

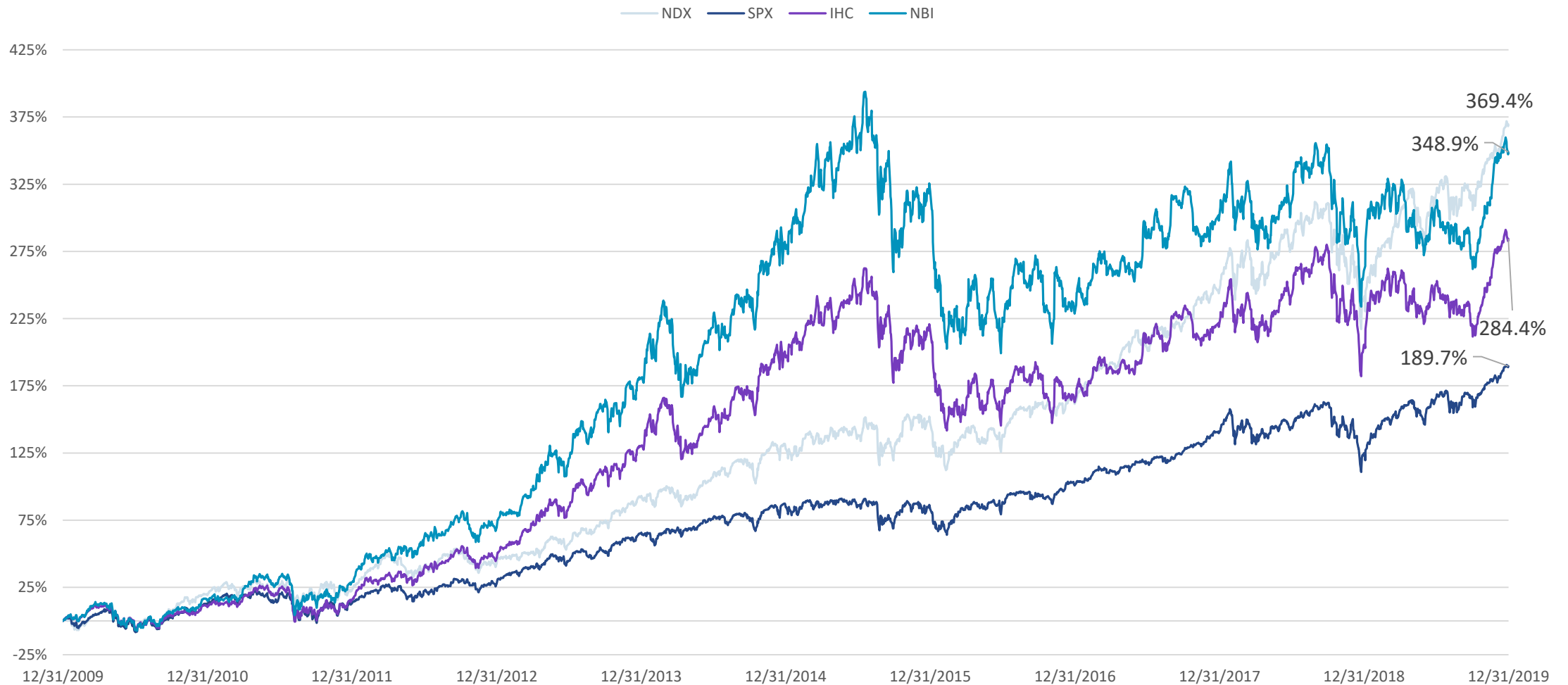


Nasdaq Biotechnology Index[®]

