

## 2021 Year in Review, Part 2: What's New with the Innovators of the Nasdaq Biotechnology Index?

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The Nasdaq Biotechnology Index™ (NBI™) was launched on November 1, 1993, when the biotech industry was still in its relative infancy. The nearly three decades-old index's methodology remains straightforward, transparent, and befitting of a true 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.

In the age of Covid-19, NBI's constituent basket has swelled to 373 companies as of year-end 2021, following the most recent annual reconstitution. A record total of 129 new components just qualified for index inclusion, following 100 such additions in December 2020. Tremendous growth has taken place within the small cap biotech space over the past two years, the overwhelming majority of which has stemmed from IPOs on the Nasdaq Stock Exchange. And yet, the sector has underperformed the broader equity market throughout most of 2021. Let's examine why that occurred, before moving on to an analysis of index benchmark construction and what it means for biotech investors. We will conclude with an update on how the ongoing Covid-19 pandemic is underscoring NBI as a relevant, thematic investment, as well as a summary of some other major, recent developments in new therapeutics and R&D across the industry.

### What Drove Biotech Performance in 2021

NBI finished 2021 with a full-year price performance of -0.6% and a total return of 0.0%, underperforming broader equity market benchmarks such as the Nasdaq-100® (NDX®) and the S&P 500 (SPX) by approximately 26%. Numerous explanations for biotech's underperformance have been offered, ranging from an overheated private market setting up too many overvalued IPOs, to regulatory uncertainty from the FDA and an overall adverse change in the US federal government's posture towards the healthcare industry following the 2020 elections. The latter may have had a big knock-on effect in terms of depressed M&A activity throughout 2021, which has historically helped underpin biotech equity returns.

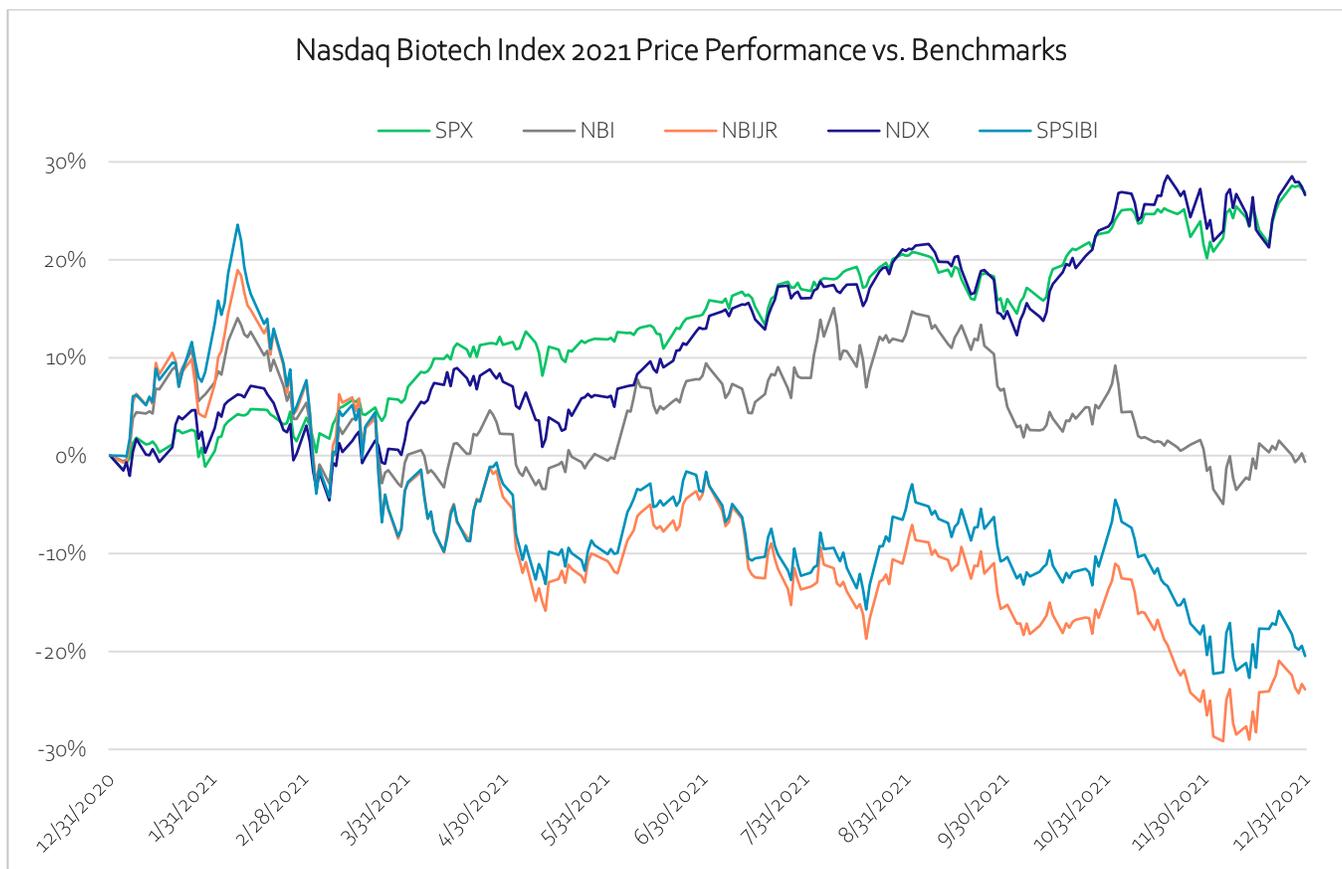
Jared Holz, Oppenheimer's healthcare equity strategist, described the sector's biggest problem as stemming from a relatively new phenomenon whereby "more and more funds are allocating dollars in the private markets and are significantly less interested with public equities and/or stock performance as a result," concluding that "early-stage private biotechs are sucking up capital" only to get abandoned "quickly as they go public." Per Josh, "the quality of this year's [IPO] crop is marginally weaker and perhaps not as ready for prime time, but to see how quickly private investors jettison these stocks on to focus on the next private is perhaps the largest reconciling item separating sector performance."<sup>1</sup>

