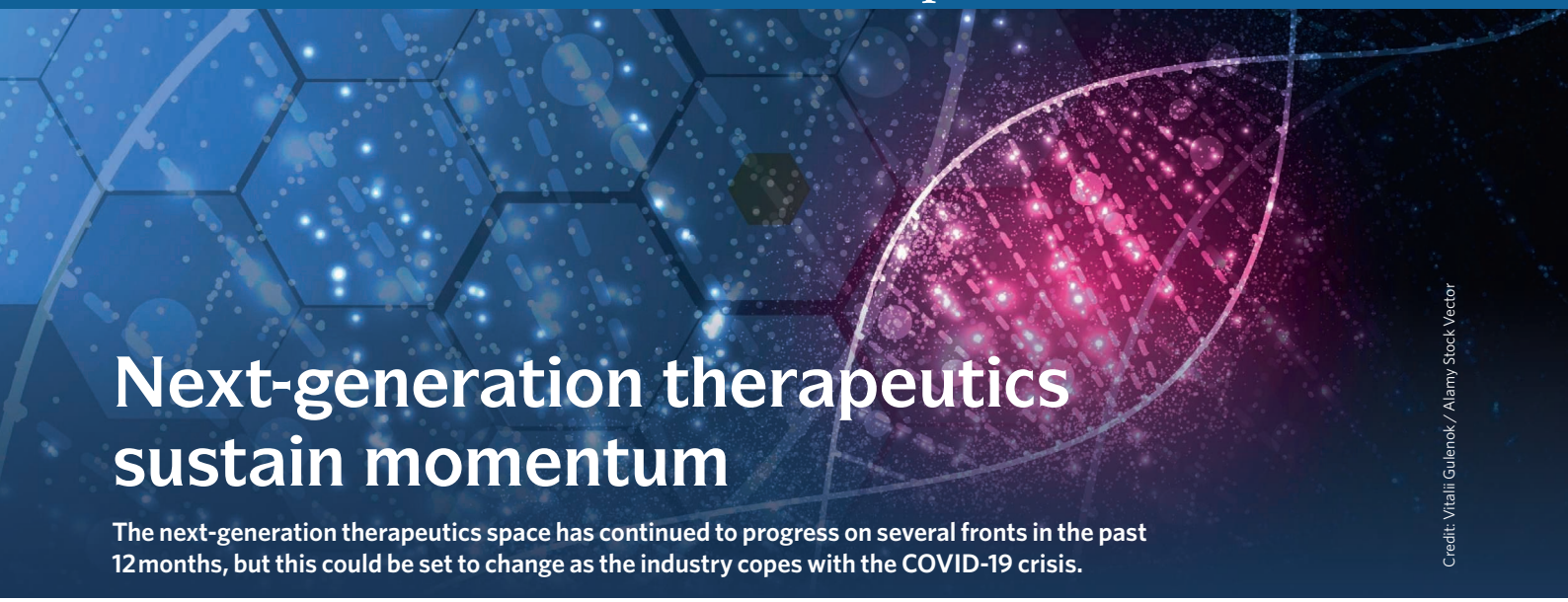

Credit: Vitalii Gulenok / Alamy Stock Vector

Next-generation therapeutics sustain momentum

The next-generation therapeutics space has continued to progress on several fronts in the past 12 months, but this could be set to change as the industry copes with the COVID-19 crisis.

Paul Verdin

In April 2019, the combined 2024 sales forecast for the cell, gene and nucleic acid therapy market was $41 billion, according to EvaluatePharma sell-side consensus forecasts (*Biopharma Dealmakers* B15–17, June 2019). One year on, we analysed the area again, and here we highlight the latest trends in market forecasts, approvals, development pipeline focus, leading companies and dealmaking for next-generation therapeutics.

Fluctuating forecasts

Although clinical progress has boosted the number of next-generation therapeutic products on the market since 2019, our analysis of the same landscape puts the overall forecast value in 2024 at $38 billion—a 7% contraction of commercial expectations (Fig. 1).

