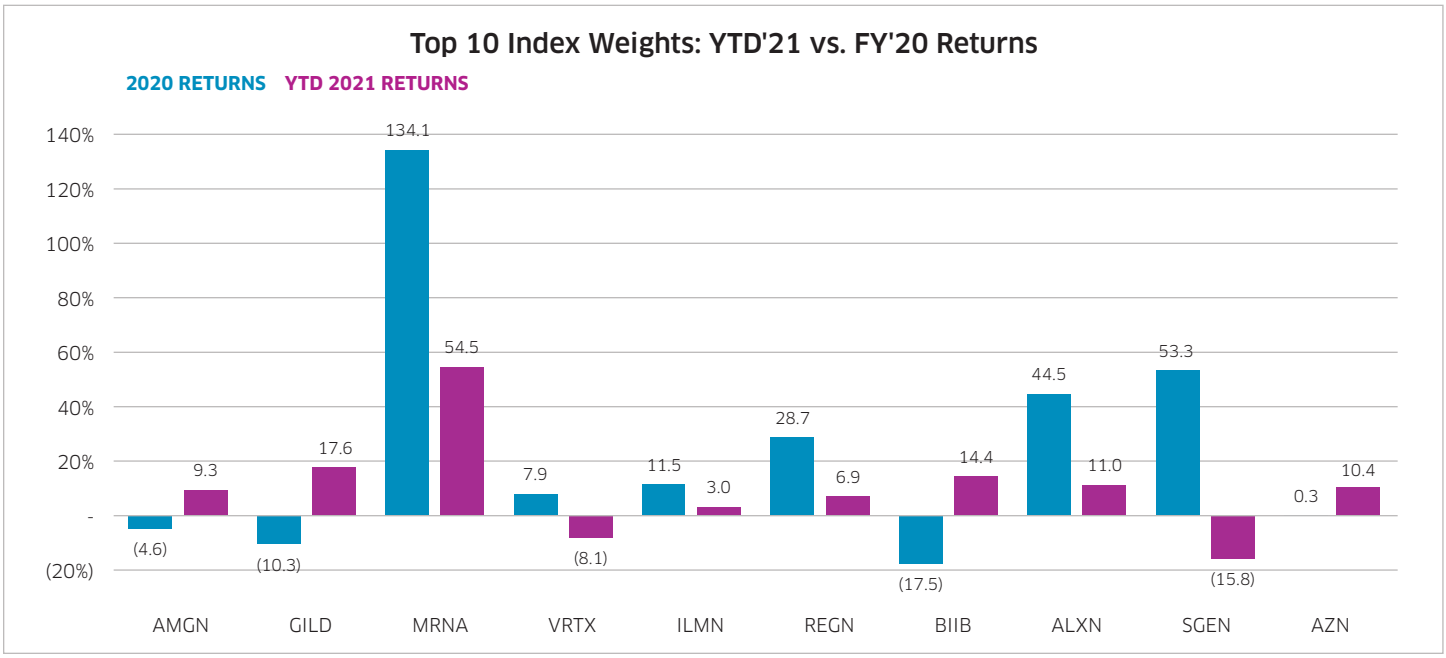
The nearly three decades-old index methodology remains straightforward, transparent, and befitting of a true industry benchmark: companies must be classified as Biotechnology & Pharmaceuticals by ICB (FTSE Russell's Industry Classification Benchmark); minimum market capitalization of $200MM; average daily trading volume of at least 100,000 shares; 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 and Top Covid-19 Thematic Names

