

# Gene Therapy: A Paradigm Shift in Medicine





## Overview

The following analysis reviews several aspects of the gene therapy market. The history of gene therapy is briefly discussed, alongside a look at the trend in the volume of candidates in development over the past 20+ years, and how the regulatory landscape in the US and EU has recently adapted to help move

the field forward. A deep dive into the pipeline with breakdowns by delivery method and therapy area is provided, as are the key companies involved and the major partnership deals that have made gene therapy a hot commodity. Manufacturing, pricing, and reimbursement issues are also addressed.

## Introduction

Gene therapy, the modification of genetic information in living cells to address a mutated gene, has the ability to dramatically change the way diseases are treated, or even cured. First conceptualized in the early 1970s, the seminal paper on the subject was published in *Science* by Theodore Friedmann and Richard Roblin, suggesting the great potential for gene therapy techniques in human

genetic disease. The researchers also stressed that development should not proceed until and unless clearly defined ethical and scientific guidelines were outlined.<sup>1</sup> The field suffered setbacks that made advancements challenging, including a patient death due to a severe immune reaction, and the development of leukemia in infants.<sup>2,3</sup>

1. Friedmann T, Roblin R (1972) Gene therapy for human genetic disease? *Science*, 175(4025), 949–55.

2. *New York Times* (2003) F.D.A. Halts 27 Gene Therapy Trials After Illness. Available from: <http://www.nytimes.com/2003/01/15/us/fda-halts-27-gene-therapy-trials-after-illness.html?mcubz=0> [Accessed August 31, 2017].

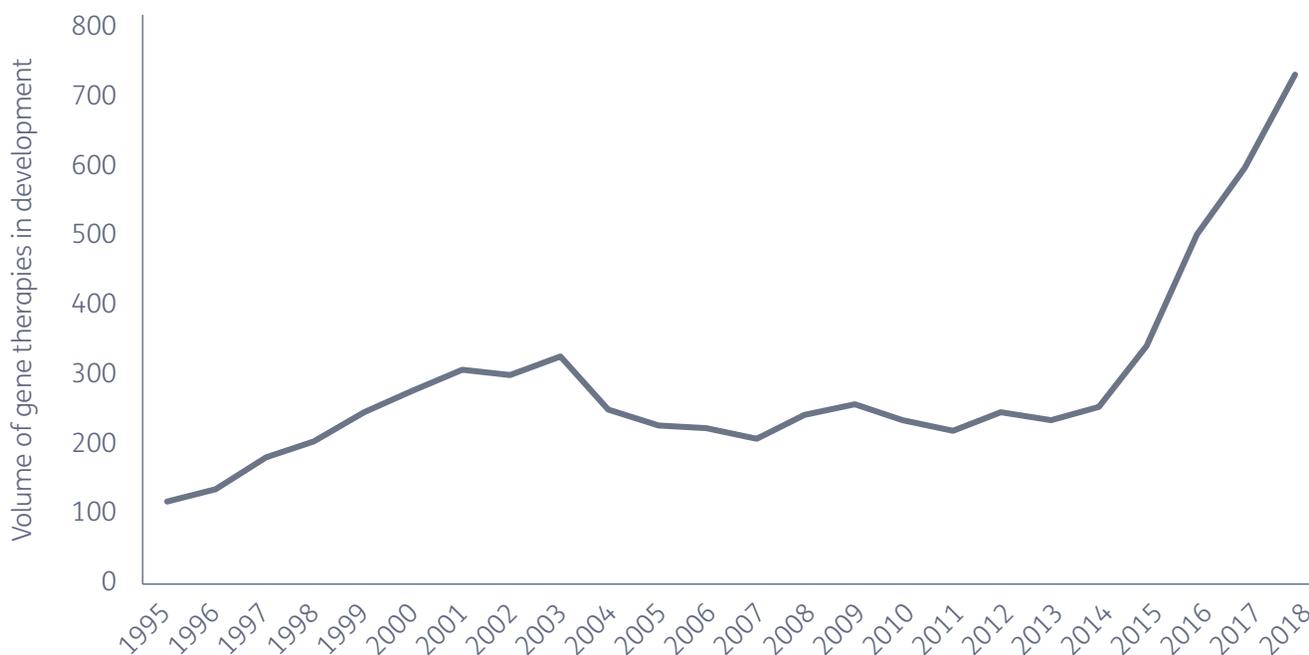
3. *ScienceDaily* (2008) Why Gene Therapy Caused Leukemia In Some 'Boy In The Bubble Syndrome' Patients. Available from: <https://www.sciencedaily.com/releases/2008/08/080807175438.htm> [Accessed August 31, 2017].

## The gene therapy pipeline is growing

Since then, though, the development of gene therapy has taken a positive turn. The safety of vectors has improved, and the strong investment from venture investors and Big Pharma, as well as mid-sized pharma and other larger pharmaceutical companies, into regenerative medicine firms pioneering work in gene therapy has made it possible for the field to move forward. As proof,

the volume of active gene therapies in the pipeline, from preclinical through pre-registration phases, has changed dramatically. For several years, particularly during the period of 2004–14, the number of therapies being worked on remained virtually flat. But volume has grown at a rapid rate in more recent years, reaching over 700 programs, and showing increased optimism about this field (see Figure 1).

**Figure 1. Gene therapy pipeline volume, preclinical through pre-registration phase, 1995–2018**



Note: Annual volume snapshots are captured in May of each year.

