

Next-generation therapeutics thrust into the spotlight

COVID-19 has accelerated development and awareness of next-generation therapeutics, including mRNA vaccines, boosting the field's dealmaking and investment activities.

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The past 12 months have seen the frontiers of life science R&D in the public eye in an unprecedented way. The phenomenal success of the development of COVID-19 vaccines, including mRNA vaccines, has put next-generation therapeutics on the front page and into the general lexicon. These globally significant developments aside, how has the broader next-generation therapeutics landscape evolved in the past 12 months?

In June 2020, the 4-year outlook for the cell, gene and nucleic acid therapy market was \$38 billion, according to Evaluate Pharma sell-side consensus forecasts (*Biopharma Dealmakers*, June 2020, B3). One year on, excluding COVID-19 vaccines, the 4-year outlook has climbed to \$41 billion. Here, we analyze the area again to highlight the latest trends in the market.

An unprecedented year

Next-generation therapeutics were already headline-generators prior to COVID-19, whether that be on the back of scientific innovations, impressive clinical outcomes, polarizing pricing debates or deal announcements. The past 12–18 months, however, would have been difficult for industry observers to predict.

In our June 2020 article we commented that the next-generation therapeutics space may have a key part to play in defining the exit strategy from the pandemic, and in some markets at least this has turned out to be the case. Evaluate Pharma sell-side forecasts size the global COVID-19 vaccine market at a staggering \$49 billion in 2021, of which the mRNA vaccines from Pfizer/BioNTech and Moderna make up the vast majority at \$46 billion (Fig. 1). Indeed, the ground-breaking success of the COVID-19 vaccine effort is such that Pfizer/BioNTech's Comirnaty is forecast to be the biggest-selling pharma product globally in 2021, leapfrogging established brands such as Humira, Keytruda, Eliquis and other big sellers. Moderna's COVID-19 vaccine is forecast to be the third biggest-selling product in 2021. Evaluate Pharma consensus also forecasts a rapid decline in sales following the initial ramp up of vaccination programs. With so much about how the pandemic will evolve still uncertain—from the emergence of new variants to booster dose programs—and such disparity in the levels of and access to vaccination by country, it would not be a surprise to see volatility in these forecasts.

Outside vaccines, Evaluate Pharma forecasts the next-generation therapeutics market at \$59 billion in 2026 (Fig. 2). The growth forecast is far in excess of the overall pharma market growth rate, as would be expected for a novel emerging area. Within the next-generation therapeutics landscape, the most rapid growth is forecast for cell therapies, including regenerative approaches, followed by gene therapy. Gene therapy is forecast

to be the largest next-generation segment in 2026 at \$20 billion, led by Novartis's Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy, highlighted as a key approval in our 2020 article.

Overall, comparing against our 2020 analysis, the outlook for the next-generation therapeutics landscape has slowed slightly. The combined 4-year compound annual growth rate for the space is currently +54%, down from +58% last year. Forecasts have slowed for all areas except cell therapy (Fig. 3), where 2026 expectations are led by programs such as Iovance's tumor-infiltrating lymphocyte cell therapy candidates LN-144 and LN-145, and Athersys's allogeneic 'off-the-shelf' stem cell product, Multistem.