Forecasts fluctuate of course, and volatility in forecast commercial performance is to be expected in such a pioneering area. Looking beyond the headline value, however, reveals that forecasts for DNA and RNA therapeutics (such as antisense oligonucleotides) and gene therapy have remained relatively stable—cell therapy is where the largest declines are apparent, as forecasts have eroded by almost $3 billion (or approximately 20%) since this time last year (Fig. 2). It is too soon to say whether this is the beginning of a cooling-off of commercial expectations for some cell therapy approaches. However, perhaps it could reflect growing recognition of the strong competition in some areas such as blood cancers, as well as the access and affordability challenges that affect cell therapies in general. It is also too soon to assess the impact of the COVID-19 pandemic, which could dramatically affect future forecasts.

Key approvals

The past 12 months have kept up the recent approval momentum in the field. Among the new products with the greatest expectations is AveXis/Novartis's Zolgensma (onasemnogene abeparvovec), which became the first US Food and Drug Administration (FDA)-approved gene therapy for spinal muscular atrophy (SMA) in May 2019. This approval also set up an interesting dynamic within the next-generation therapeutics space, with Zolgensma launching into a market already occupied by Biogen's Spinraza (nusinersen, an antisense oligonucleotide). Both therapies target the underlying cause of SMA, but Zolgensma is theoretically a 'one-and-done' treatment, while Spinraza requires repeated administration. Zolgensma has checked Spinraza's growth and is forecast to be the leader in an increasingly crowded SMA market by 2024, with sales of $2.04 billion compared with $1.57 billion for Spinraza.

Vyondys 53 (golodirsen), the second of Sarepta Therapeutics' growing portfolio of exon-skipping antisense oligonucleotides for Duchenne muscular dystrophy (DMD), was approved by the FDA in December 2019. And in Europe, there was a first approval for bluebird bio, with a European Medicines Agency (EMA) nod for Zynteglo (autologous CD34$^+$ cells encoding the

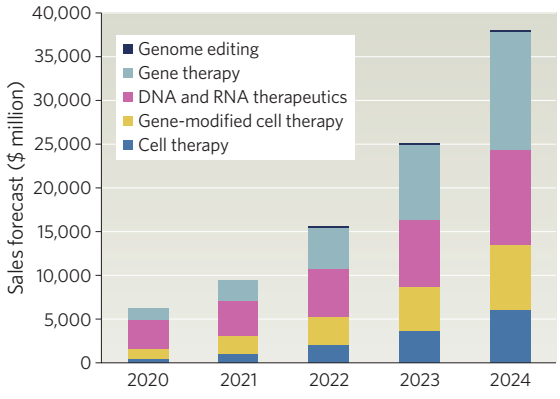

Fig. 1 | Sales growth forecasts of cell, gene and nucleic acid therapy products from 2020 to 2024. Source: EvaluatePharma, April 2020.

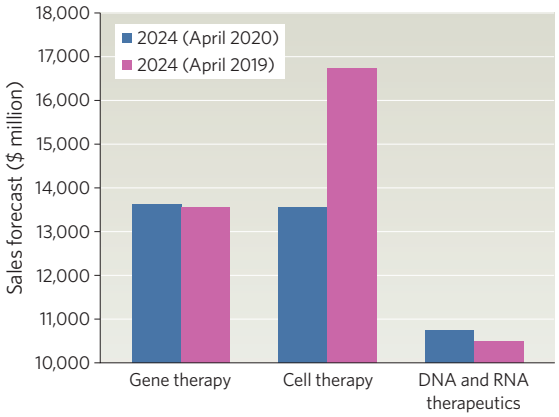

Fig. 2 | Changes in sales growth forecast trends of cell, gene and nucleic acid therapy products in 2024. Source: EvaluatePharma, April 2020.