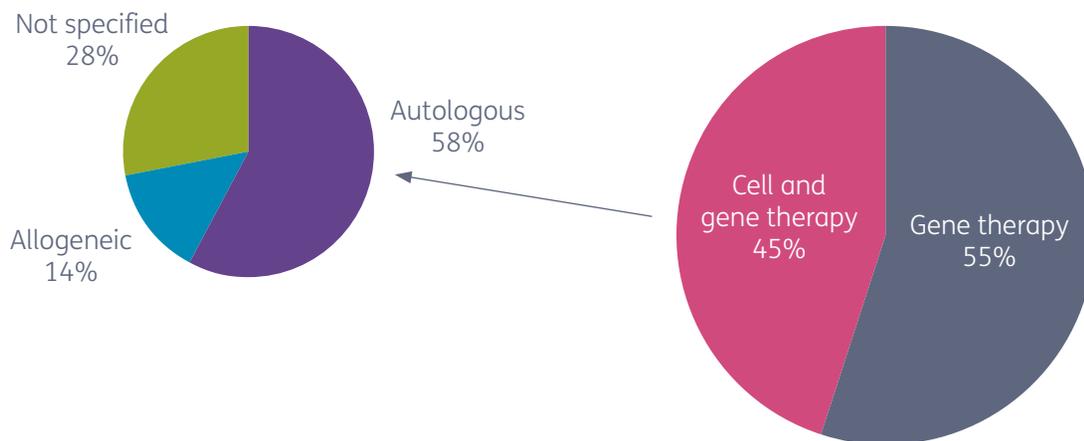
Source: Pharmaprojects®, August 2018

## Developers are evaluating both in vivo and ex vivo approaches

Broadly, the gene therapy pipeline can be segmented based on the primary delivery methods required to enable the gene to reach its target cell. Both in vivo and ex vivo approaches are used to deliver genes. In vivo involves administering targeted genes or genetic modifications directly into cells that are inside the body. Alternatively, an ex vivo approach (also commonly referred to as “cell and gene” therapy) is used when the genetic modifications are made to cells, for example bone marrow cells or blood cells, that have been physically extracted and isolated from the body. Following gene transfer to the cells in a lab and cell expansion, the cells are then reintroduced back into the body, with the process known as autologous cell therapy. More recent approaches to gene therapy have involved ex vivo allogeneic cell therapy, which uses genetically modified donated cells “off the shelf.”

The approach taken will vary depending on many factors including the site of the disease and how accessible those targets are. For that reason, one approach does not trump the other. The slight majority (55%) of the pipeline is considered gene therapy – mainly medicines that are delivered in vivo. The rest of the candidates in development are cell and gene therapies, with the genetic modification performed to cells ex vivo. Within that latter group, currently most of these cells are autologous, patient-specific cells that are reintroduced back into the body following genetic engineering, as opposed to allogeneic or donor cells, which only represent 14% of cell and gene therapies (see Figure 2). While the benefits of allogeneic cell therapy are wide, namely the fact that a larger number of patients can be treated with reduced pressure and time compared with manufacturing patient lots from autologous cells, there are immune reactions to consider with the use of allogeneic cells.

**Figure 2. Gene therapy versus cell and gene therapy: breakdown of pipeline**



Note: The “gene therapy” category also includes several candidates that are being developed for oral or inhaled delivery.

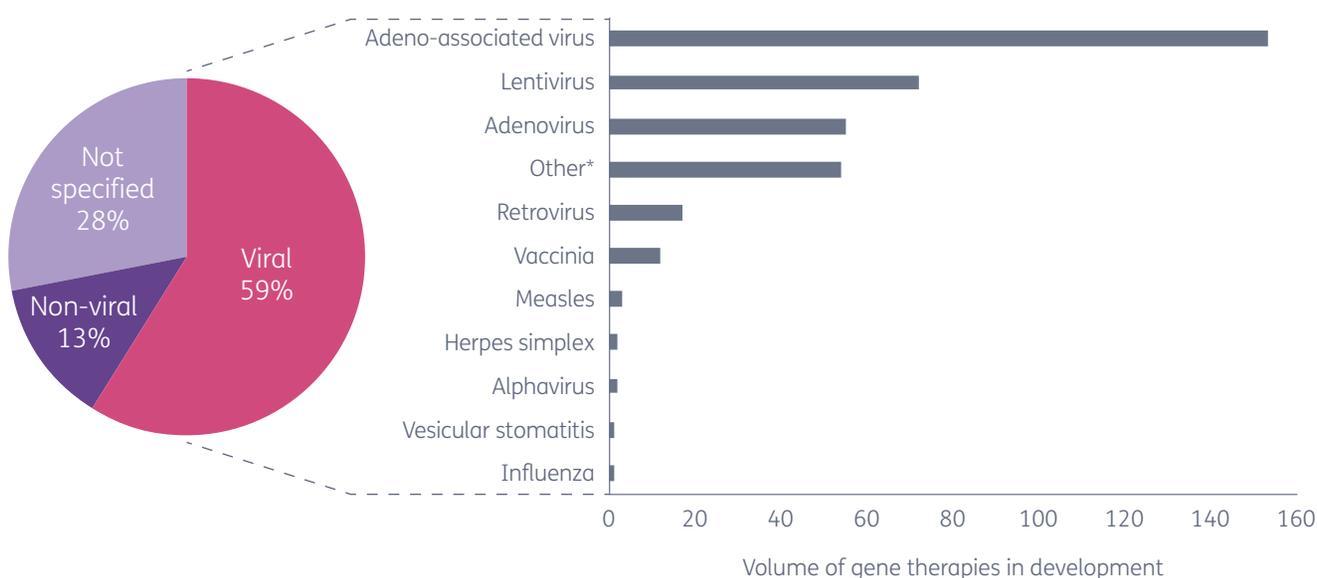
Source: Pharmaprojects®, December 2017

## Viral vectors are most prominent, especially AAV

Whether in vivo or ex vivo, gene therapies require a vector for delivery, and in the current pipeline most often the choice for developers is a virus. Approximately 59% of gene therapy candidates use a viral vector, while only 13% are delivered by non-viral means (mainly plasmids), but other modes are also used, such as messenger RNA, liposomes, or bacterial vectors. Among viral vectors,