Investing in the Next Generation of Healthcare Innovators

Performance Throughout the 2010s

2010-2019 Price Performance vs. Market Benchmarks



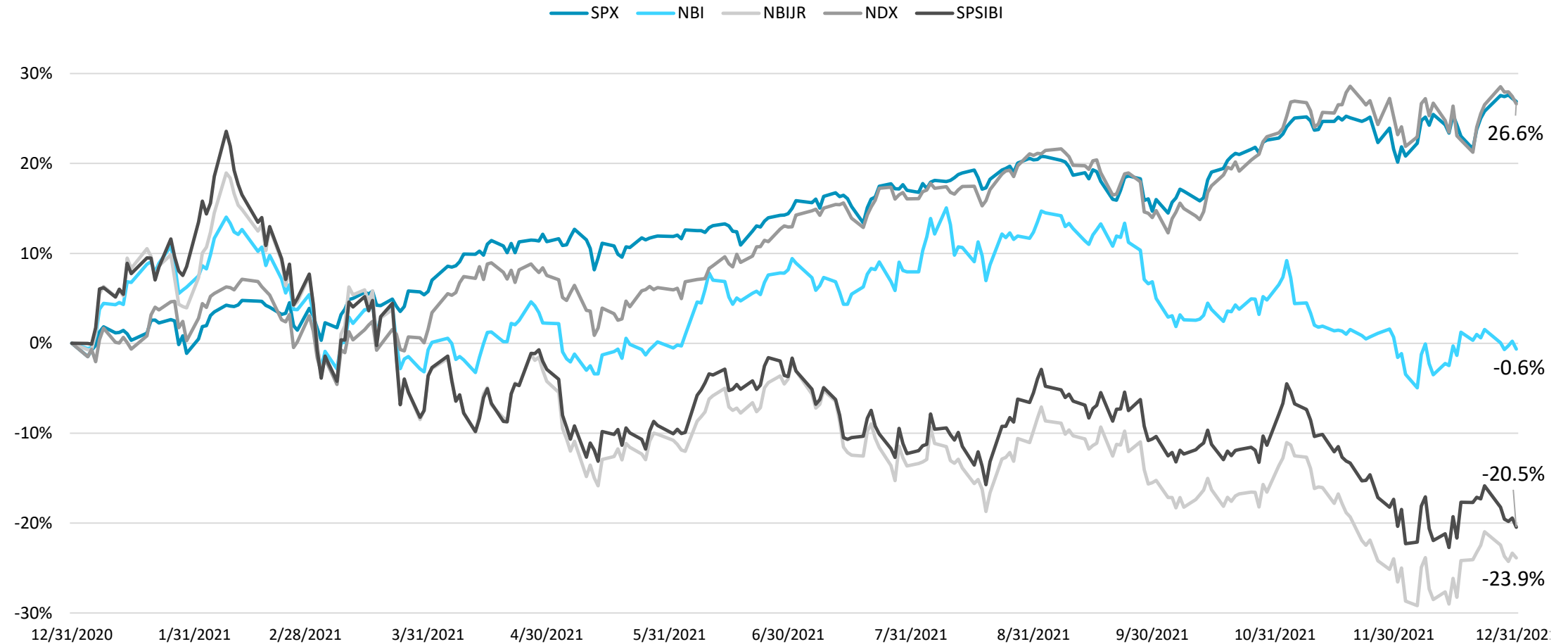
NBI 2020 Performance

Price Performance vs. Market Benchmarks



NBI 2021 Performance

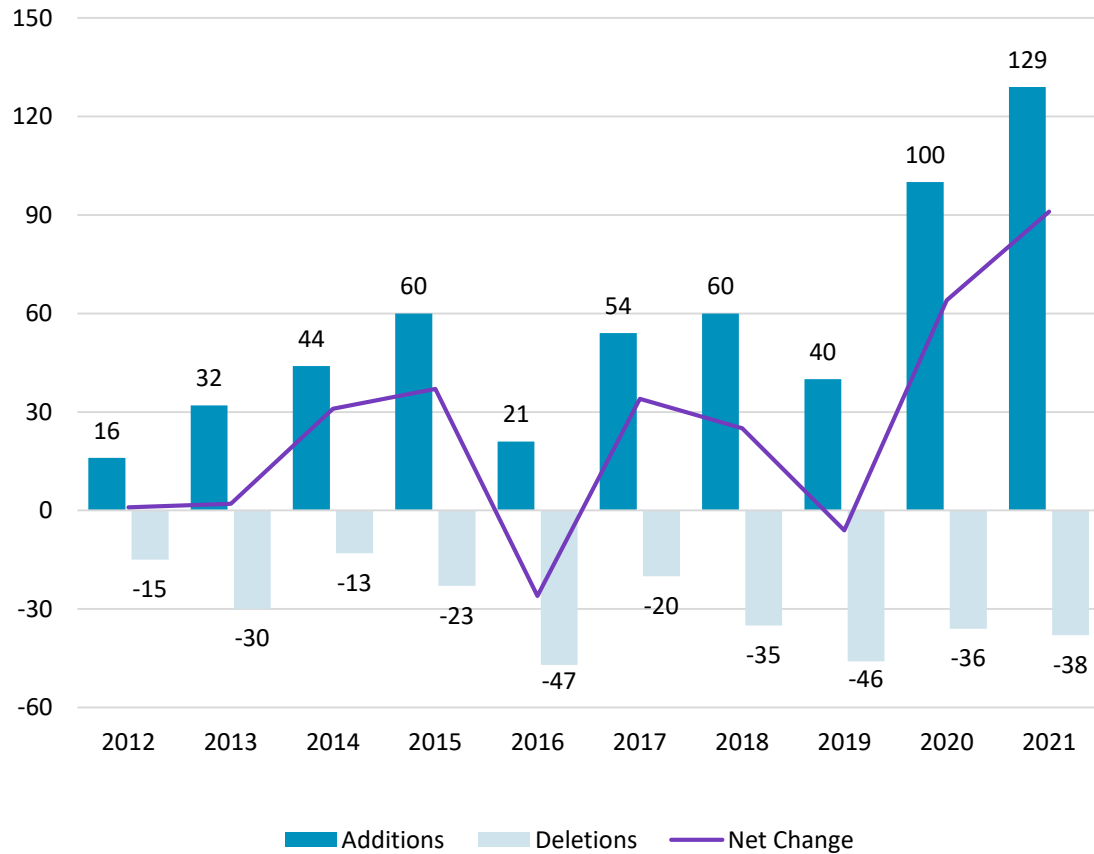
Price Performance vs. Market Benchmarks & Other Biotech Indexes



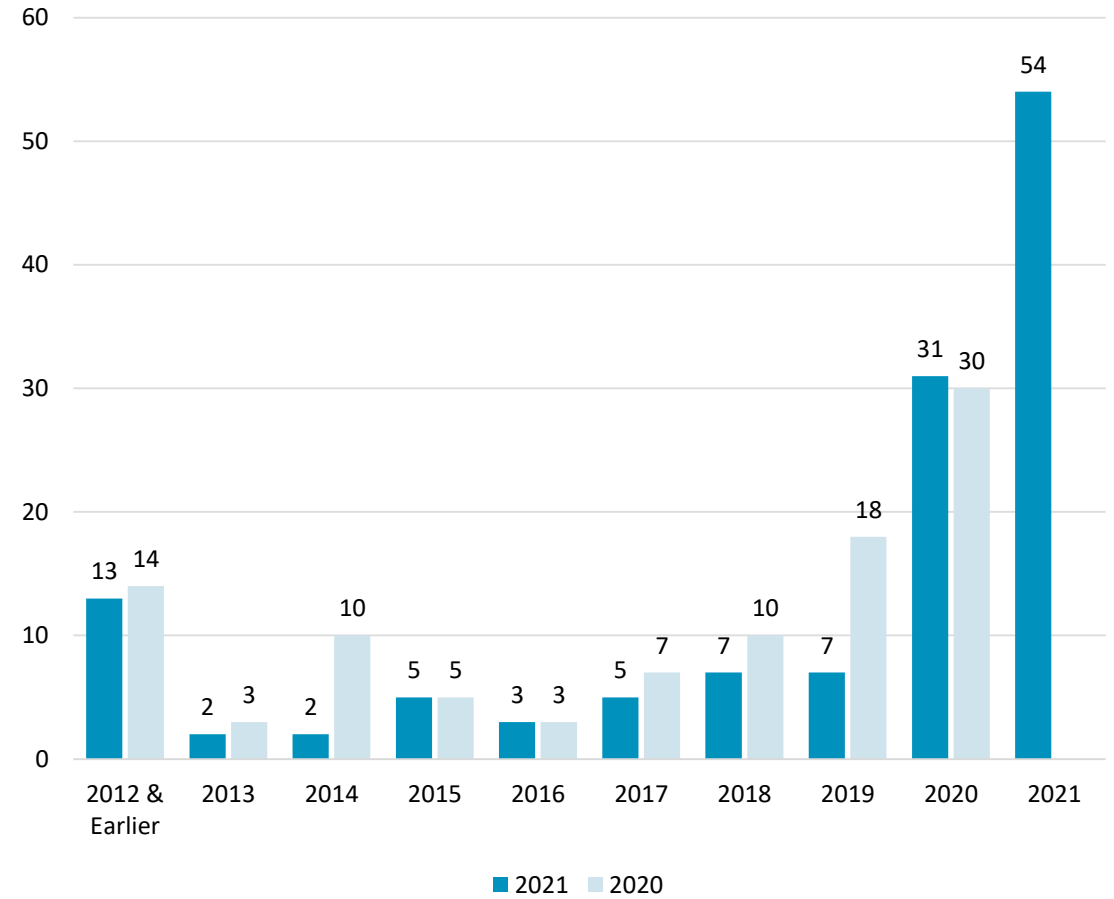
Source: Nasdaq Global Indexes, FactSet, Bloomberg as of December 31, 2021.