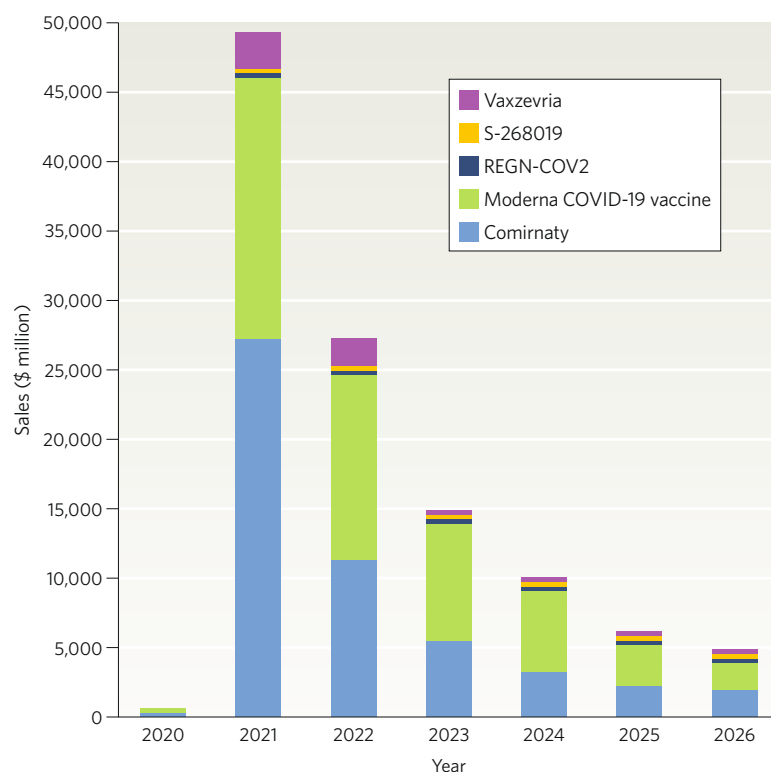


Fig. 1 | COVID-19 related next-generation therapeutics, current and forecasted sales (2020–2026). Next-generation therapeutics include vaccine, cell, gene, regenerative and nucleic acid therapy products. Source: EvaluatePharma, July 2021.

Key approvals

Looking past the COVID-19 headlines, several other key regulatory approvals in the next-generation therapeutics landscape have been secured in the past year. Novartis's PCSK9-targeting small interfering RNA (siRNA) Leqvio (inclisiran), forecast to be the biggest-selling next-generation therapeutic in 2026 with sales of \$2.1 billion, was approved by the EMA towards the end of 2020. An unexpected complete response letter from the Food and Drug Administration (FDA) has delayed an approval decision in the US, though this was related to a European manufacturing plant and has had no appreciable impact on sales forecasts according to Evaluate Pharma. Leqvio will be competing in a hyperlipidemia market in which two PCSK9-targeting monoclonal antibodies (mAbs) have already been approved.

In March 2021, Bristol Myers Squibb secured FDA approval for its B cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T cell therapy Abecma (idecabtagene vicleucel). Abecma is the first cell therapy approved for multiple myeloma, following earlier CAR T cell therapy successes in other hematological malignancies.

December 2020 saw Orchard Therapeutics secure European approval for the lentiviral vector-based gene therapy Libmeldy (atidarsagene autotemcel) for the treatment of the rare disease metachromatic leukodystrophy (MLD). The UK's NICE subsequently rejected the product for NHS use based on uncertainty about long-term stabilization of symptoms in patients with MLD. Clearly the commercial model for next-generation therapeutics is still evolving; Orchard is no stranger to the commercial challenges the space presents, having registered sales of just \$2.5 million in both 2019 and 2020 for the severe combined immunodeficiency ('bubble boy') product, Strimvelis, that it acquired from GSK in 2018—insufficient to cover costs. Sales forecasts in 2026 for Libmeldy are \$359 million according to Evaluate Pharma.

Evaluate Pharma now lists almost 6,500 active cell and nucleic acid therapeutic R&D programs, up >1,000 (20%) compared with the same analysis from 12 months ago. The clinical pipeline has grown by closer to 25%. These growth statistics are a substantial increase over the same comparison for 2019 to 2020 (6% growth in the pipeline and 8% in the clinical pipeline) and suggest that far from dampening R&D, the COVID-19 era is characterized by an acceleration of progress in the next-generation therapeutics landscape.

Novartis leads the pack

In our previous articles we commented that relatively few large biopharma companies feature in the top 20 in terms of sales forecasts for next-generation therapeutics. This is still the case, though there are signs of larger pharma taking an increasing interest. Six large pharma companies (defined as in the top 25 by prescription drug sales in 2026) now make it into the top 20, up from five in 2020 (Fig. 4). Pfizer is the new large pharma entrant into the top 20 ranking, with forecasts for gene therapy programs in Duchenne muscular dystrophy and hemophilia, and antisense programs in diabetes and cardiometabolic indications.