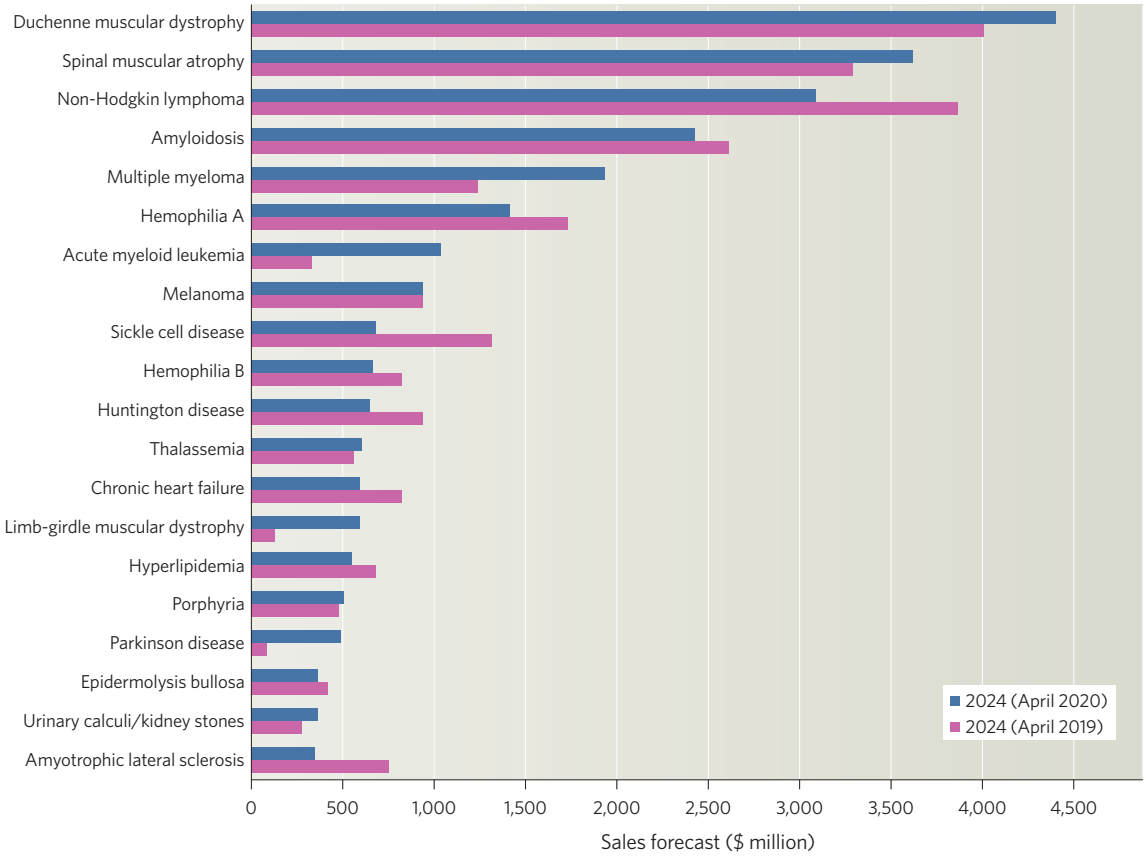

Fig. 3 | Top 20 indications in the field of cell, gene and nucleic acid therapies, based on 2024 sales forecasts. Source: EvaluatePharma, April 2020.

βA-T87Q-globin gene) for patients with β-thalassemia, as well as an EMA approval for Akcea/Ionis's Waylivra (volanesorsen), an antisense oligonucleotide therapy for familial chylomicronemia syndrome.

The scale and diversity of progress being made in the next-generation therapeutics space is a testament to the industry's ability and effort in developing novel science into commercial products. Across the industry, EvaluatePharma lists >5,300 active R&D programs in cell and nucleic acid medicine, an increase of 6% on the same analysis 12 months ago. Just over 2,000 of these next-generation therapeutic programs are in clinical development (an increase of 8% over 12 months), with more than 200 programs in phase 3 trials or at the regulatory filing stage.

Leading indications

Current clinical development pipelines in the field have a large focus on oncology, with 16 of the top 20 indications in cancer. The most studied non-oncology indications are rare ophthalmology conditions, Parkinson disease, osteoarthritis and peripheral vascular disease (Fig. 3). In preclinical research, the trend is different: 13 of the top 20 most studied indications are outside oncology.

Looking at where the value is anticipated to rise, at least in the near term, the picture is similar to 12 months ago. The top ranked indications by 2024 sales are those for which next-generation therapeutics are more clinically and commercially mature, with DMD, SMA and non-Hodgkin lymphoma topping the rankings.

Interestingly, 2024 forecasts for DMD are based on substantial sales growth from pipeline products: of the 10 next-generation therapeutics contributing to the 2024 sales forecast of $4.4 billion only two are currently marketed—Sarepta's Vyondys 53 and Exondys 51 (eteplirsen)—and 80% of this forecast figure is tied to R&D-stage programs. For SMA, the picture is the opposite: two of the three products contributing to 2024 sales are already marketed (Zolgensma and Spinraza), and >99% of the 2024 forecast of $3.6 billion is contributed by these marketed products.