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<sup>1</sup> <https://www.marketwatch.com/articles/biotech-sector-stocks-performance-51638806212>

Indeed, 2021 was a blowout year in terms of biotech IPO activity, and we [previously discussed](#) how it drove the largest number of new additions to NBI’s constituent base in the index’s history of annual reconstitutions, exceeding the previous record set in 2020. Analyzing the individual constituents’ contributions to NBI’s price returns in 2021, we found that there was indeed a stark bifurcation: the top 20 largest companies’ overall positive contribution was almost perfectly offset by the remainder of the index’s negative performance. In other words, large-cap biotech had a decent year of performance in 2021, with an average return of 27.6% across the top 20 NBI constituents (which as a group, represented nearly 60% of the index’s aggregate weight as of year-end). But the deep pool of recently-listed biotechs and their older small-cap brethren had a bad enough year to cancel that all out.

Brad Loncar, biotech investor and CEO of Loncar Investments, also offered a compelling explanation in terms of equity market microstructure not being able to handle a flood of cash into certain sub-themes within biotech. This was largely driven by the recent success of ARK Investment and their Genomic Revolution ETF (ARKG), which “grew from \$2.5 billion in assets to \$12.5 billion over a three-month period from mid-Nov 2020 to the mid-Feb 2021 biotech peak. Approximately \$7 billion of this was due to pure cash flowing into the fund. This kind of explosion in AUM (assets under management) for one fund is unprecedented in our sector” and “caused a big problem for stocks. Biotech is a shadow of the tech sector and individual biotech companies do not have the scale to take in the kind of money that comes with those inflows over such a short period of time without stock prices being significantly moved.”<sup>2</sup> Indeed, ARKG finished 2021 with a loss of 33.9%, down approximately 45% from its peak on February 8. In the performance chart below, one can clearly see this same peak in the return paths taken by NBIJR™ – the Nasdaq Junior Biotechnology Index™ which tracks only the sub-\$5 billion market capitalization segment of companies within NBI – and by SPSIBI, the S&P Biotechnology Select Industry Index. This brings us to the next relevant topic for biotech investors, which is the importance of choosing the proper benchmark to track the space.