It is Novartis, however, that retains the top spot and continues to cement its position as the global next-generation therapeutics leader, with 2026 forecasts of \$5.4 billion. This outlook is led by Leqvio, discussed above, as well as a diverse portfolio of marketed products: gene therapy Zolgensma indicated for spinal muscular atrophy; CAR T cell therapy Kymriah (tisagenlecleucel) indicated for acute lymphoblastic leukemia and diffuse large B cell lymphoma; and, to a lesser extent, Luxturna (voretigene neparvovec), a gene therapy indicated for retinal dystrophy. The spinal muscular atrophy market is an increasingly competitive space since the approval of Roche's Evrysdi (risdiplam), an oral small-molecule modulator of SMN2 gene splicing approved by the FDA in August 2020. Indeed, the early signs are that sales for both Zolgensma and Biogen's antisense product Spinraza (nusinersen; the first disease-modifying treatment for spinal muscular atrophy) are

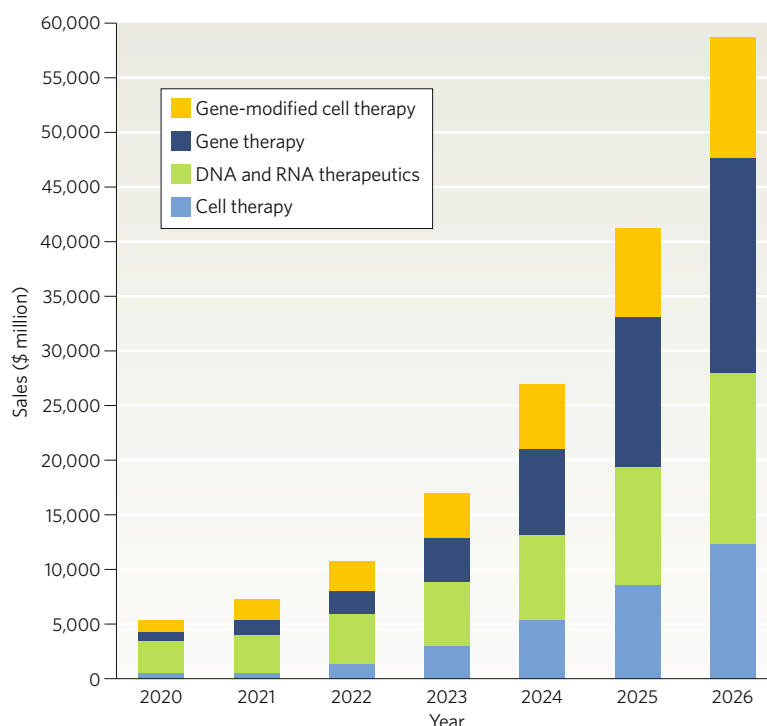


Fig. 2 | Current and predicted sales of cell, gene, regenerative and nucleic acid therapy products (2020–2026). Source: EvaluatePharma, July 2021.

plateauing in the US, with Evrysdi gaining market share. These early commercial battles indicate that for all the unique promise of next-generation therapeutics, they are not immune to the broader trend of increasing competitive pressure.

Sarepta, previously vying with Novartis for top spot in this ranking, has fallen several places to 4th in our latest analysis. This is largely due to revision of forecasts for Sarepta's biggest growth driver SRP-9001, in development for Duchenne muscular dystrophy, following the January 2021 announcement that the product had failed to meet the primary endpoint in the Study-102 trial.

If any further evidence of the dynamism of the next-generation therapeutics landscape were needed, across the top 20 ranked companies by sales forecasts in 2026 only 6 booked any next-generation product sales in 2020.