The risk inherent in these forecasts is therefore very different, even without factoring in uncertainty around commercial performance once on the market. Across the top 20 indications by 2024 sales, only 6 are currently validated to the extent of regulatory approval and so clearly the space will continue to be highly dynamic.

Companies taking the lead

This dynamism is also reflected in the company rankings (Fig. 4). This time last year Sarepta led the pack in terms of 2024 forecast sales, and few major biopharma players featured in the top 20 by forecast revenues. Again, only 5 of the top 20 companies are large biopharma: Novartis, Bristol-Myers Squibb (following the acquisition of Celgene), Biogen, Gilead and Roche. In this year's analysis, however, Novartis leapfrogs Sarepta—albeit marginally—to become the top-ranked company in the field, with sales forecasts of $4.25 billion versus Sarepta's $4.14 billion in 2024.

Indeed, something of a niche is opening up in an otherwise highly fragmented landscape, with Novartis and Sarepta cementing

Methodology box

This analysis used data extracted from EvaluatePharma (data extracted in April 2020). Company and total product sales forecasts are Evaluate Consensus Forecasts, and represent an unweighted average of up to six forecasts from equity analyst research. Sales by indication are adapted from total product sales using a proprietary methodology. Historical sales, R&D pipelines and product classifications are based on company-disclosed information. All analysis, modelling, mapping and aggregation of data uses proprietary Evaluate methodologies.