Nasdaq Biotech Index Reconstitution History

NBI Additions & Deletions by Year, 2012-2021



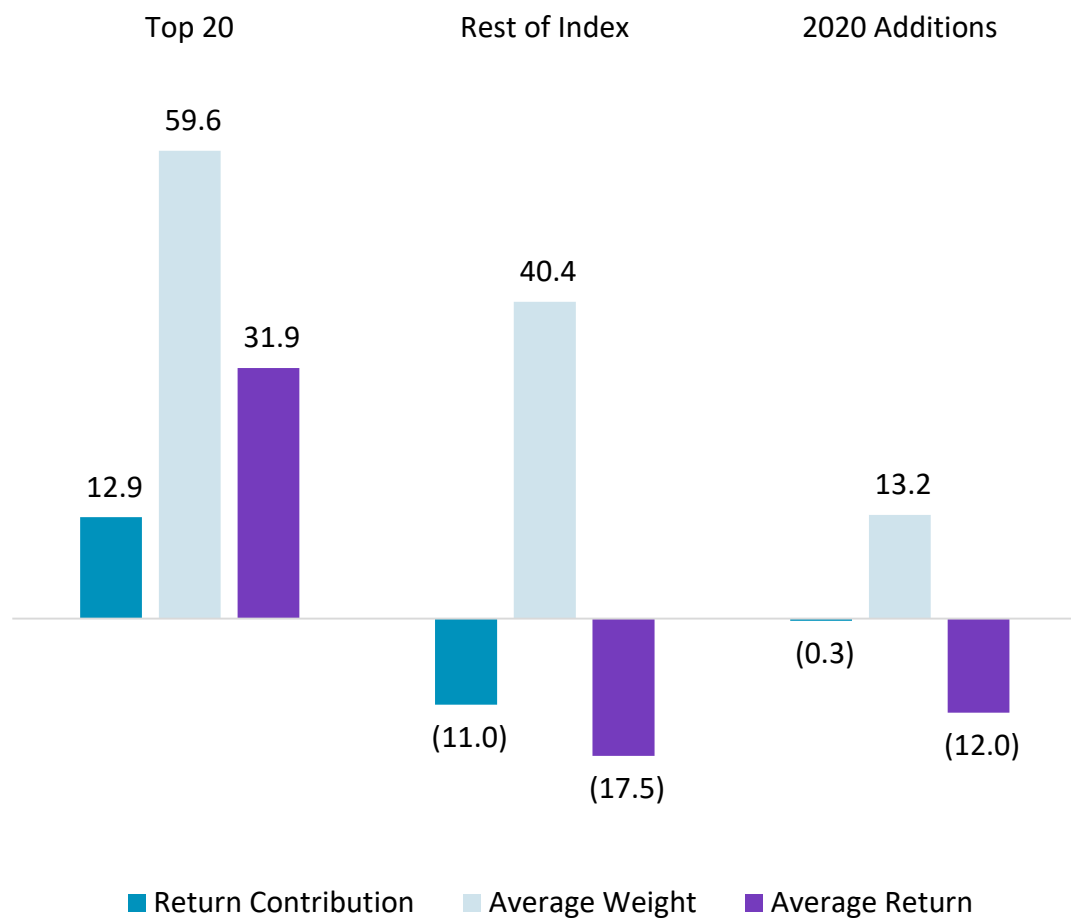
NBI Additions by Year of IPO, 2020-2021



Source: Nasdaq Global Indexes, FactSet, Bloomberg as of December 31, 2021.