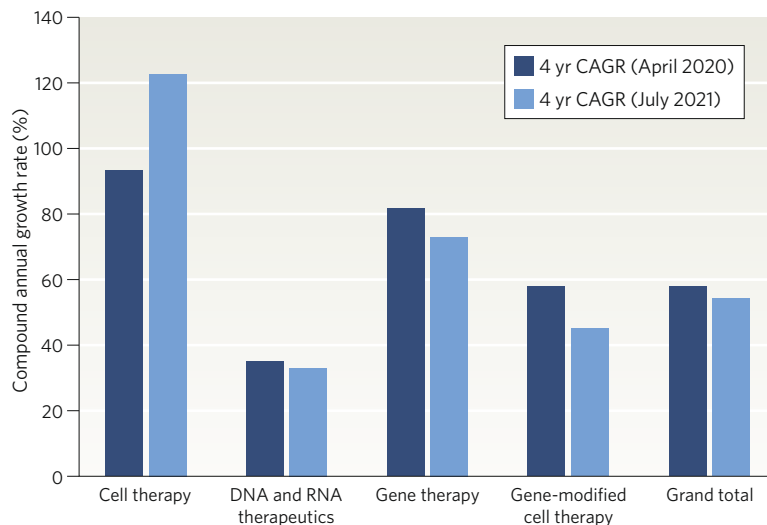


Fig. 3 | Cell, gene, regenerative and nucleic acid therapy products by compound annual growth rate (CAGR) from 2020 to 2021. Source: EvaluatePharma, July 2021.

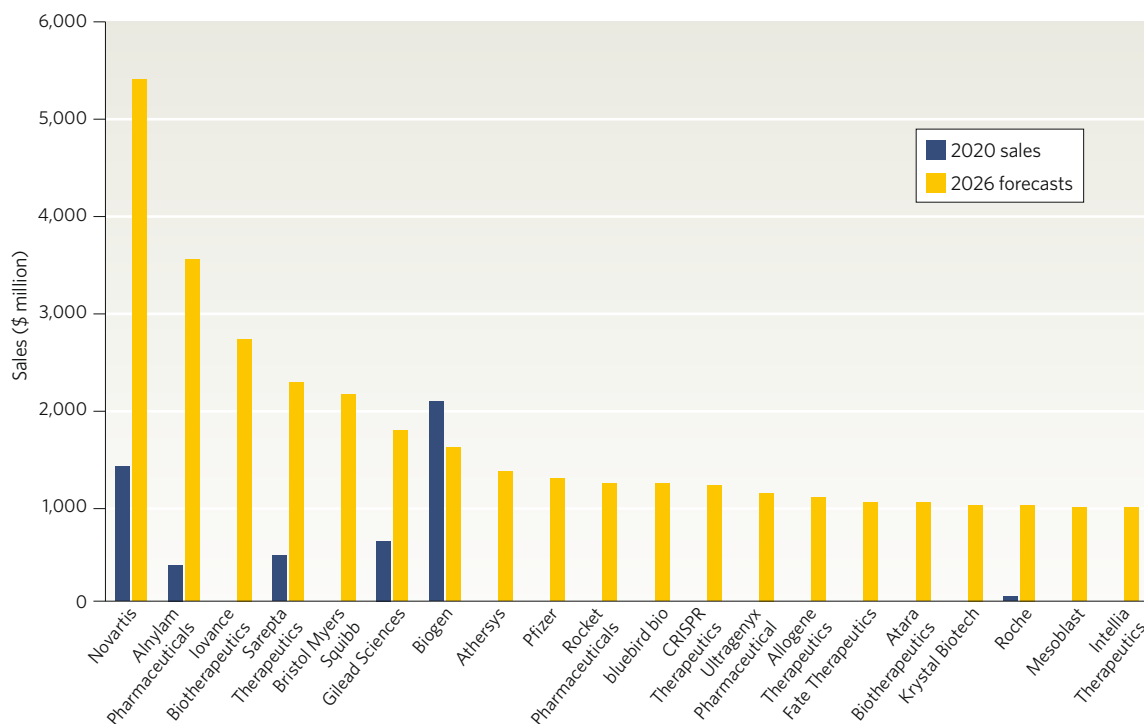


Fig. 4 | Top 20 companies in the field of cell, gene, regenerative and nucleic acid therapies based on current and forecasted sales (2020–2026). Source: EvaluatePharma, July 2021.