<sup>2</sup> <https://www.nasdaq.com/articles/heres-what-happened-to-biotech-this-year>

## Why NBI Remains an Industry-Leading Benchmark

In addition to boasting one of the longest live track records among biotech indexes, NBI can also claim to be one of the most representative. Its constituent base of 373 companies is approximately double that of SPSIBI, with only 189 index members. Furthermore, NBI's modified market-cap weighting approach ensures that investment returns from tracking the index are driven proportionally by the largest and most important biotech companies. This explains why NBI outperformed SPSIBI by a stunning 20.4% on a total return basis in 2021. SPSIBI's index methodology utilizes modified equal weighting, leading to substantial underweights of the largest biotech players, and dozens upon dozens of overweight small-cap companies. One need only look at the 10 largest NBI overweights vs. SPSIBI to see just how much the construction of a benchmark matters:

Company Name	NBI Weight	SPSIBI Weight	Market Cap (\$B)*
Amgen	9.22%	0.83%	\$126.7
Gilead Sciences	7.36%	0.80%	\$91.1
Moderna	5.87%	0.76%	\$103.0
Regeneron Pharmaceutical	5.39%	0.73%	\$66.8
Vertex Pharmaceutical	4.51%	0.82%	\$55.8
Biogen	2.85%	0.80%	\$35.2
Seagen	2.28%	0.84%	\$28.3
Horizon Therapeutics	1.97%	0.83%	\$24.4
Alnylam Pharmaceutical	1.64%	0.76%	\$20.3
BioMarin Pharmaceutical	1.31%	0.80%	\$16.2

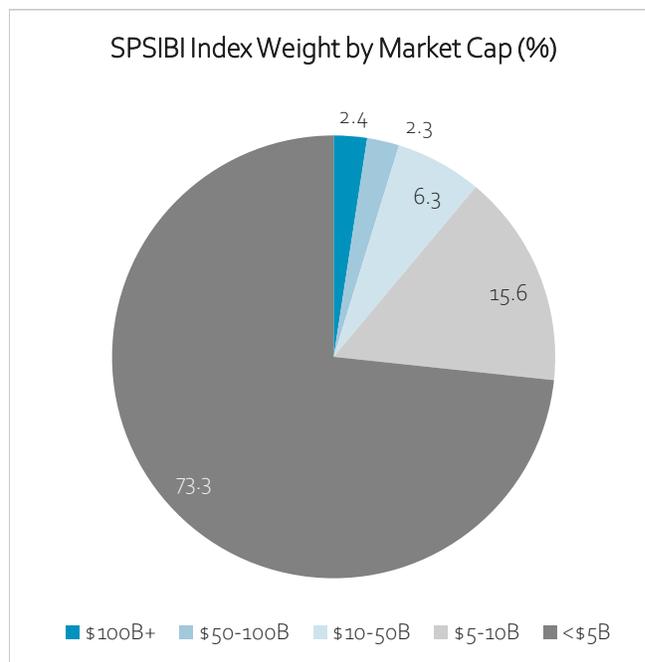
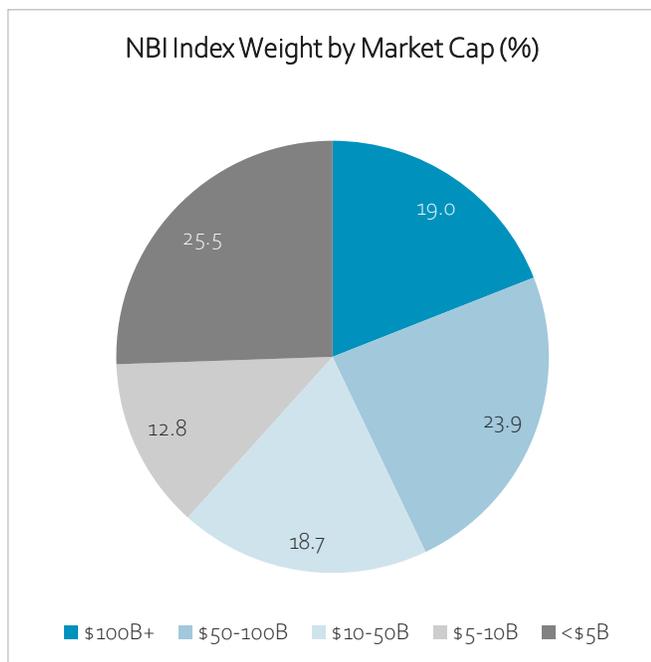
In terms of the breadth of constituents included, NBI opts to permit companies from any country of incorporation, whereas SPSIBI is US-focused. This has allowed the non-US-based subset of the index to grow to 57 members, representing 16% of the aggregate weight of NBI. And while SPSIBI permits US-based biotech companies listed on exchanges other than Nasdaq, it is a very miniscule segment of the universe that has a negligible impact on index breadth and performance. The overwhelming majority of biotech companies choose to list with Nasdaq year after year, with recent annual IPO win rates of 97-98%. Below are the 10 largest exclusions from SPSIBI; half of them are based outside the US.