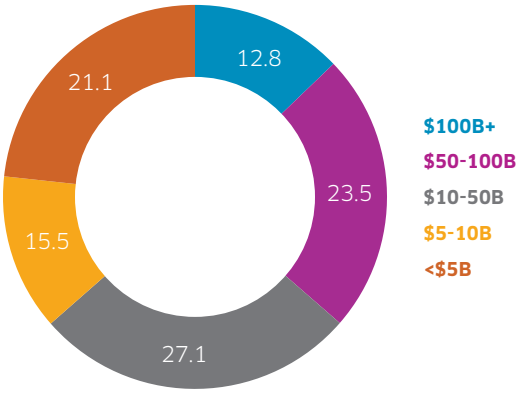



Of the 274 constituents in NBI, the top 10 represented approximately 48% of the index weight as of May 14, 2021. The top 20 names represented 61%, while the top 5 represented 32%. The largest of these was Amgen (AMGN) with a market cap of $144Bn, followed by Gilead Sciences (GILD / $86Bn), Moderna (MRNA / $65Bn), Vertex Pharmaceutical (VRTX / $56Bn), and Illumina (ILMN / $56Bn). Most in the top 10 have seen positive recent performance, with an average YTD return of nearly 9%. Only Vertex and Seagen (SGEN) have registered negative YTD returns thus far, while the clear standout has been Moderna (MRNA, up over 50%) thanks to its industry-leading mRNA vaccine for Covid-19, which continues to win massive new orders from countries across the globe. AstraZeneca (AZN) remains positioned to be the most common vaccine supplier to much of the developing world, as well as certain countries in the EU and its home base of the UK. Outside the top 10, BioNTech (BNTX) – the 17th largest constituent – continues to advance its partnership with Pfizer in manufacturing and refining the only other approved mRNA vaccine besides Moderna's. Meanwhile, Gilead has made numerous headlines as its previously-developed antiviral therapeutic – Remdesivir – was discovered to fight Covid-19 with modestly encouraging success; Regeneron (REGN), on the other hand, has developed an antibody-based therapeutic that began seeing limited use for high-risk patients in late 2020.

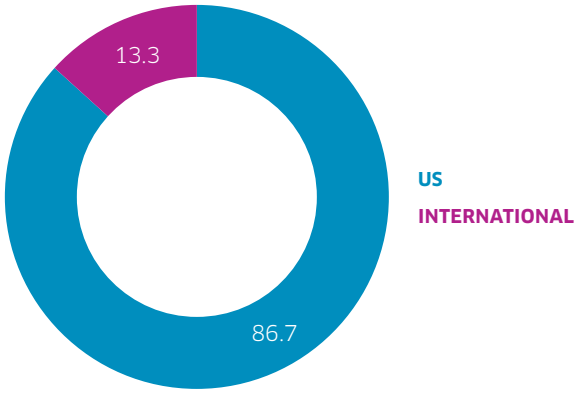


In terms of market capitalization for the overall group, the average was $5.7Bn, while the weighted average was $43.9Bn. The median was only $1.1Bn, however. This is reflective of the substantial representation of smaller stocks in the index, with 220 components under $5Bn of market cap comprising 21% of the index weight. 122 of these constituents measured at less than $1Bn.[1] In terms of international exposure – because the Index methodology permits non-US companies with listings on the Nasdaq Exchange – there exists a sizable component with just over 13% of index weight spread across 43 constituents.

**Index Weight by Market Cap (%)**




**Index Weight by Domicile Country (%)**




Perhaps the most interesting aspect of NBI's composition stems from its subsector classifications, namely the split between Biotechnology and Pharmaceuticals. ICB currently classifies 230 companies as Biotechnology, and the remaining 44 as Pharmaceuticals. The resulting split by index weight is approximately 65% and 35%, respectively. This immediately indicates one major difference between the two groups: Pharmaceutical companies tend to be much larger than Biotechnology firms. Within the NBI Index, the size gap is almost 4x, with the average market cap for a Pharma constituent at $15.5Bn vs. only $3.8Bn for Biotech. The corollary is that Pharma companies tend to be older and more mature in their lifecycle, clocking in at an average of 10.5 years since the date of their IPO vs. only 8 years for Biotech. What is the practical implication of this finding, and why does the NBI Index include Pharmaceutical companies to begin with?

The two subsectors are closely related, with Biotechnology firms often focusing intensely on R&D for many years until a breakthrough product receives approval from the FDA following extensive periods of clinical trials, safety testing, and the like. These highly uncertain, multiyear periods of R&D result in limited revenues and potentially significant losses, as was the case with Moderna before its untested mRNA vaccine technology produced its first, history-making Covid-19 shot. The resulting impact on company market values is therefore intuitive. Once a company successfully launches a flagship product into the market, it may continue focusing disproportionately on R&D and remain closer to a "pureplay" Biotech, or it may expand into a biotech-driven Pharmaceuticals company with vertically integrated processes for the ongoing development, production, marketing and distribution of new therapeutics. The Index's largest constituent, Amgen, just recently had such a transformation formalized by ICB when it was reclassified from Biotechnology to Pharmaceuticals. Thus the decision to include both subsectors in the Index is logical, not only in the respect that companies may transition from Biotech to Pharma at a certain stage of their lifecycle, but also because companies can straddle the two classifications for some period of time, too. In fact, 41 Biotechnology companies in the Index currently contain the word "Pharma" or "Pharmaceutical" in their legal corporate names, while 140 Biotechnology companies contain the same in their full-length company descriptions

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.