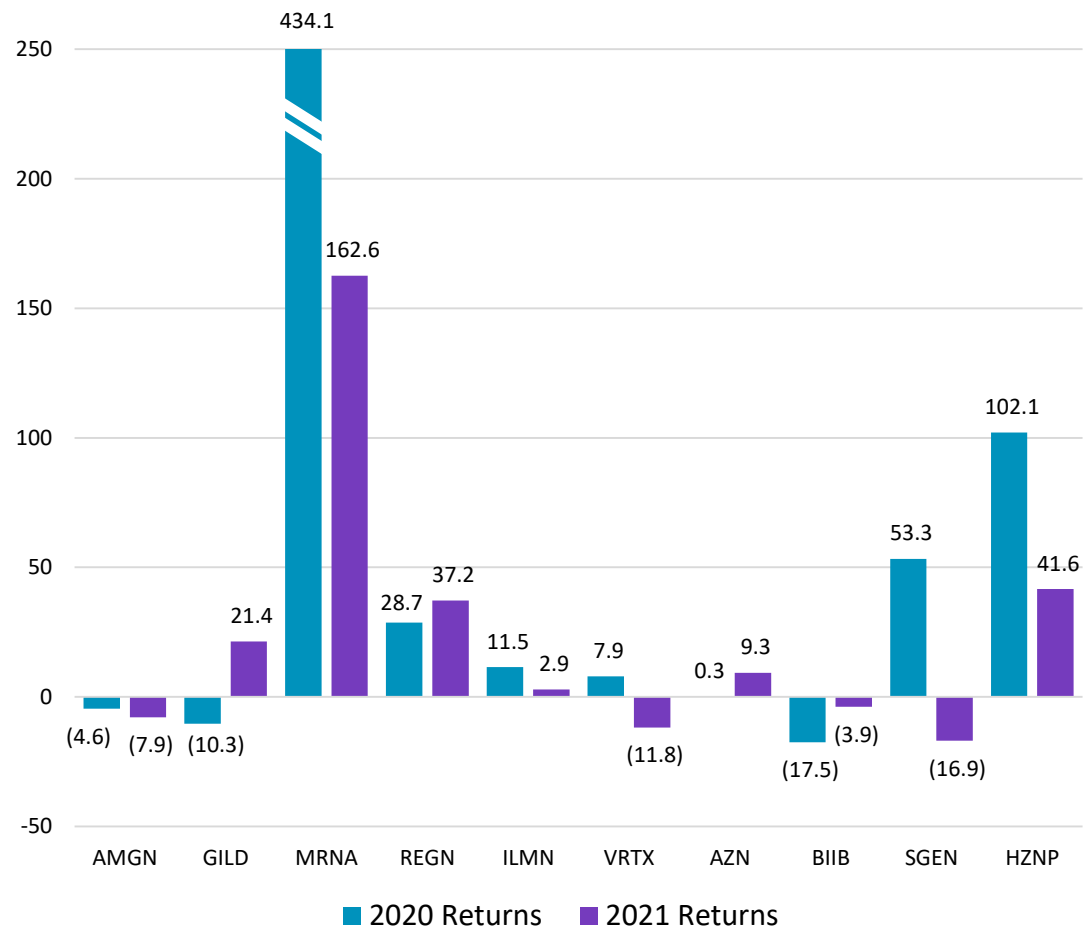
NBI 2021 Performance Drivers

NBI Return Attribution (%), YTD 2021 as of December 17



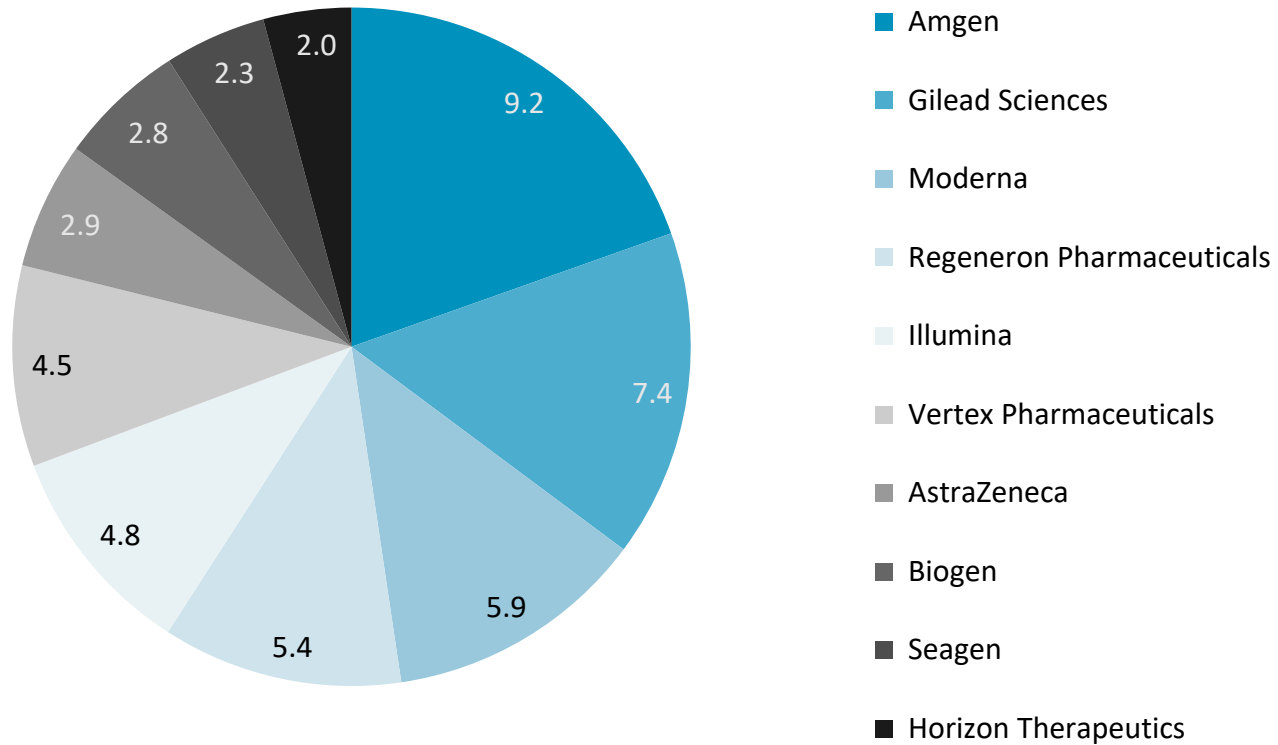
Source: Nasdaq Global Indexes, FactSet, Bloomberg as of December 31, 2021.

Top 10 Index Weights: FY'21 vs. FY'20 Returns (%)

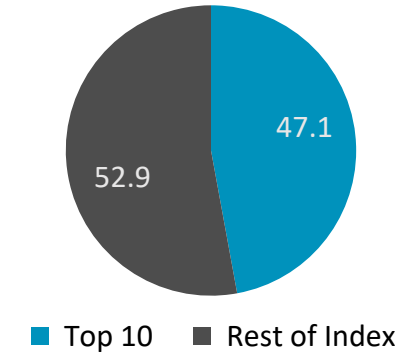


Nasdaq Biotech Index Composition

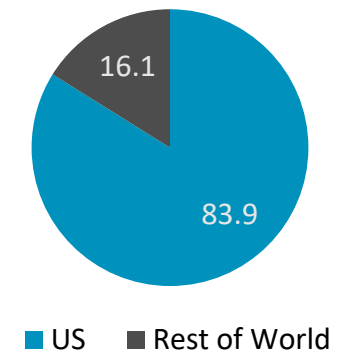
Top 10 Index Weights as of December 31, 2021 (%)



Top 10 vs. Rest of Index (%)



US vs. Rest of World (%)



NBI vs. S&P Biotechnology Index (SPSIBI)