developers have many options for the delivery of gene therapies; however, the adeno-associated virus (AAV) is by far the most actively used (see Figure 3). AAV has emerged as a vector of choice because of its safety, low immunogenicity, and long-term transgene expression. Besides AAV, other commonly used viral vectors in gene therapy development include the lentivirus and adenovirus.

**Figure 3. Viral vector delivery is most prominent in gene therapy**



\*Other category contains gene therapies with unspecified viral vector types

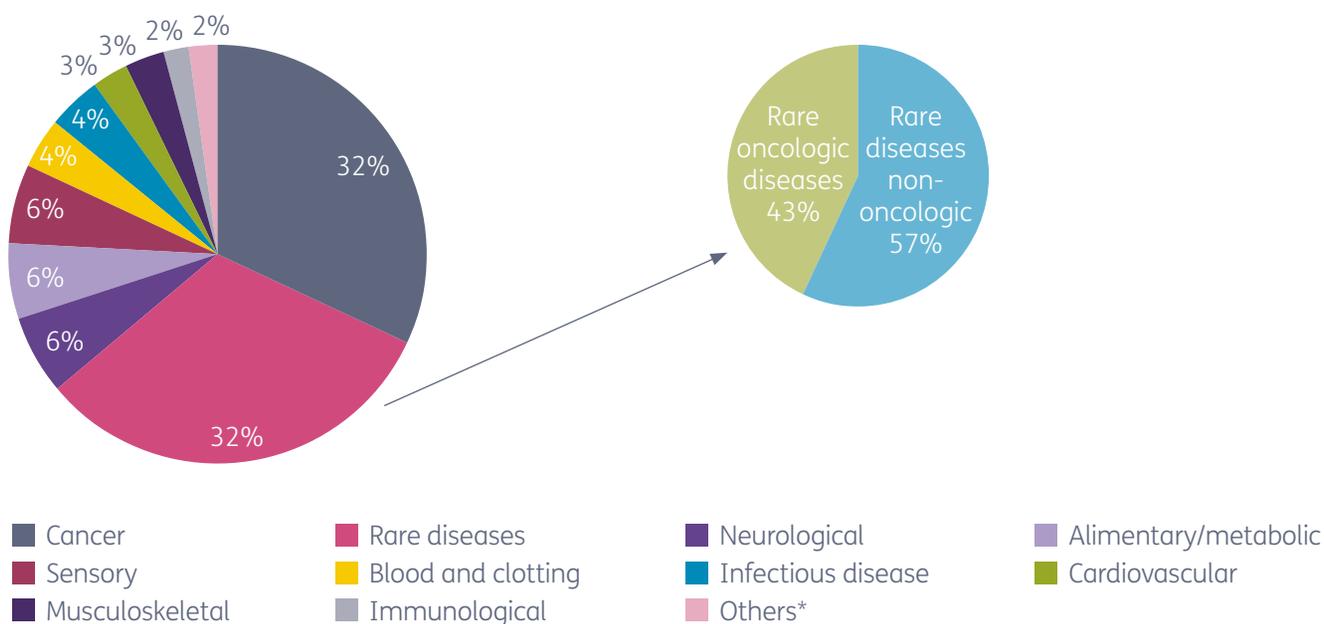
Source: Pharmaprojects®, December 2017

## Oncology and rare diseases are focus therapy areas

One-third of the gene therapy pipeline consists of candidates in development for cancer (see Figure 4). Rare diseases also represent one-third of the gene therapies being developed; however, it is important to note that many of these candidates are also represented in the other primary therapy area categories. In fact, 43% of the rare disease

gene therapy pipeline is considered rare oncologic diseases. Besides oncology and rare diseases, activity in other therapy areas is comparatively much lower. The next highest-ranked areas – neurological, alimentary/metabolic, and sensory diseases – have volumes in the 60-candidate range.

**Figure 4. Oncology dominates gene therapy drug development**



Notes: \*Others represents dermatological, respiratory, and genitourinary. The chart covers preclinical through pre-registration candidates. The phase signifies the most advanced for a therapy in any of its targeted indications. Most of the diseases that are rare are also classified in another relevant therapy area.

Source: Pharmaprojects®, December 2017

## Regulatory incentives have played an important role in gene therapy development

In the EU and US, gene therapies have the potential to benefit from specialized regulatory pathways established broadly for regenerative medicines (see Figure 5). The European Medicines Agency (EMA) introduced a regulation in 2007 that created a regulatory framework for advanced therapy medicinal products (ATMPs). Gene therapies, along with somatic cell therapies, tissue-engineered medicines, and combined ATMPs, represent the four main ATMP product groups. Sponsors of such products enjoy dedicated scientific assessment from a separate multidisciplinary committee. The EMA's

Committee for Advanced Therapies (CAT) reviews and provides a draft opinion on the quality, safety, and efficacy of an ATMP, as well as performing other duties such as recommending which ATMP class the therapy should be placed in, and providing scientific expertise and advice. Following the CAT's decision, an ATMP will go through a similar regulatory process to other medicines, moving next to the Committee for Medicinal Products for Human Use for an opinion on approval, before a final decision by the European Commission.<sup>4</sup>