(per Factset). Similar-sounding benchmarks from other index providers, such as the S&P Biotechnology Select Industry Index (SPSIBI), select for only those companies classified as Biotechnology by their respective industry classifications, leaving separate indexes such as the Dow Jones US Select Pharmaceuticals Index (DJSPHM) to track Pharmaceuticals.

The upshot of all of the above is that attempting to construct an ideal benchmark index – with transparent, systematic construction guidelines – to track the Biotechnology industry is far more challenging than it sounds, given the existence of pureplay biotech firms, hybrid biopharmaceutical companies, and less R&D-intensive, generally older and more diversified pharmaceutical manufacturers. Given Nasdaq's extensive history of attracting the overwhelming majority of biotech IPOs both in the US and internationally, it stands to reason that the unique methodological approach of the NBI Index results in something very close to the ideal benchmark: capturing all but a few of the investable listings providing exposure to pureplay Biotechnology, in addition to preserving the names that have matured and transitioned to Pharmaceuticals while still maintaining a strong biotech heritage. In spite of a couple large, diversified international pharma exceptions (e.g. Sanofi & AstraZeneca, the latter completing its acquisition of biotech giant Alexion Pharmaceuticals in 3Q'21), the Index excludes the majority of traditional pharmaceutical manufacturers such as NYSE-listed Pfizer, Merck, Johnson & Johnson, and Bristol-Myers Squibb, as well as European-listed Bayer, GlaxoSmithKline, Novartis, and Roche.

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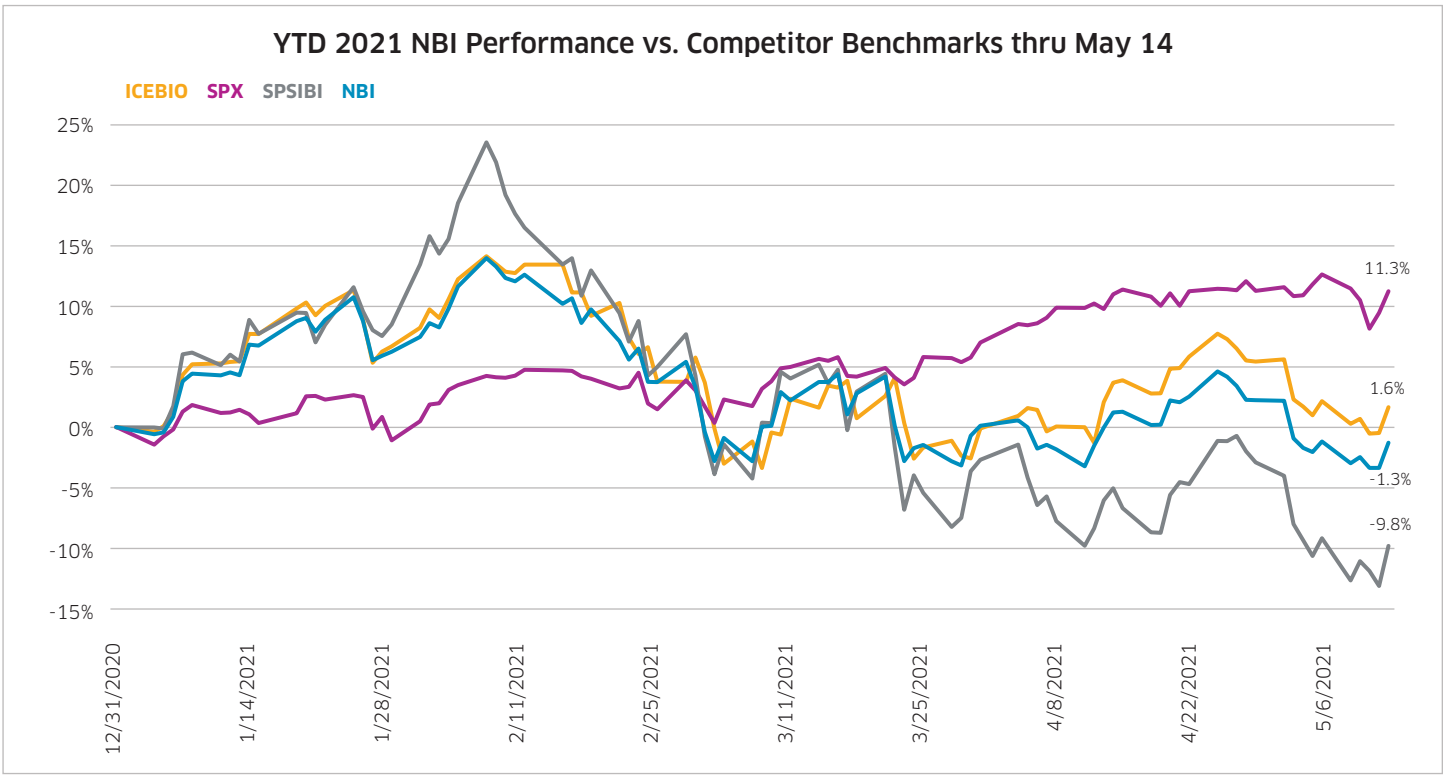
## Recent Performance