Index Name	Index Ticker	Weighting Description	Weighting Constraints	Industry Classification	Launch Year	Count	Listing Venue
Nasdaq Biotechnology Index	NBI	Modified Market Cap-Weighted	8% cap for Top 5; 4% cap for rest	ICB: Biotechnology or Pharmaceuticals Subsectors	1993	373	Nasdaq-Only
S&P Biotechnology Select Industry Index	SPSIBI	Modified Equal-Weighted	Each constituent has liquidity to allow 100% daily turnover of a \$2Bn tracking portfolio	GICS: Biotechnology Sub-Industry	2006	189*	Nasdaq/NYSE/CBOE

*49/189 companies with zero revenue
100/189 < \$10MM quarterly revenue

Top 10 SPSIBI underweights vs. NBI:

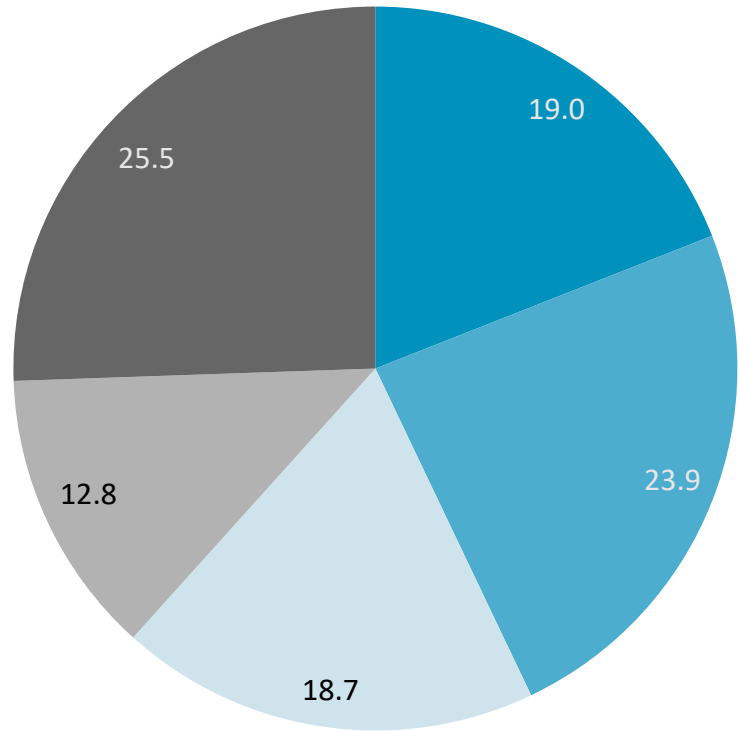
Company Name	NBI Weight	SPSIBI Weight	Market Cap (\$B)*
Amgen	9.22%	0.83%	\$126.7
Gilead Sciences	7.36%	0.80%	\$91.1
Moderna	5.87%	0.76%	\$103.0
Regeneron Pharmaceutical	5.39%	0.73%	\$66.8
Vertex Pharmaceutical	4.51%	0.82%	\$55.8
Biogen	2.85%	0.80%	\$35.2
Seagen	2.28%	0.84%	\$28.3
Horizon Therapeutics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

Top 10 SPSIBI exclusions vs. NBI:

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

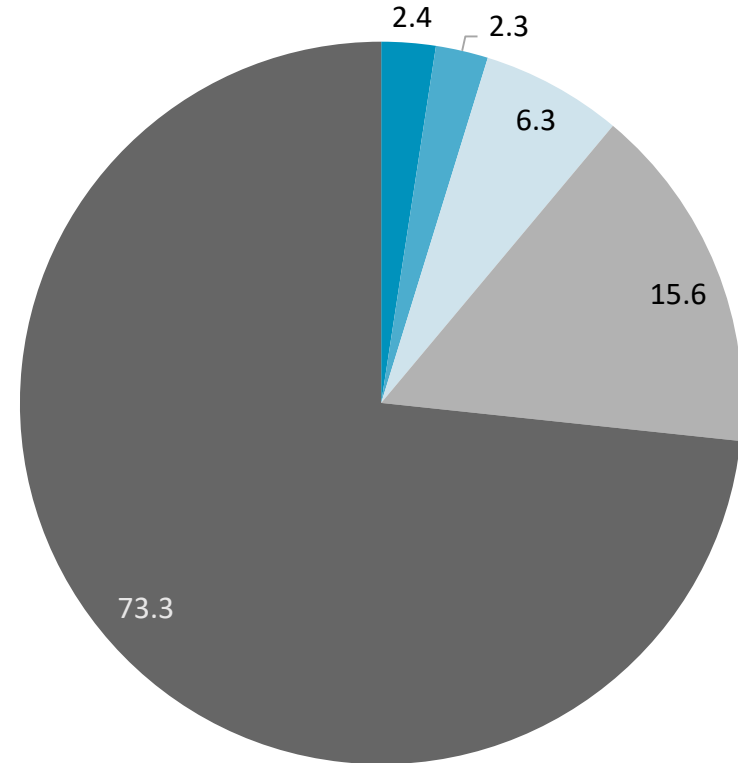
NBI vs. SPSIBI: Size Factor Profile

NBI Index Weight by Market Cap (%)



■ \$100B+ ■ \$50-100B ■ \$10-50B ■ \$5-10B ■ <\$5B

SPSIBI Index Weight by Market Cap (%)



■ \$100B+ ■ \$50-100B ■ \$10-50B ■ \$5-10B ■ <\$5B

Source: Nasdaq Global Indexes, FactSet, Bloomberg as of December 31, 2021.