**Figure 5. Product class inclusions in EU and US specialized regenerative medicine regulatory pathways**

EMA'S ATMP	FDA's RMAT
<ul style="list-style-type: none"> <li>• <b>Gene therapies</b></li> <li>• Somatic cell therapies that contain cells or tissues</li> <li>• Tissue-engineered medicines</li> <li>• Combined ATMPs (one or more devices integrated with the medicine)</li> </ul>	<ul style="list-style-type: none"> <li>• Cell therapy</li> <li>• Therapeutic tissue engineering product</li> <li>• Human cell and tissue product</li> <li>• Any combination product using such therapies or products</li> <li>• <b>Gene therapies*</b></li> </ul>
<p><i>*Inclusion is planned as part of FDA's commitment to fully implement the RMAT pathway. ATMP = advanced therapy medicinal product; EMA = European Medicines Agency; FDA = US Food and Drug Administration; RMAT = regenerative medicine advanced therapy</i></p>	

Source: EMA, 2017; FDA, 2017

4. EMA (2017) Advanced therapy medicinal products. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000294.jsp&mid=WC0b01ac05800241e0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0) [Accessed August 31, 2017].

In the US, the regenerative medicine advanced therapy (RMAT) designation came into existence under the passage of the 21st Century Cures Act in 2016. RMAT designation provides US filers with several benefits. Companies may take advantage of frequent access and communications with the US Food and Drug Administration (FDA), including early on in the development timeline, plus an expedited regulatory review cycle, such as through priority review and accelerated approval, based on the requirement that the RMAT will “treat, modify, reverse, or cure a serious or life-threatening disease or condition.”<sup>5</sup> Gene therapies initially were not explicitly part of the RMAT pathway; however, FDA commissioner Scott Gottlieb announced in

August 2017 that in the FDA’s efforts to continue implementing RMAT, certain gene therapies would be included. Gottlieb specifically called out gene therapies that permanently alter tissue and produce a sustained therapeutic effect as an example of what would be in scope.<sup>6</sup> Following up on this promise, in draft guidance published by the FDA in November 2017, explaining what the FDA considers a regenerative medicine, a gene therapy including genetically modified cells would qualify as long as it leads to a durable modification of cells or tissues.<sup>7</sup> As of October 2018, the FDA has granted 27 RMAT designations, approximately 22 of which have been disclosed.

5. FDA (2017) Regenerative Medicine Advanced Therapy Designation. Available from: <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm> [Accessed August 31, 2017].

6. FDA (2017) Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA’s new policy steps and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine. Available from: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573443.htm> [Accessed August 31, 2017].

7. FDA (2017) FDA announces comprehensive regenerative medicine policy framework. Available from: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585345.htm> [Accessed November 17, 2017].

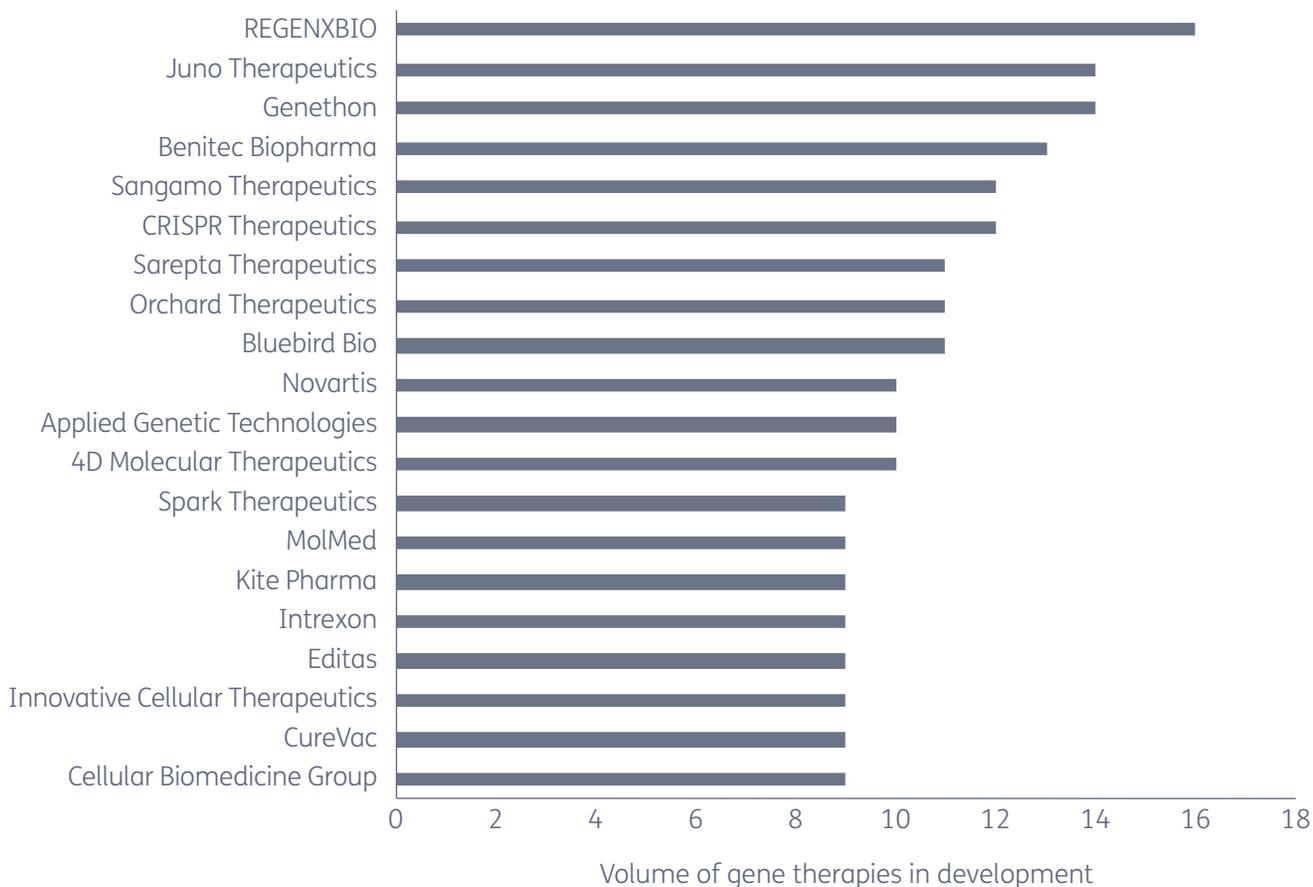
## Key company players include small biotechs and Big Pharma