Dealmaking trends

Bayer is the latest major pharmaceutical company to commit further to the space via the October 2020 acquisition of Asklepios Biopharmaceuticals, also known as Askbio, in a deal worth up to \$4 billion. Askbio strengthens Bayer’s emerging cell and gene therapy business through its adeno-associated virus (AAV)-based technology platform.

In December 2020, Eli Lilly added the first gene therapy program to its portfolio by acquiring Preveil Therapeutics and its disease-modifying AAV9-based gene therapies for patients with neurodegenerative diseases, for \$1.04 billion.

Sanofi has been active at the dealmaking table over the past 12 months, including a first major investment in cell therapy. Sanofi in-licensed Kiadis’s K-NK004 in July 2020 based on its potential to improve the potency of its anti-CD38 monoclonal antibody Sarclisa, which was subsequently launched for multiple myeloma. Sanofi’s broader recognition of the platform and associated off-the-shelf natural killer (NK) cells led to the acquisition of Kiadis for \$358 million, announced in November 2020. Sanofi followed up by acquiring Tidal Therapeutics, a next-generation biotech that utilizes a novel mRNA-based approach to reprogram immune cells in vivo, in a deal worth up to \$470 million. And in August 2021, Sanofi announced that it would acquire the mRNA vaccines and therapeutics company Translate Bio for \$3.2 billion.

As expected, the largest drug deals over the past year predominantly involve major pharma. In April 2020, Janssen entered into a strategic collaboration and option agreement with Fate Therapeutics for the development of T cell cancer immunotherapies. Under a deal worth up to \$3 billion, Fate will leverage its induced pluripotent stem cell product platform to generate CAR NK and CAR T cell product candidates, and Janssen retains option rights for development and commercialization.

Similarly, Merck & Co. has engaged in a global collaboration with Artiva Biotherapeutics, a company focused on the development of allogeneic NK cell therapies to treat cancer. The partnership will leverage Artiva’s off-the-shelf allogeneic NK cell manufacturing platform and proprietary CAR-NK technology to

develop novel therapies targeting solid tumor-associated antigens. The collaboration initially involves two CAR-NK programs, with an option for a third in a deal worth up to \$1.88 billion.

The above examples highlight a dealmaking theme of the past year: major pharma entering the next-generation therapeutic space, including through large deals for relatively early-stage drug programs.

Outlook

While the COVID-19 pandemic has undoubtedly had an impact on the next-generation therapeutics space—for example, general disruption caused by lockdowns was said to have slowed new patient starts on Novartis’s gene therapy Zolgensma—overall the macro trends describe a landscape that is going from strength to strength. Evaluate Pharma consensus forecasts major growth to 2026, far outstripping the background growth rate of the industry as a whole. The forecasts predict growth from a market of \$5 billion in 2020 to \$58 billion in 2026. While the space is largely made up of smaller niche players, trends also indicate an increasing focus from major pharma.

The landscape is clearly highly volatile. In our 2020 report the product attracting the biggest forecasts was Sarepta’s SRP-9001, in development for the relatively ‘established’ next-generation therapeutic target Duchenne muscular dystrophy. A clinical setback has pushed this product down the list to be replaced at the top by Novartis’s siRNA Leqvio, approved in Europe, a product that will launch into new ground for next-generation therapeutics: the large and complex hypercholesterolemia and dyslipidemia markets.

The next-generation therapeutics landscape continues to break new ground, and no better evidence of that could be found than the phenomenal clinical and commercial success of the mRNA COVID-19 vaccines. It will be fascinating to watch how the market evolves over the coming 12 months as the world emerges, hopefully, from the COVID-19 pandemic.

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