Biotechnology vs. Pharmaceuticals

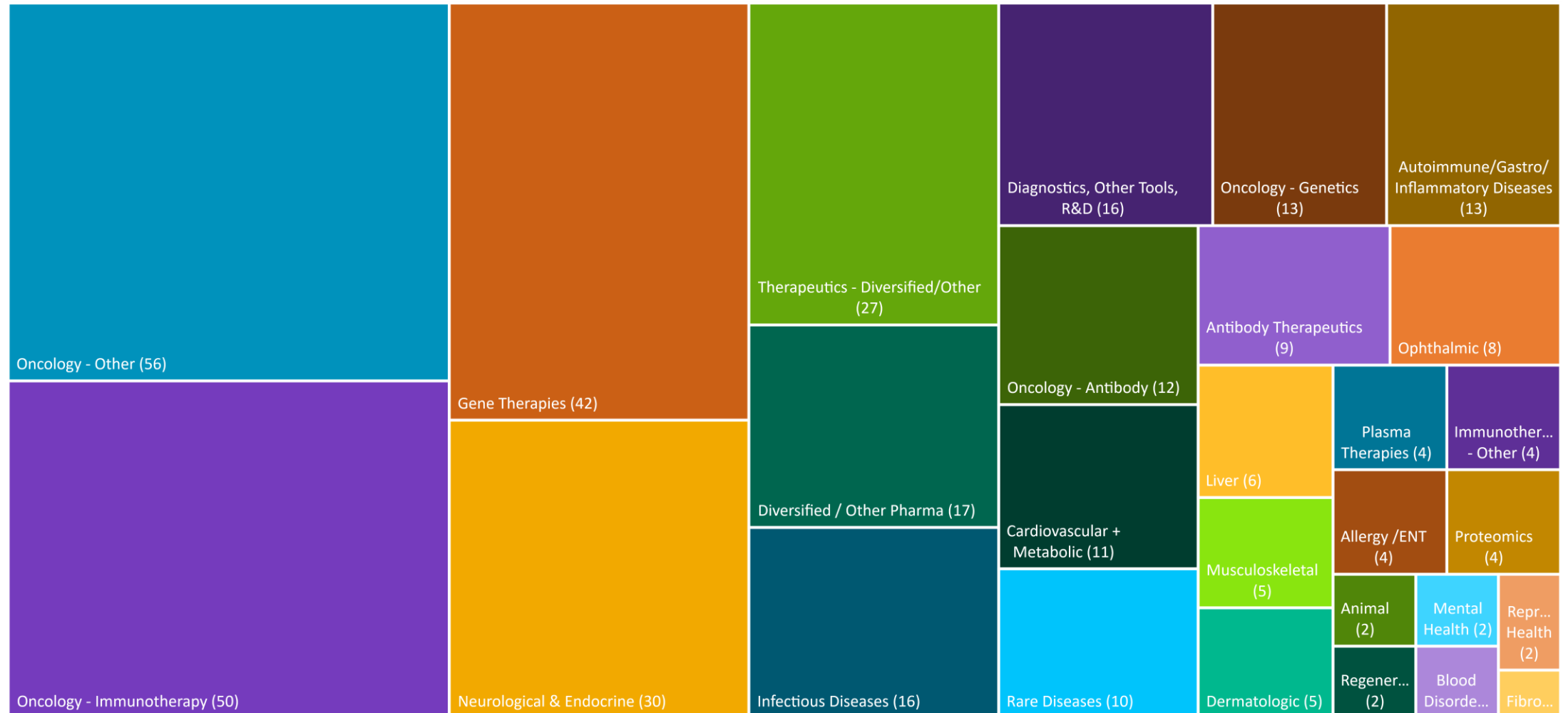
- 1) Biotechnology is a complex, hybrid industry comprised mainly of 2 types of companies:
 - R&D-intensive, often clinical trial-stage companies focused on intellectual property/patents
 - More mature companies with approved products already on the market, participating in all phases of Discovery / Development / Manufacture of treatments

- 2) Companies exist which blur the line between “pure-play Pharma” and “pure-play Biotech”
 - Amgen – largest NBI Index constituent – was reclassified by ICB in 2021 from Biotechnology to Pharmaceuticals
 - 53 companies representing 13% of NBI weight are classified as Biotechnology by ICB Subsector, but contain the word “Pharma” or “Pharmaceutical” in their Company Name
 - 185 companies classified as Biotechnology by ICB (35% of index weight) contain “Pharma” or “Pharmaceutical” in their Company Description, per Factset

- 3) Nasdaq-listed Pharmaceutical companies tend to be much younger than NYSE-listed (average time of 15 years since IPO vs. 37 years, respectively) based on Dow Jones US Select Pharmaceuticals Index
 - To construct the perfect benchmark for Biotechnology, ideally the index will capture all pure-play Biotechnology firms (most of which are Nasdaq-listed) + certain Pharmaceuticals that are “biotech-adjacent” or were originally founded as pure-play biotech (most of which are also Nasdaq-listed)

Biotechnology & Pharmaceutical Diversity

Number of NBI Companies by Area of Specialization



Moderna

NBI Weight: 5.87%

Moderna is a leading developer of vaccines, using messenger ribonucleic acid (mRNA) technology. Along with BioNTech (which partnered with Pfizer), Moderna created one of the first two – and the most effective overall – vaccines against Covid-19 in record time. As of October, 250 million people globally have received its vaccine. In addition to Covid-19, its product pipeline includes prophylactic vaccines, cancer vaccines, intratumoral immuno-oncology, localized regenerative therapeutics, systemic secreted therapeutics, and systemic intracellular therapeutics.

- Founded in 2010 and headquartered in Cambridge, Massachusetts
- Current Market Cap: \$122B
- 3-Year Price Return: **1,563%**
- FY'21 Revenue (est.): \$17.4B, up **2,070%** vs. \$0.8B in FY'20
- Q3'21 R&D Expense: \$451MM (**9%** of Revenue)
- Q3'21 Gross Margin: **84.1%**
- Q3'21 Free Cash Flow: \$3.2B
- Q3'21 Net Income: \$3.3B
- # of Employees: ~1,300
- Key Customers: US Government, COVAX



The Harvard Gazette

HEALTH & MEDICINE

Moderna edges out Pfizer vaccine in head-to-head comparison

Researchers found both the Pfizer and Moderna vaccines highly effective against breakthrough infections.

©Stock by Getty Images



COVID-19 Vaccination Record Card
Please keep this record card, which includes medical information about the vaccines you have received.