In the gene therapy market, there are approximately 391 unique companies with development-stage candidates. These include very small players, which are only working on one or two therapies, all the way up to more active companies with larger pipelines totaling over a dozen programs. The group encompasses biotech, Emerging Pharma, Mid Pharma, and Big Pharma companies.

Within the top 20 most active companies by pipeline size (see Figure 6), REGENXBIO leads by volume with 16 gene therapies in development. REGENXBIO has a dual business model, both advancing an internal pipeline of gene therapy candidates using its NAV AAV platform, while also monetizing the NAV technology through partnerships with fellow

gene therapy players. Its most advanced in-house gene therapies, in Phase II, include RGX-121, a one-time treatment for mucopolysaccharidosis II (Hunter syndrome), and RGNX-001 for familial hypercholesterolemia. At 14 candidates, Juno Therapeutics, which was acquired by Celgene in January 2018, ties with Genethon as the second most active gene therapy company. Among larger-sized pharma firms, Novartis and Kite Pharma (now owned by Gilead) make the top 20 list. Also included are the gene editing players Sangamo Therapeutics, CRISPR Therapeutics, and Editas. While not in the top 20, other Big Pharma players that are pursuing gene therapies include Sanofi, Biogen, GlaxoSmithKline, Pfizer, and Johnson & Johnson.

**Figure 6. Top 20 gene therapy companies by pipeline size**



Source: Pharmaprojects®, August 2018

## Partnerships help advance the pipeline

Partnerships provide an important vehicle for both the licensor and licensee to grow. Over the 2012–18 time period (through September 2018), 351 gene therapy alliances were signed, with a total deal value of \$41bn. Overall, both the volume and value of alliances have generally increased year over year (see Figure 7). Notably, there was a big drop in 2017's dollar value, but concurrently that year featured the highest number of partnerships. In contrast, 2018 featured the most dollars invested

in alliances to date in a single year, including four billion-dollar-plus agreements. At the top is a \$3.2bn deal in which Gilead's Kite Pharma received exclusive rights to Sangamo Therapeutics' zinc finger nuclease gene editing technology, which Kite will use to develop AAV T-cell and natural killer cell therapies, both autologous and allogeneic. Gilead bought Kite Pharma in 2017 to establish a dedicated presence in oncology cell therapy.

**Figure 7. Gene therapy alliances volume and value, 2012–18**



Source: Medtrack; Strategic Transactions, September 2018

Several Big Pharma and Mid Pharma companies have featured as active gene therapy in-licensors over the past several years, allowing these major players to be involved or further invest in gene therapies. Based on which approach the deals focus on, whether in vivo (gene therapy) or ex vivo (cell and gene therapy), it is possible to get a gauge on where large pharmaceutical companies see the most potential (see Figure 8).

With the highest volume, Novartis has accumulated

a strong collection of alliances in the cell and gene therapy market. Notably, in 2012 the company in-licensed chimeric antigen receptor T-cell (CAR-T) technologies from the University of Pennsylvania, culminating in the development and approval of the first CAR-T therapy in the US, Kymriah (tisagenlecleucel-t) in 2017. To secure the stable manufacturing of Kymriah, Novartis has in-licensed non-exclusive rights to lentiviral vectors from both Oxford BioMedica (through a \$190m deal) and bluebird bio, and has also been building up

its intellectual property portfolio with licenses to Celyad's CAR-T patents. In addition, Novartis made an investment in gene editing, signing a five-year agreement with Intellia Therapeutics in 2015 to apply CRISPR/Cas9 to CAR-T therapies. Novartis has also set its sights on in vivo gene therapy, notably securing exclusive rights to sell Spark Therapeutics' Luxturna (voretigene neparvovec-rzyl) outside of the US.

Similar to Novartis, Celgene, GlaxoSmithKline, Shire, Gilead, and Amgen have also focused most of their gene therapy partnerships on ex vivo therapies (note that GlaxoSmithKline sold most of its cell and gene therapies as part of the rare disease portfolio divestment to Orchard Therapeutics in 2018). On the other hand, Pfizer, Biogen, and Sanofi, for instance, have concentrated more on in vivo gene therapy.