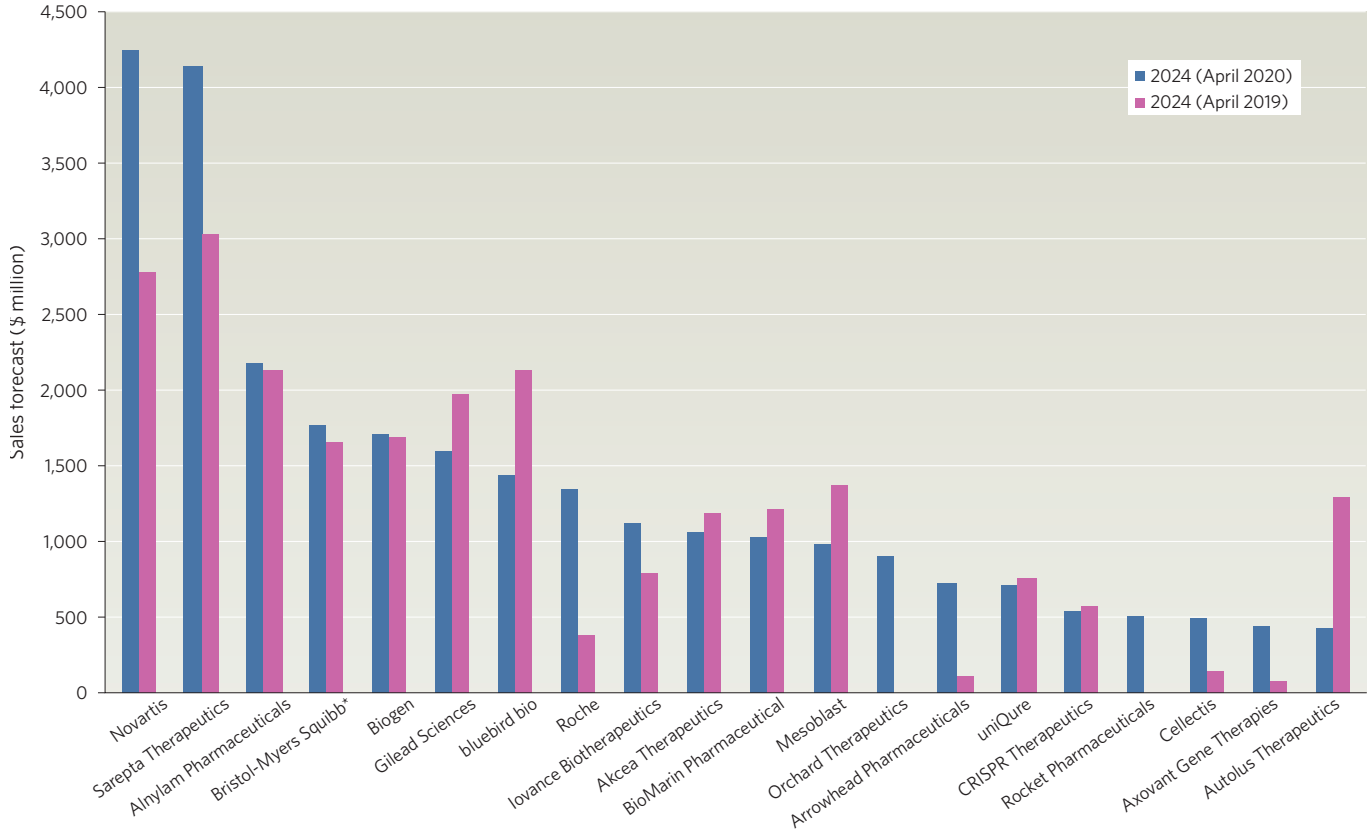

Fig. 4 | Top 20 companies in the field of cell, gene and nucleic acid therapies, based on 2024 sales forecasts.
*Celgene forecasts in Apr 2019. Source: EvaluatePharma, April 2020.

their leading positions and each expected to generate sales approximately double those of the next highest selling company in 2024 (Alnylam, in third place with $2.2 billion sales in 2024).

The Novartis portfolio delivering these sales is highly diversified, and includes the gene therapy Zolgensma for SMA (sales over $2 billion in 2024), the chimeric antigen receptor (CAR)-T cell therapy Kymriah (tisagenlecleucel) for blood cancers (sales over $1 billion in 2024) and the filed lipid-lowering RNAi candidate inclisiran (sales over $1 billion in 2024), which was obtained through acquisition of The Medicines Company in November 2019. For Sarepta, the near-term focus is on DMD, with far and away the biggest catalyst to 2024 being the micro-dystrophin gene therapy SRP-9001. Despite only being in phase 2 development, SRP-9001 is forecast to be the biggest-selling product in the cell and gene therapy space in 2024, with sales of more than $2.5 billion.

The remainder of the top 20 company ranking is comprised of numerous smaller and focused players, with several of their peers serving as take-out targets for major biopharma in the recent past—for example, AveXis, Spark and The Medicines Company.

Dealmaking trends

Major pharmaceutical companies have predominantly entered the space through acquisition. Novartis has been particularly active in building its leading position through acquisition—its $8.7 billion purchase of AveXis in 2018 was followed up in November 2019 with an even bigger pay-out of $9.7 billion for The Medicines Company.

Astellas is another major player that has been active at the deal table, picking up Xyphos Biosciences (CAR-T cell therapies) for $665 million in December 2019 and Audentes Therapeutics (gene therapy) for $3 billion in January 2020. Biogen continued its dealmaking in the space through the June 2019 acquisition of Nightstar Therapeutics for $800 million (gene therapy in ophthalmic disorders), and a February 2020 worldwide development and commercialization licensing deal with Sangamo Therapeutics for gene regulation therapies in Alzheimer disease, Parkinson disease and other neurological disorders (including $350 million upfront). In December 2019, Roche bought in to Sarepta's SRP-9001 through licensing of ex-US rights in a deal worth $750 million upfront and potentially up to $2.85 billion.

Outlook

On the face of it, progress in the next-generation therapeutics space continued unabated in the past 12 months—pipelines progressed, more innovative new products were approved by the regulators, deals were done and sales forecasts anticipating rapid growth in the space largely held up, barring some declines in cell therapy.

But it should be noted this activity predates the COVID-19 pandemic that has swept across the world. It seems unavoidable that the industry will feel a negative impact from this unparalleled crisis; for example, in delays to clinical trial progress and potential delays in regulatory approval for new products—and next-generation therapeutics will not be immune to this.

It is less clear how industry and societal thinking may evolve based on the impact of the pandemic; for example, in terms of allocation of R&D and healthcare spending, and prioritization of research into infectious diseases over rare genetic and oncology settings. According to EvaluatePharma data, <3% of currently active next-generation therapeutic R&D programs are focused on infectious diseases. Nevertheless, several of the most talked-about vaccines in development for COVID-19 are RNA-based approaches, and so the next-generation therapeutics space may have a key part to play in defining the exit strategy from the pandemic.

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