Last Name	First Name	Patient Number	Date
Date of Birth	Name/Manufacturer	Lot Number	
Vaccine			mm dd Y
1st DOSE COVID-19			mm dd Y
2nd DOSE COVID-19			mm dd Y

Large-scale study finds Moderna slightly more effective in preventing COVID-19 infection, hospitalization, and death



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Coronavirus Updates

THE CORONAVIRUS CRISIS

Moderna Says Studies Show Its Vaccine Is Effective Against The Delta Variant

June 30, 2021 · 11:23 AM ET

LAUREL WAMSLEY



COVID-19 Vaccine Moderna
0.20 mg/mL Dispersion for Intramuscular Use
COVID-19 mRNA Vaccine (nucleoside modified)
Discard Date/Time:
Multidose vial (10 doses of 0.5 mL)


Moderna says recently completed studies have found its vaccine to have a neutralizing effect against all COVID-19 variants tested, including the delta variant.
Free Tombeau/AFP via Getty Images

Regeneron Pharmaceuticals

NBI Weight: 5.39%

Regeneron is a leading biotechnology company. In early 2020, it started developing and testing hundreds of virus-neutralizing Covid-19 antibodies in genetically engineered mice, and in June, combined the two most potent, complementary and non-competing antibodies into a single cocktail for large-scale manufacturing and clinical trials (REGEN-COV). Regeneron's other products target patients with eye diseases, allergic & inflammatory diseases, cancer, cardiovascular & metabolic diseases, hematologic conditions, infectious diseases, and rare diseases.

- Founded in 1988 and headquartered in Tarrytown, New York
- Current Market Cap: \$68.2B
- 5-Year Price Return: **72.0%**
- FY'21 Revenue (est.): \$15.4B, up **218%** vs. \$4.9B in FY'16 (**26% CAGR**)
- Q3'21 R&D Expense: \$592MM (**17%** of Revenue)
- Q3'21 Gross Margin: **84.8%**
- Q3'21 Free Cash Flow: \$3.3B
- Q3'21 Net Income: \$1.6B
- # of Employees: ~9,100
- Key Customers: US Government, Sanofi



REGEN-COV®
(casirivimab and imdevimab)

The first COVID-19 combination therapy to receive EUA

Program Initiation

5 months

➔

Clinical Trials

10 months

➔

EUA Granted

Clinical Data

- ✓ **EUA granted** for 1.2g dose (for subcutaneous / IV administration) in high-risk, non-hospitalized patients after showing **70% reduction in deaths or hospitalizations**
- ✓ **EUA granted** for post-exposure prophylaxis in certain patients after showing **reduction in symptomatic infections by 81%**
- ✓ Two Ph3 studies have shown REGEN-COV may **reduce risk of death by 20-56%** in seronegative hospitalized patients*
- ✓ **Retains potency against all known variants**

Supply

- ✓ Signed new supply agreement in Sept. 2021 to supply **1.4 million additional doses** to the U.S. Government
- ✓ **Partnered with Roche** to manufacture and distribute **Ronapreve™ outside of the U.S. and to ensure availability** in low- and middle-income countries
- ✓ Expect capacity to manufacture **4 to 5 million additional doses** in 2022

Upcoming Milestones

- FDA decision regarding expansion of EUA to include pre-exposure prophylaxis and hospitalized indications
- Regulatory decision on BLA submission in treatment and prophylaxis indications (target action date of April 13, 2022)
- Regulatory submission for treatment in hospitalized patients

18 EUA: Emergency Use Authorization
BLA: Biologics License Application
MAA: Marketing Authorization Application

*Use in this population currently under regulatory review

REGEN-COV is an investigational medicine that is authorized by FDA under an EUA for certain uses. The development and manufacturing of REGEN-COV have been funded in part with federal funds from BARDA.

REGENERON

As of Q3'21:

- 26 active Phase 3 trials / 17 in Phase 1
- 30+ programs in Research and Candidate Selection
- Regeneron Genetics Center conducting one of the largest sequencing efforts in the world



Intellia Therapeutics

NBI Weight: 0.71%

Intellia Therapeutics is a clinical stage genome editing company, using CRISPR technology (discovered in 2012) to develop therapeutics for treatment of cancers and immunological diseases by permanently editing and/or correcting disease-associated genes in the human body with a single course. In August, researchers published results of a six-person clinical trial – the first of its kind – using Intellia’s drug technology to fix a genetic defect that causes a rare, fatal liver condition. Patients in the trial saw as much as a 90% reduction in faulty liver cells.

- Founded in 2014 and headquartered in Cambridge, Massachusetts
- Current Market Cap: \$8.2B
- 5-Year Price Return: **802%**
- FY'21 Revenue (est.): \$29.6MM, up **80%** vs. \$16.5MM in FY'16 (**12.4% CAGR**)
- Q3'21 R&D Expense: \$58.7MM (**815%** of Revenue)
- Q3'21 Gross Margin: **N/A**
- Q3'21 Free Cash Flow: \$(67.4)MM
- Q3'21 Net Income: \$(71.6)MM
- # of Employees: ~300
- Key Customers: Novartis, Regeneron Pharmaceuticals

A big step forward for gene therapy



NTLA-2001 by Intellia Therapeutics and Regeneron Pharmaceuticals

In a first, researchers successfully treated a genetic liver disease by injecting the CRISPR gene editing tool directly into a person's body.

Intellia Therapeutics

CRISPR breaks ground as a one-shot treatment for a rare disease

CRISPR reached a big milestone this year by treating a disease inside the body—here's what's next for the technology.

BY REBECCA SOHN | UPDATED JUL 26, 2021 5:01 PM

SCIENCE HEALTH



THE GENE EDITING TECHNOLOGY, CRISPR, REACHED A BIG MILESTONE LAST MONTH BY EDITING CELLS INSIDE THE HUMAN BODY.

Amgen

NBI Weight: 9.22%


Amgen, Inc. is a biopharmaceutical company, which engages in the discovery, development, manufacture and marketing of human therapeutics across a wide range of diseases. Its products include the following brands: Aranesp, Aimovig, KANJINTI, EVENITY, AMGEVITA, AVSOLA, BLINCYTO, MVASI, Corlanor, Enbrel, EPOGEN, IMLYGIC, Kyprolis, Neulasta, NEUPOGEN, Nplate, Parsabiv, Prolia, Repatha, Sensipar, Vectibix, Otezla, RIABNI, and XGEVA. Its current pipeline of drugs focuses on treating cancer, inflammatory, and cardiovascular diseases.