**Figure 8. Big Pharma and Mid Pharma gene therapy in-licensing volume by category, 2012–18\***



\*2018 through September

Source: Medtrack; Strategic Transactions, September 2018

## Gene therapies present opportunities and barriers in commercialization

Modern-day commercialization of gene therapies, thanks to advancements made in the safety, efficacy, and delivery, is now a reality. Across global regulatory markets there have been 11 products approved to date (see Table 1). Many of the initial ones were cleared in developing markets where there is little to no regulation of advanced therapies. Gene therapy approvals in the western part of the world first came in Europe, with Glybera in 2012

(which was later withdrawn from the market), followed by further approvals in Europe. The current generation of gene therapies has emerged with the approvals of the CAR-T therapies Kymriah and Yescarta (axicabtagene ciloleucel; Gilead) in both the US and EU, plus the in vivo gene therapy Luxturna, which has been approved in the US and is on its way toward EU approval.

**Table 1. Approved gene therapies worldwide, October 2018**

Product name	Year approved	In vivo or ex vivo	Vector	Disease(s)	Mechanism(s) of action	Countries where approved/launched	Originator	Licensee(s) (in approved countries)
Gendicine (recombinant p53 gene)	2004	In vivo	Viral (adenovirus)	Head and neck cancer	p53 stimulant	China	Shenzhen SIBiono GeneTech	n/a
Imlygic (talimogene laherparepvec)	2015	In vivo	Viral (herpes simplex virus)	Melanoma	GM-CSF agonist	EU, US	Amgen	n/a
Invossa (tonogonchancel-L)	2017	Ex vivo, allogeneic	Viral (retrovirus)	Osteoarthritis	Transforming growth factor beta 1 agonist	South Korea	Kolon TissueGene	Kolon Life Science; Mundipharma
Kymriah (tisagenlecleucel-t)	2017	Ex vivo, autologous	Viral (lentivirus)	ALL; DLBCL	CD19 antagonist	EU, US, Canada	Novartis	n/a
Luxturna (voretigene neparvovec-rzyl)	2017	In vivo	Viral (adeno-associated virus)	Leber's congenital amaurosis; retinitis pigmentosa	RPE65 stimulant	US	Spark Therapeutics	n/a
Neovasculgen (vascular endothelial growth factor gene)	2011	In vivo	Non-virus (plasmid)	Peripheral vascular disease; limb ischemia	VEGF receptor agonist	Russian Federation	Human Stem Cells Institute	n/a
Oncorine (E1B/E3 deficient adenovirus)	2005	In vivo	Viral (adenovirus)	Head and neck cancer; nasopharyngeal cancer	n/a	China	Shanghai Sunway Biotech	n/a
Rexin-G (mutant cyclin-G1 gene)	2006	In vivo	Viral (retrovirus)	Solid tumors	Cyclin G inhibitor	Philippines	Epeius Biotechnologies	n/a
Strimvelis (autologous CD34+ enriched cells)	2016	Ex vivo, autologous	Viral (retrovirus)	Adenosine deaminase deficiency	Adenosine deaminase stimulant	EU	GlaxoSmithKline	Orchard Therapeutics
Yescarta (axicabtagene ciloleucel)	2017	Ex vivo, autologous	Viral (retrovirus)	DLBCL; non-Hodgkin's lymphoma; follicular lymphoma	CD19 antagonist	EU, US	Kite Pharma (now owned by Gilead)	n/a
Zalmoxis (allogeneic T cells genetically modified to express human low-affinity nerve growth factor receptor and the herpes simplex I virus thymidine kinase)	2016	Ex vivo, allogeneic	Viral (retrovirus)	Graft-versus-host disease	Thymidine kinase stimulant; DNA-directed DNA polymerase inhibitor	EU	MolMed	Dompé

ALL = acute lymphocytic leukemia; CD = cluster of differentiation; DLBCL = diffuse large B-cell lymphoma; GM-CSF = granulocyte-macrophage colony-stimulating factor; RPE = retinal pigment epithelium; VEGF = vascular endothelial growth factor

Source: Pharmaprojects®, October 2018

## Certain challenges make reimbursement of gene therapies an issue

The potentially curative effect and one-off administration of gene therapies are creating a unique set of reimbursement challenges as healthcare systems, as well as drug manufacturers, grapple with ensuring adequate patient access. The burden – as well as the opportunity – of shaping new access and funding mechanisms, as well as finding ways to articulate product value to payers, falls onto the first companies to launch these innovative products.

### Cost is the biggest concern

Although payers recognize that gene therapies could provide great benefits to patients, and even cures in some instances, they are concerned mostly with the high potential prices of such medicines. The cost of these therapies can be extremely expensive and present a large burden to the healthcare system, in the range of \$400,000 to \$850,000 at the high end, currently, for the approved gene therapies, and could be amplified depending on the size of the patient population. According to estimates from the Institute for Clinical and Economic Review, if gene therapies were used just by one in 10 patients who had a genetic condition, the cumulative budget impact of therapies priced at \$1m–\$2m (which some may consider an overestimate now) could reach \$3tn in the US alone. Even for gene therapies addressing smaller populations, several of which should come to market over the next few years, the cumulative effect of the high costs would be substantial.<sup>8</sup>

### There is great uncertainty around long-term benefit

Many of the gene therapies have the potential to improve long-term patient outcomes or even cure a disease, but upon approval only a limited follow-up time is available, raising concerns regarding the value they bring. The approval may be based on single-arm trials without a comparator, and on a

small number of patients. Further, the pathway to approval of gene therapies, especially if expedited, may yield shorter-term data on efficacy than what is needed to prove the long-term benefits of the therapy. This results in considerable uncertainty around how long the therapeutic benefit of the gene therapy will last in certain patients, and whether a single administration will be sufficient. In turn, this impacts the maximum amount payers are willing to pay for a therapy that potentially brings lifelong benefits but where only a few years' worth of data are available at launch. There are some new proposed payment mechanisms for gene therapies that could factor in long-term performance. Still, the longer a gene therapy takes to have a significant benefit, the more likely that payers are not incentivized to cover it.