Biotechnology has been a relative underperformer in 2021, with the Nasdaq Biotechnology Index (NBI) down 1.3% on a YTD, price-return basis as of May 14 vs. a broader market gain of 11.3% as indicated by the S&P 500 Index (SPX). Looking at the S&P Biotechnology Select Industry Index (SPSIBI), the YTD loss is more material, down almost 10%. The difference is driven by SPSIBI's modified equal-weighted methodology, which systematically overweights the smaller companies in the space while underweighting the largest. In 2020, the roles were reversed, as NBI handily outperformed SPX with a gain of almost 26% vs. approximately 16%, respectively. Through the first three quarters of the year, SPSIBI performance closely tracked that of NBI, only to accelerate dramatically in the final quarter along with a broader outperformance of small cap stocks vs. large cap. With its emphasis on smaller companies to the detriment of the industry leaders, SPSIBI is subject to higher volatility, and may experience periods of both over and underperformance vs. NBI. SPSIBI restricts index constituents to firms classified as Biotechnology by GICS Subsector, leaving out numerous biopharmaceutical names. It is also a US-only index by design, excluding key international players such as BioNTech.


YTD 2021 NBI Performance vs. Competitor Benchmarks thru May 14
ICEBIO
SPX
SPSIBI
NBI
25%
20%
15%
10%
5%
0%
-5%
-10%
-15%
11.3%
1.6%
-1.3%
-9.8%
12/31/2020
1/14/2021
1/28/2021
2/11/2021
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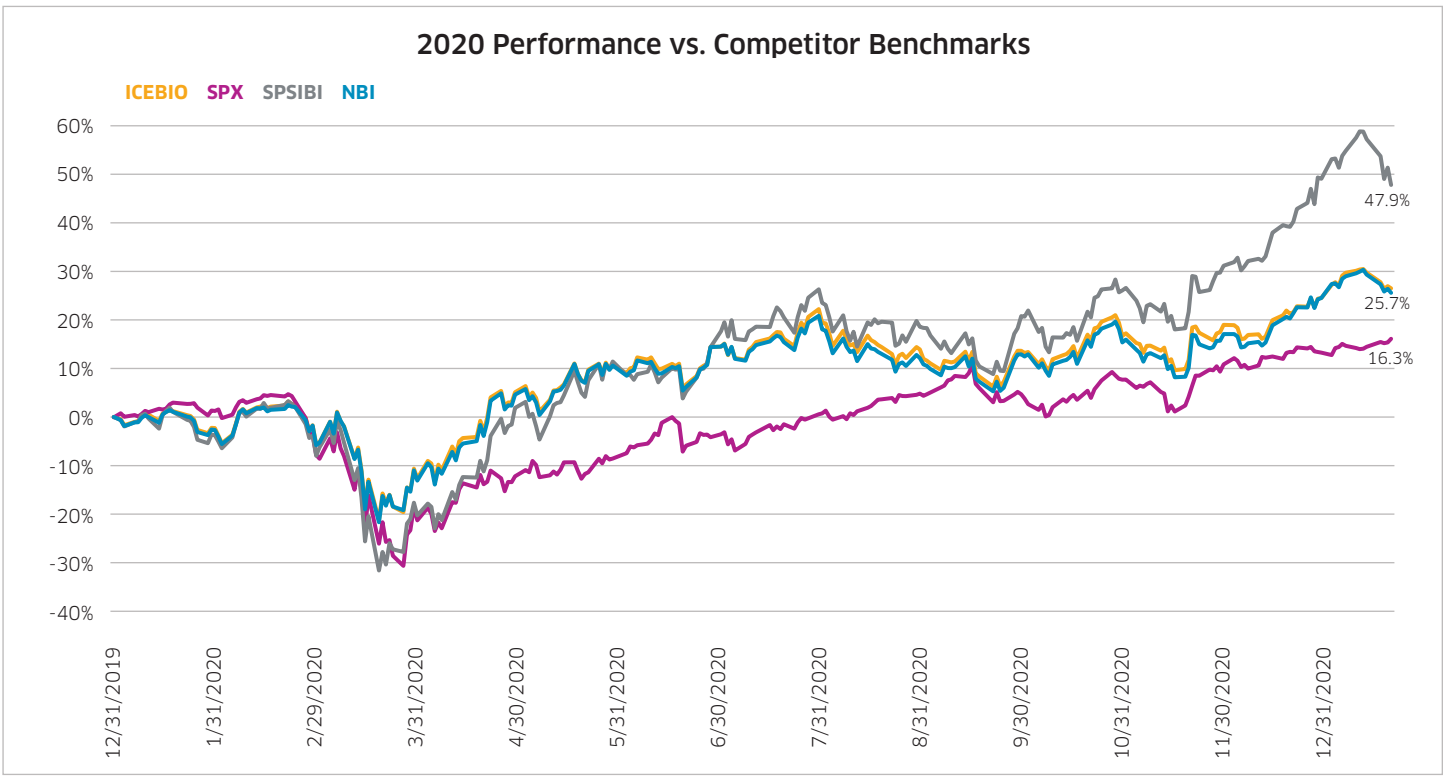
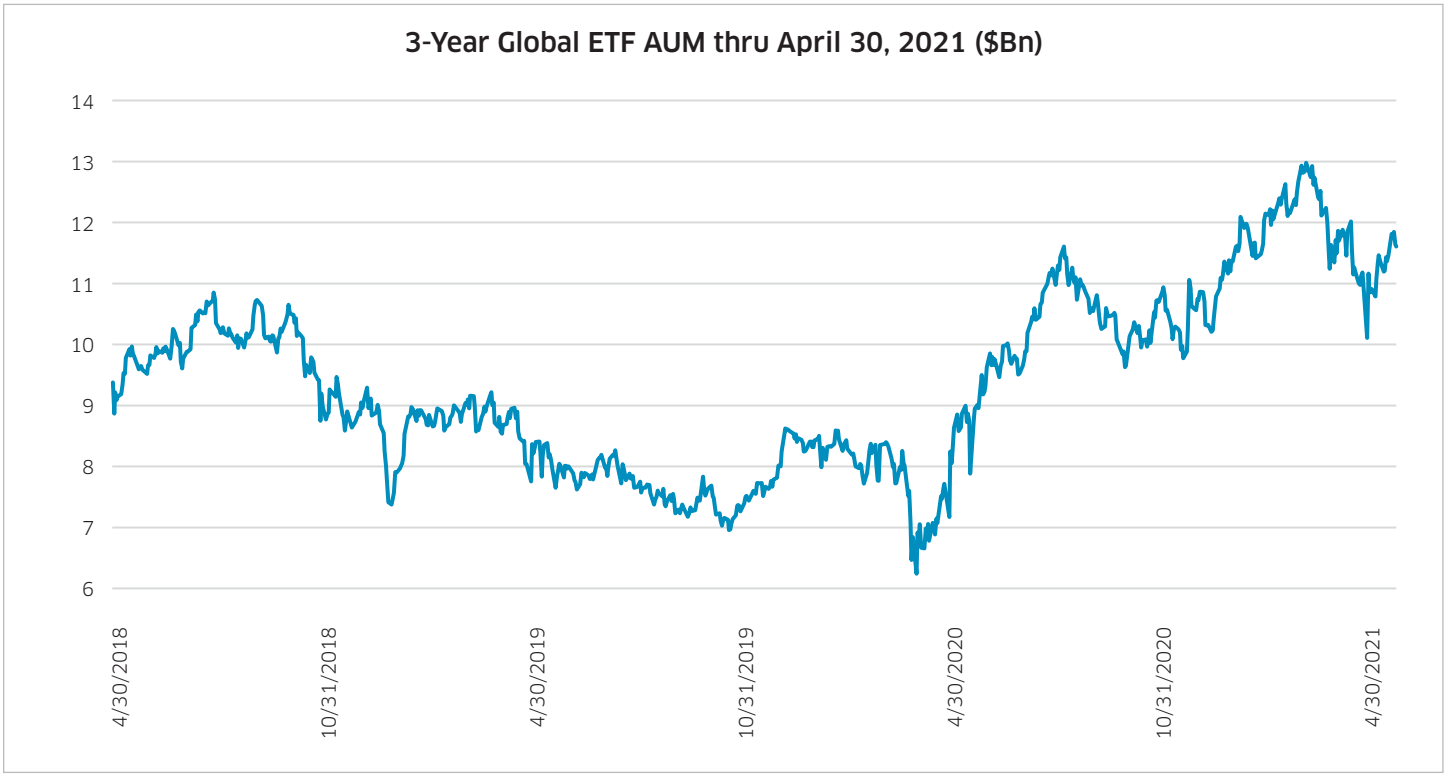
3/11/2021
3/25/2021
4/8/2021
4/22/2021
5/6/2021