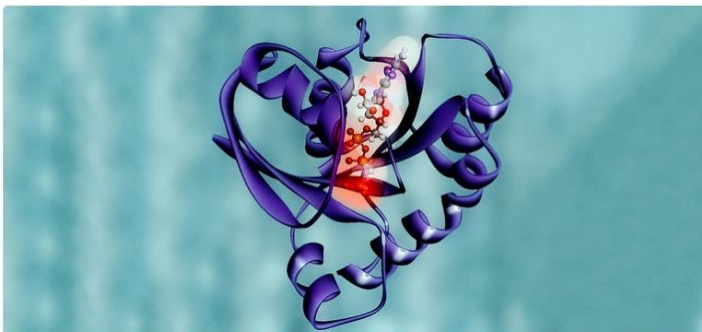
- Founded in 1980 and headquartered in Thousand Oaks, California
- Current Market Cap: \$130B
- 5-Year Total Return: **77.6%**
- FY'21 Revenue (est.): \$26.0B, up **15%** vs. \$22.7B in FY'16
- Q3'21 R&D Expense: \$1.4B (**21%** of Revenue)
- Q3'21 Gross Margin: **76.0%**
- Q3'21 Free Cash Flow: \$2.2B
- Q3'21 Net Income: \$1.9B
- # of Employees: ~24,300
- Key Customers: McKesson, AmerisourceBergen, Cardinal Health

BIOPHARMADIVE Deep Dive Library Events Topics

In first, FDA approves KRAS-blocking cancer drug from Amgen

Published May 28, 2021 • Updated May 29, 2021

 Ned Pagliarulo
Lead Editor



National Cancer Institute, NIH

Since the early 1980s, cancer researchers have chased a gene called KRAS that's frequently mutated in many lung, colon and pancreatic tumors. Their efforts to target it repeatedly came up short, earning the elusive gene a reputation as "undruggable."

Amgen and Arrakis Aim to Destroy Disease with Targeted RNA Degraders

Published: Jan 11, 2022 | By Alvin Clavines



Al Seib / Los Angeles Times via Getty

Amgen will partner with Arrakis Therapeutics for an innovative collaboration to research and develop RNA degrader therapeutics against a range of difficult-to-drug targets in multiple therapeutic areas.

This new class of "targeted RNA degraders" consists of small molecule drugs that selectively destroy RNAs encoding disease-causing proteins by inducing their proximity to nucleases.

Amgen and Arrakis will work together to design and functionalize these molecules to precisely degrade targeted RNAs, and Amgen will advance further preclinical and clinical development activities.

As of Q4'21:

- 21 Phase 1 trials
- 9 Phase 2 trials
- 16 Phase 3 trials

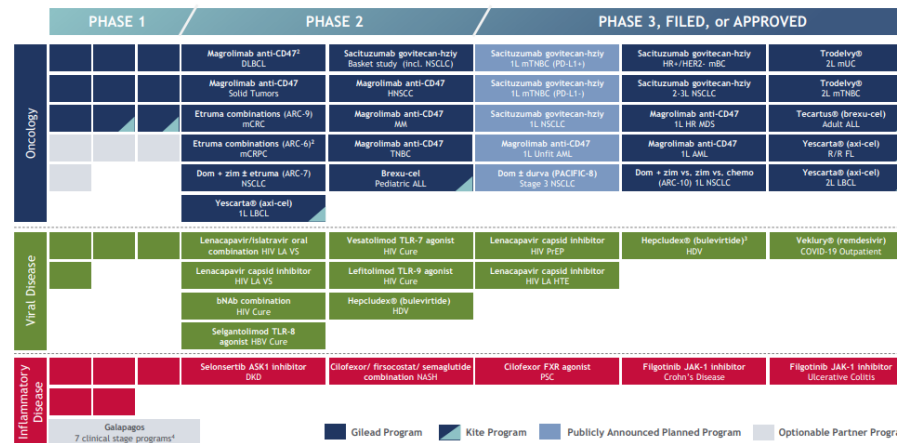
Gilead Sciences

NBI Weight: 7.36%

Gilead Sciences, Inc. is a biopharmaceutical company, which engages in the research, development, and commercialization of medicines in areas of unmet medical need. The firm's primary areas of focus include human immunodeficiency virus, acquired immunodeficiency syndrome, liver diseases, hematology, oncology, and inflammation and respiratory diseases. It offers antiviral products under Harvoni, Genvoya, Epclusa, Truvada, Atripla, Descovy, Biktarvy, Stribild, Viread, Odefsey, Complera/Eviplera, Sovaldi, Vosevi, and Veklury (remdesivir) brands.

- Founded in 1987 and headquartered in Foster City, California
- Current Market Cap: \$85B
- 5-Year Price Return: **21.4%**
- FY'21 Revenue (est.): \$26.6B, down 12% vs. \$30.3B in FY'16
- Q3'21 R&D Expense: \$1.15B (**15%** of Revenue)
- Q3'21 Gross Margin: **83.6%**
- Q3'21 Free Cash Flow: \$3.1B
- Q3'21 Net Income: \$2.6B
- # of Employees: ~13,600
- Key Customers: McKesson, AmerisourceBergen, Cardinal Health

Robust Pipeline with Upcoming Catalysts



55 Clinical stage programs¹

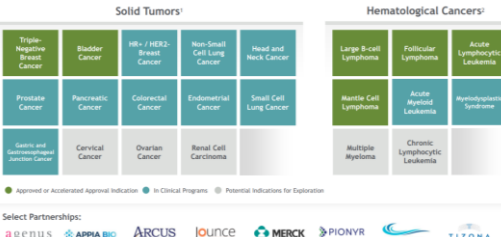
18 NDA/BLA/MAA filings, P3 and registrational P2

11 Potential clinical stage opt-in assets

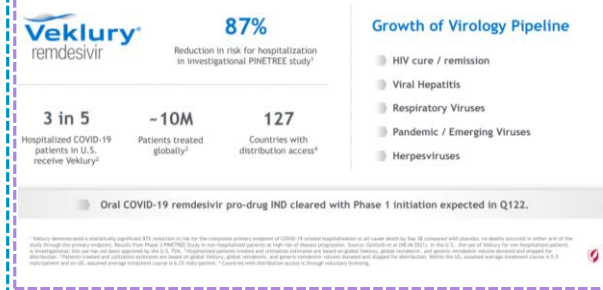
Delivering a World-Class Oncology Portfolio



Expanding Across Breadth of Indications



Applying Antiviral Expertise to COVID-19 and Beyond



Gilead's Remdesivir Covid-19 Therapy Cuts Risk of Hospitalization in Study



Vials of the Covid-19 drug remdesivir at a Gilead Sciences manufacturing site. Gilead has asked the FDA to expand authorization to nonhospitalized patients based on recent study findings.

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