### Payers also struggle with defining value of gene therapy

The idea of the value of gene therapies and how it is defined is debatable, and therefore a challenge in terms of reimbursement. Stakeholders need to consider that value will mean different things to different people, and payers, as a result, must figure out how to measure a healthcare intervention against that value.<sup>9</sup> Payers may have to incorporate measurements of value to patients, the healthcare system, and society in their standard value assessments, beyond what they normally evaluate: the health gain for the patient and net direct costs to the healthcare system. Some additional metrics of value to consider for gene therapy include disease severity, age of disease onset, lifetime burden of the illness, and informal care elements, such as returning to work or study, increases in productivity, and reductions in burden of care for family members.<sup>8</sup> Many payers may be resistant to the idea of pricing and reimbursement being tied to these measurements, which are novel compared with the offset of the medical cost.

8. Institute for Clinical and Economic Review (2017) *Gene Therapy: Understanding the science, assessing the evidence, and paying for value*. Available from: <https://icer-review.org/wp-content/uploads/2017/03/ICER-Gene-Therapy-White-Paper-030317.pdf> [Accessed June 15, 2018].

9. Werner M (2017) Panel discussion at CAR-T Approval: What's Next?, October 24, 2017, Webinar.

## Funding flows need to be changed to relieve financial pressure on providers and reduce mark-ups

In addition to the administrative burden, gene therapies can also create financial pressures for the providers. Payers require demonstration of medical need and funding requests for these therapies that carry a high budget impact. This documentation, along with billing and coding issues, can be burdensome and complex for the healthcare providers administering gene therapies, and can cause delays for the patient. The time and energy required to secure reimbursement is a key challenge, and could possibly lead to providers funding the cost of the therapy themselves without getting reimbursed, or being only partially reimbursed.<sup>10</sup> Some cancer specialists have noted that each time they are administering a CAR-T therapy, they must write a single-patient agreement, because most commercial insurers are currently only covering the therapies on an individual basis.<sup>11</sup>

Payers themselves also encounter financial pressure in the form of mark-ups from hospitals or specialized treatment centers that administer gene therapies. This comes in as a percentage of the payment in addition to the cost of the therapy itself. One option is for payers to purchase the gene therapies directly from the manufacturer, or pay the manufacturer directly, to avoid the mark-up, a mechanism that Spark Therapeutics has in place with Express Scripts for Luxturna.<sup>12</sup>

## Payment options for gene therapies

It is clear the traditional financing mechanisms that have been used to pay for pharmaceuticals and biologics to date are not adequate for gene therapies. Significant changes need to be made to enable patient access, but also at the same time to address the high cost of gene therapies, and the uncertainty around how effective they will be in the

long term, as well as to reward/compensate the innovator company for the efforts to produce the therapy.

Payers tend to be reactive rather than proactive when it comes to handling how to pay for gene therapies. As a result, industry players and advocacy groups have taken up the issue themselves, and have suggested a wide range of alternative financing or payment models that may be applied to gene therapy (see Figure 9). Any one, or combination, of these models have the potential to incentivize payers to invest in a gene therapy that may produce a better health outcome and lower cost over time, as opposed to paying for a competing product that is repeatedly administered, with higher long-term costs, or even with a larger one-time/upfront cost for a curative therapy. They may also provide flexibility in terms of addressing the problem of paying for expensive gene therapies.

In general, there seems to be an openness to evaluating and testing alternative payment models in the US. In Europe, however, there may be a challenge due to the public procurement strategy adopted by the EC in 2017.<sup>13</sup> The policy provides minimum harmonized rules to guide public authorities, including those in health services, to purchase goods, works, or services, and could create a barrier to implementing alternative payment models. The newly enforced regulation on data protection in the EU – the General Data Protection Regulation (GDPR) – could pose an issue with the pay-for-performance mechanism, which is seen as having the most promise and best application in gene therapy. Legal exceptions or changes may be required for such deals to move forward, and such modifications may take years to implement. In the meantime, gene therapy sponsors will need to work with payers and healthcare systems to find the best ways to pay for these therapies.

10. In Vivo (2018) *Paying For Gene Therapy: Will Pharma Be First In Line?* Available from: <https://invivo.pharmaintelligence.informa.com/IV005347/Paying-For-Gene-Therapy--Will-Pharma-Be-First-In-Line> [Accessed June 20, 2018].

11. National Public Radio (2018) *Insurers And Government Are Slow To Cover Expensive CAR-T Cancer Therapy*. Available from: <https://www.npr.org/sections/health-shots/2018/07/17/629543151/insurers-and-government-are-slow-to-cover-expensive-car-t-cancer-therapy> [Accessed July 18, 2018].

12. Spark Therapeutics (2018) *Spark Therapeutics Announces First-of-their-kind Programs to Improve Patient Access to LUXTURNA™ (voretigene neparvovec-rzyl), a One-time Gene Therapy Treatment*. Available from: <http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-announces-first-their-kind-programs-improve> [Accessed October 11, 2018].

13. European Commission (2018) *Public Procurement*. Available from: [https://ec.europa.eu/growth/single-market/public-procurement\\_en](https://ec.europa.eu/growth/single-market/public-procurement_en) [Accessed July 26, 2018].