Company Name	NBI Weight	SPSIBI Weight	Market Cap (\$B)*	Country
Illumina	4.80%	0.00%	\$59.5	US
AstraZeneca (ADR)	2.85%	0.00%	\$182.1	UK
BioNTech (ADR)	1.83%	0.00%	\$62.3	Germany
Royalty Pharma	1.38%	0.00%	\$17.1	US
Viatis	1.32%	0.00%	\$16.4	US
Beigene (ADR)	1.09%	0.00%	\$30.1	China
Sanofi (ADR)	1.08%	0.00%	\$127.3	France
Syneos Health	0.86%	0.00%	\$10.6	US
Guardant Health	0.82%	0.00%	\$10.2	US
Argenx (ADR)	0.79%	0.00%	\$18.3	Netherlands

\*All data as of December 31, 2021. Market caps shown reflect fully-diluted company valuations.

Note that NBI index weightings are based on individual security market values. In the case of an ADR, a constituent's weighting in NBI will correspond solely to the market value of its ADR shares.

Perhaps this particular method of index construction was justifiable back in 2006, when S&P launched SPSIBI. Back then, the universe of investable biotech companies numbered fewer than 200, and was heavily concentrated in the US. Indeed, many of today's thematic indexes that aim to provide exposure to emerging technologies, industries, or trends employ some version of equal-weighting to make unconcentrated bets on the various players in a given space – justifiable because it's impossible to know which companies will become leaders of their respective niches. But for an industry that's been around for decades, biotech deserves an index benchmark that recognizes there are established leaders, and weights them accordingly. NBI delivers exactly that, resulting in a balanced distribution of index weight across various market capitalization buckets. SPSIBI, on the other hand, ends up resembling a primarily small-to-midcap index. It is thus no surprise that its performance diverged from NBI's in a year with such pronounced weakness in small-cap biotech and IPOs in general.<sup>3</sup>



A final point to highlight in terms of benchmark construction is NBI's methodology welcoming both Biotechnology and Pharmaceuticals companies into index membership. This unique feature has permitted 50 Pharmaceuticals to join the 323 pure-play Biotech companies (as determined per the Industry Classification Benchmark / ICB system). We explored the nuances of this outcome in [our previous research](#) published in 2021. While other biotech benchmarks tend to exclude Pharmaceuticals, the reality is that the distinction between them and pure-play Biotech firms is often blurred. Most recently, 53 companies in NBI were classified as Biotechnology by ICB Subsector, but contained the word "Pharma" or "Pharmaceutical" in their company name. A whopping 185 NBI constituents classified as Biotechnology referenced "Pharma" or "Pharmaceuticals" in their official company description (per Factset). And finally, Amgen – the largest NBI constituent – was itself reclassified by ICB in 2021 from Biotechnology to Pharmaceuticals. The upshot of all of this is that NBI, by virtue of including only Nasdaq-listed companies, skips over most of the older, larger pharmaceutical companies with outsized consumer-products divisions, while preserving exposure to the younger, more biotech-driven pharmaceuticals that have listed with Nasdaq.

<sup>3</sup> <https://www.bloomberg.com/news/articles/2021-12-22/record-setting-year-for-ipos-fails-to-deliver-historic-returns>

## Preventing and Treating Covid-19: NBI's Innovators Lead the Way

In our previous research, we took time to outline a wide range of vaccines, pharmaceuticals, and therapeutics at various stages of development in the fight against Covid-19. As the virus progresses from a pandemic to an endemic stage, the human race is armed with a number of tools already on the market to prevent severe disease across the majority of us, and to effectively treat those who are most at-risk.