2020 Performance vs. Competitor Benchmarks
ICEBIO
SPX
SPSIBI
NBI
60%
50%
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
47.9%
25.7%
16.3%
12/31/2019
1/31/2020
2/29/2020
3/31/2020
4/30/2020
5/31/2020
6/30/2020
7/31/2020
8/31/2020
9/30/2020
10/31/2020
11/30/2020
12/31/2020

## 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 ETF industry, including funds tracking NBI in the United States and internationally in Europe and Asia. AUM staged an impressive comeback in 2020, up from a multiyear low of $6.2Bn on March 16 to roughly $11.5Bn by end of year. By mid-February 2021, approximately $13Bn in AUM was attained before moderating back down to a range between $11-12Bn. Even though there is a clear end in sight for the pandemic, allocations have remained elevated as investor interest clearly extends far beyond.




## Biotech IPOs in 2020-21

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 April, there have been 37 IPOs of Biotechnology firms in the US in 2021, all of which listed with Nasdaq. Over the course of 2020, there were a total of 86 IPOs, only three of which did not list with Nasdaq. Collectively, these listings raised $21.5Bn.

Nasdaq's market dominance in attracting biotech IPOs over several decades has resulted in an overall market share of 98% of current listings representing $1.1 Trillion in total market capitalization as of April 2021, including 7 companies large enough to warrant inclusion in the Nasdaq-100 Index. In contrast, NYSE is home to 11 biotech listings in total representing approximately $40Bn in market cap. In terms of constructing an ideal benchmark to track the industry, there is very little to be gained by including NYSE-listed companies.

## 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 $68.5Bn in 2020, a stunning 31% of these companies' total revenues. (As a reference point, weighted average R&D expense as a percentage of total sales was 9.9% for the Nasdaq-100, and 7.1% for the S&P500 in 2020.) To some extent, this is a distorted measure to consider given that nearly a quarter (66) of these firms recorded no revenues whatsoever in 2020; more than 20% (59) of NBI constituents IPO'ed in 2019 or 2020, contributing to roughly half of this population of zero-revenue companies. Even for those that did report some level of sales, 188 (two-thirds of the constituents of the index, totaling nearly 35% 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 pureplay Biotech. R&D expense in 2019 totaled $465MM, far exceeding revenues of $60MM. In 2020, R&D jumped to $1.3Bn vs. $800MM in revenues. In 2021, it is estimated that Moderna's revenues will exceed $18Bn – a stunning increase of 300x in just two years. Its differentiated, m-RNA vaccine technology has positioned Moderna as one of the two leading developers of the highest-effectiveness Covid-19 vaccines, and perhaps the fastest-ever-to-market. The other leading developer, of course, is BioNTech, whose revenue trajectory is very similar: $121MM in 2019, to $550MM in 2020, to an estimated $14Bn in 2021. Its partner Pfizer (excluded from NBI), while clearly benefitting from the relationship, experienced a 19% drop in revenue in 2020 vs. 2019, driven by the net-negative impacts from the pandemic on its diversified business model. As a result, its stock price was up only 14.5%, while both Moderna and BioNTech were up more than 1,200% each since October 9, 2019 – the date of BioNTech's IPO.

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 (along with aforementioned AstraZeneca). 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. In addition to exploring an ultimately unsuccessful vaccine venture with GlaxoSmithKline, Sanofi is partnering with Translate Bio – yes, yet another member of NBI – to develop its own m-RNA vaccine candidate, while assisting Pfizer and Johnson & Johnson in scaling production of their respective, successful vaccines.

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 $2-4T 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 biopharmaceutical 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 $9 trillion to the market capitalization of therapeutics companies (currently estimated at closer to $2 trillion) 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 biopharmaceutical R&D are projected to increase dramatically after stalling out during the last two decades.

## 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 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).

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

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

Notes: Unless otherwise indicated, data is as of May 14, 2021.



II | 2021-06 | 5015