Moderna's mRNA vaccine, long recognized as one of the most effective vaccinations against Covid-19, has proven itself as providing the strongest, most durable form of immunity with the rise of recent variants (Delta, Omicron).<sup>4</sup> Moderna's success with this new vaccine technology has vaulted it into the upper ranks of biotech companies, making it the 3<sup>rd</sup> largest constituent of NBI. It is now exploring a wide range of diseases to immunize for the first time using similar mRNA technology.

AstraZeneca continues to deliver its less powerful, but still generally effective, vaccine to hundreds of millions in the developing world and Europe alike.<sup>5</sup> Its advantages in terms of lower cost to produce, ease of transport, and longer shelf life, have made it one of the most important vaccinations in the quest to ensure global coverage. Following the closing of its \$39B acquisition of US biotech giant Alexion Pharmaceuticals, AstraZeneca is making a strong case for its revamped reputation as a leading, science-driven biopharmaceutical company. It has climbed to become the 7<sup>th</sup> largest constituent of NBI based on the value of its ADRs alone.

BioNTech continues to partner with pharmaceutical giant Pfizer to produce the only other mRNA vaccination besides Moderna. BioNTech's success in developing its own version of mRNA for Covid-19 has propelled it into the 11<sup>th</sup> largest holding of NBI, also based on the value of its ADRs alone.

Novavax, after a long and difficult journey developing its Covid-19 vaccine candidate, is on the cusp of becoming the 4<sup>th</sup> FDA-approved option for Americans, and has climbed up the NBI ranks to 19<sup>th</sup> largest.

Regeneron's cocktail of monoclonal antibodies recently received authorization in the EU (following approvals in the US, Japan, Australia, and the UK) to treat and prevent Covid-19 in certain high-risk patients. Its product "was shown to reduce the risk of hospitalization or death by 70%" in "non-hospitalized infected individuals"; "in the prevention setting it reduced the risk of symptomatic infections by 82%."<sup>6</sup> Regeneron is the 4<sup>th</sup> largest constituent of NBI, and has long been one of the biggest, most important pure-play biotech firms globally.

Gilead's remdesivir, a powerful antiviral, has established itself as one of the most effective treatments for Covid-19 in "patients who were at a high risk for Covid-19 progression, [...] and resulted in an 87% lower risk of hospitalization or death than placebo" in a new study published in December 2021 in the New England Journal of Medicine.<sup>7</sup> Gilead remains the 2<sup>nd</sup> largest constituent of NBI, a position it held throughout most of 2021.

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<sup>4</sup> <https://www.webmd.com/vaccines/covid-19-vaccine/news/20211202/pfizer-or-moderna-head-to-head-study-shows-one-shot-has-an-edge>

<sup>5</sup> <https://www.reuters.com/business/healthcare-pharmaceuticals/astrazeneca-shot-third-dose-works-against-omicron-study-2021-12-23/>

<sup>6</sup> <https://investor.regeneron.com/news-releases/news-release-details/regeneron-antibody-cocktail-approved-european-commission-treat>

<sup>7</sup> <https://www.nejm.org/doi/full/10.1056/NEJMoa2116846>

## Looking Past Covid-19: A Round-Up of the Latest in Groundbreaking Biotech Innovation

2021 saw several exciting updates in both traditional drug development and cutting-edge therapeutics like gene editing. One of the biggest came from Biogen and its highly anticipated Alzheimer's drug, Aduhelm. The FDA approved it in June, sending the company's shares soaring, but they have since dropped by more than 40%. Despite the approval, much uncertainty remains within the scientific and medical communities about the effectiveness of the drug – a monoclonal antibody that seeks to address the underlying causes of Alzheimer's disease, as opposed to simply treating its symptoms. Doctors have been reluctant to prescribe the expensive treatment, and Biogen has already cut the price tag by half while awaiting a decision on whether Medicare will cover the drug for seniors.<sup>8</sup> Since its peak on June 10, Biogen's share decline has contributed more than 2% of the 7.5% loss in NBI through year-end 2021, and put something of a "general chill" on the biotech sector given the controversy of the FDA's decision.

On the brighter side, Amgen scored an FDA approval for its new oncology drug, Lumakras – the first therapy for non-small-cell lung cancer that targets a specific protein mutation long thought "undruggable." The KRAS protein is present in around 25% of lung cancers and some colorectal cancers, as well. Thanks to rapid advancements in genetic sequencing of tumors and protein imaging, Amgen was able to develop and trial the treatment on an accelerated timeline.<sup>10</sup> Initial approval came at the end of May, and Amgen is now assessing the drug in various indications and combinations.

In July, Intellia Therapeutics (24<sup>th</sup> largest NBI constituent) released promising data from a Phase 1 trial of a gene-editing CRISPR therapy, a first-of-its-kind outcome. Intellia said it was successful in genetically editing mutated cells inside the livers of several patients suffering from a rare disease stemming from a protein misfolding disorder.<sup>11</sup> Intellia started partnering with Regeneron in 2016 to advance the CRISPR technology for *in vivo* therapeutic development. In October, the FDA granted Intellia's product an official Orphan Drug Designation, meant for drugs targeting a population of fewer than 200,000 in the US.

On September 30, Editas Medicine (99<sup>th</sup> largest NBI constituent) followed up with the second-ever evidence of successful *in vivo* gene editing by releasing favorable initial data from its Phase I/II trial of a therapy to treat a form of inherited blindness.<sup>12</sup>

And looking ahead to 2022, Beam Therapeutics (44<sup>th</sup> largest NBI constituent) is expected to investigate the potential of base editing, a "more targeted, precise editing than offered by the much-hyped CRISPR/Cas9 approach. At the beginning of November, the FDA gave Beam clearance to begin a phase I/II study testing whether the technology could be used to treat sickle cell disease by reactivating fetal hemoglobin, a form of the oxygen-carrying protein that normally disappears soon after birth."

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<sup>8</sup> <https://www.cnn.com/2022/01/04/why-biogens-alzheimers-drug-aduhelm-is-so-controversial-.html>

<sup>9</sup> <https://www.nytimes.com/2021/12/20/health/alzheimers-aduhelm-price.html>

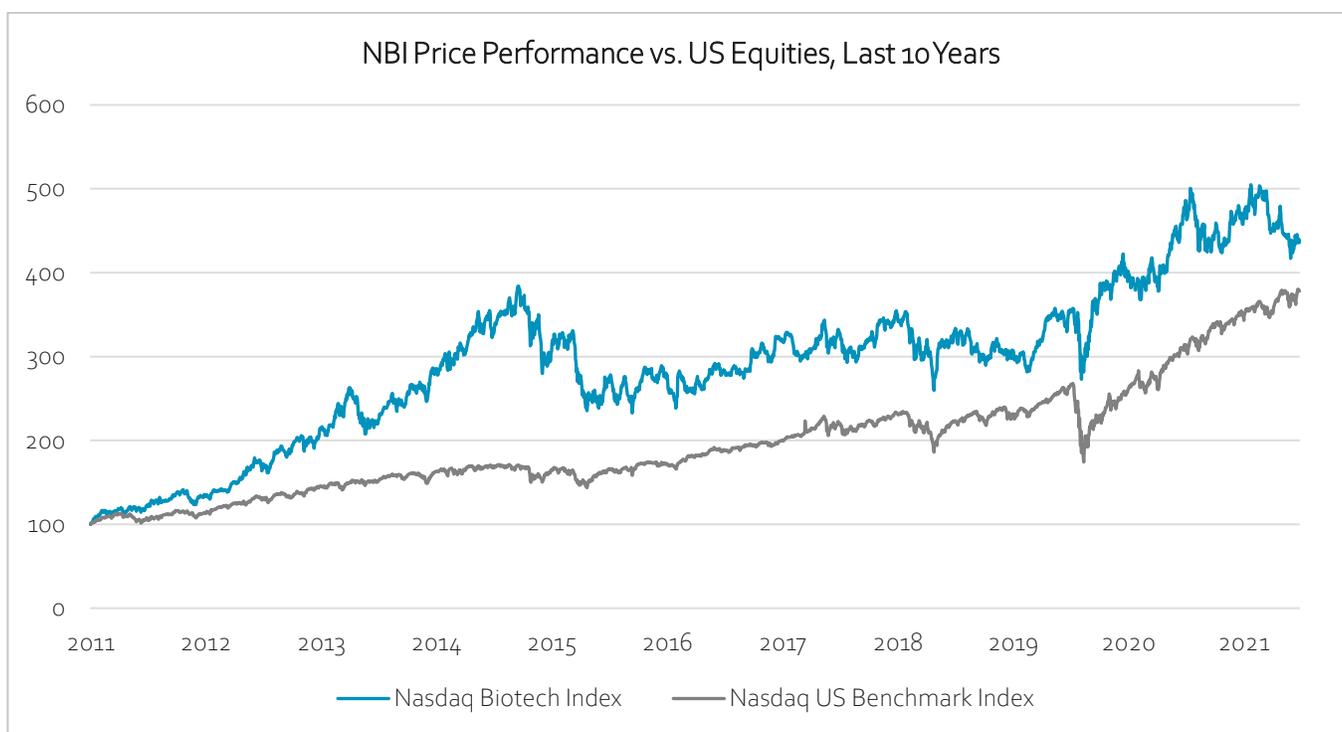
<sup>10</sup> <https://www.fiercepharma.com/pharma/amgen-s-lumakras-becomes-first-fda-approved-kras-inhibitor-for-lung-cancer-patients>

<sup>11</sup> <https://www.biospace.com/article/intellia-regeneron-announce-first-ever-clinical-data-in-vivo-genome-editing-/>

<sup>12</sup> <https://www.biospace.com/article/intellia-s-milestone-in-vivo-crispr-therapy-granted-fda-orphan-drug-designation-/>

## Summary

As an industry, biotech experienced a pivotal year in 2021 in terms of new treatments, proof-of-concept for mRNA vaccines, and IPOs. Conversely, sector performance within public equities – especially across small and midcaps – was forgettable. Over the past decade, there have been other times when the Nasdaq Biotech Index has underperformed the broader market, as measured by the Nasdaq US Benchmark Index™ (NQUSB™). In 2016, NBI underperformed NQUSB by 32.4% – a continuation of a prolonged bear market, which coincided with the highly uncertain US election campaign. In the first half of 2014, the index briefly entered a bear market, plunging 21% in less than two months while NQUSB remained almost unchanged. NBI's trailing 10-year correlation with NQUSB is only 0.69, vindicating the claim that Health Care plays a defensive role in many portfolios. Yet biotech is ultimately a sector with greater than average uncertainty, and thus higher volatility. The length of time it takes most companies to research, develop, and commercialize a new product is an order of magnitude above other sectors. Add in another layer of unpredictability from politicians and regulators, and it comes as no surprise that biotech can diverge meaningfully from the broader equity market in times good and bad.



Performance re-based to 100. Data from 12/31/2011 – 12/31/2021.

With all this said, it is perhaps more important than ever for investors to utilize an appropriate benchmark to track the biotech industry. The trend towards higher IPO volumes established during the Covid-19 pandemic may very well continue into 2022. The bear market in small-cap biotechs may be nearly complete, or only halfway through – impossible to predict. The Fed's impetus to quicken the pace of rate hikes in the face of elevated inflation may well doom the earliest stage companies in biotech (and other sectors) to continuing multiple compression. In that kind of outcome, investors will fare better tilting away from the smaller, more speculative corners of biotech and towards the larger, more established players. The Nasdaq Biotechnology Index offers investors a transparent, effective benchmark for tracking new entrants into the public markets, while maintaining appropriate weightings among the more volatile, younger small-cap segment of the industry and its more stable, older large-cap members. There is so much groundbreaking innovation taking place within biotech that it behooves investors to stay allocated to this crucially important sector, even in the face of occasional underperformance and uncertainty. NBI shows us the way.

ETFs currently tracking NBI include the Invesco Nasdaq Biotechnology ETF™ (Nasdaq: IBBQ), 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), Capital Nasdaq Biotechnology Index ETF™ (Taiwan: 00678), and Mirae Asset TIGER Nasdaq BIO ETF™ (Korea: 203780).

Sources: Nasdaq Global Indexes, FactSet, Bloomberg.

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