**Figure 9. Financing and payment options for gene therapies**

<b>Annuity</b>	Payments are spread out and made over a defined period of time, from months to years
<b>Consumer mortgage</b>	A loan taken out directly by the patient
<b>Direct payment/distribution</b>	Payer purchases the gene therapy directly from the manufacturer
<b>Discounts/revenue caps</b>	Therapy price is reduced by a percentage if total revenue exceeds a certain target
<b>Expanded risk pools</b>	Dedicated fund where several stakeholders allocate a proportion of their premiums or budget toward an expanded group of patients who are eligible for gene therapy
<b>Patient assistance/subsidy</b>	Financial aid for patients for their expenses related to gene therapy
<b>Pay for performance/outcomes</b>	Innovator companies are paid for their gene therapies based on mutually agreed upon timed measures and achievements of clinical performance or outcomes in the real world
<b>Re-insurance</b>	Catastrophic insurance coverage purchased for gene therapy
<b>Supplier credit</b>	Gene therapy is purchased by a third-party financial entity that negotiates payment with payer

Source: Datamonitor Healthcare payer research; *In Vivo*, 2017, 2018; Institute for Clinical and Economic Review, 2017; *Managed Healthcare Executive*, 2018; *Penn Medicine News*, 2014; *Reuters*, 2015

## Challenges also exist in manufacturing and supply

While much attention has been given to the need to overcome access challenges, finding solutions to more sustainable – and cheaper – manufacturing and supply chain will be as critical to ensuring future commercial success of the class. As companies move from smaller-scale trials to larger studies, and then to mass production for commercialization, the supply of vectors for gene therapies becomes a mission-critical issue. “Right now, viral vector manufacturing is probably one of, if not the single biggest limitation in the cell and gene therapy

space,” says Bruce Thompson, then senior scientific director, therapeutic products program at Fred Hutchinson Cancer Research Center, and could ultimately affect those therapies about to come onto the market.<sup>14</sup> (*Editor’s note: Thompson has since moved to Lyell Immunopharma as vice president of manufacturing.*) Further, manufacturing of the vectors used to deliver these gene therapies has been an expensive and time-consuming endeavor, and is more of a custom process at this point.

14. Personal correspondence (2018) Telephone interview with Bruce Thompson, former senior scientific director, therapeutic products program at Fred Hutchinson Cancer Research Center. Conducted on July 6, 2018.

FDA commissioner Scott Gottlieb has highlighted vector production as a big concern, noting that approximately 80% of the standard review time for gene therapies is spent on manufacturing and quality issues.<sup>15</sup> In 2018, the FDA announced a new initiative, called the INTERACT (Initial Targeted Engagement for Regulatory Advice on CBER Products) program, which will include cell-based regenerative medicines and gene therapies, and encourage those sponsors to set up formal meetings with the FDA at the early or preclinical stage of development to discuss chemistry, manufacturing, and control issues related to clinical trials, much like discussions RMAT-granted sponsors would have.<sup>16,17</sup> Major academic manufacturing centers, where many vectors are produced for clinical trials, all have long queues, of somewhere between 12 months and probably 18–24 months, according to Thompson,<sup>14</sup> and some manufacturing rooms at academic institutions have been booked years in advance, including ones at Moffitt Cancer Center and Dana-Farber Cancer Institute.<sup>18</sup>

To meet the high demand as the pipeline advances and grows, gene therapy developers will turn to contract manufacturing organizations (CMOs) or contract development and manufacturing

organizations (CDMOs) for vector supply services. The demand for manufacturing will provide lucrative opportunities for CMOs and CDMOs in the specialized market of cell and gene therapy, but that demand will likely exceed the supply. There is only a select group of companies currently with these capabilities, which are considered highly specialized, and it is likely that new CMO/CDMO players will emerge as well to address this demand, says Morrie Ruffin, co-founder and senior advisor of the Alliance for Regenerative Medicine.<sup>19</sup>

While there are many advantages to outsourcing gene therapy vector manufacturing, several industry players have invested in in-house capabilities to secure a stable vector supply (see Table 2). The reliability of supply that comes with a company's own manufacturing is important as it advances through the clinical development process, according to Ruffin. Another potential benefit, says Ruffin, are the future uses for such facilities, including meeting commercial demand and post-approval requirements.<sup>18</sup> AveXis, BioMarin Pharmaceutical, and Spark Therapeutics are among several companies that have built internal manufacturing plants.

15. FDA (2018) Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine's Annual Board Meeting. Available from: <https://www.fda.gov/NewsEvents/Speeches/ucm608445.htm> [Accessed October 2, 2018].

16. Pink Sheet (2018) BIO Notebook Day 4: Gottlieb Seeks Early Engagement On Gene Therapy; Ireland's Brexit Opportunities; AMAG's Bremelanotide Strategy; Alzheimer's 'Learnings'. Available from: <https://pink.pharmaintelligence.informa.com/PS123256/BIO-Notebook-Day-4-Gottlieb-Seeks-Early-Engagement-On-Gene-Therapy-Irelands-Brexit-Opportunities-AMA> [Accessed June 8, 2018].

17. Pink Sheet (2018) CBER Implements Pre-Clinical Meeting Program For Biologics, Gene Therapy Sponsors. Available from: <https://pink.pharmaintelligence.informa.com/PS123351/CBER-Implements-PreClinical-Meeting-Program-For-Biologics-Gene-Therapy-Sponsors> [Accessed June 25, 2018].

18. In Vivo (2018) Partnering In Cell And Gene Therapy Is A Unique Endeavor. Available from: <https://invivo.pharmaintelligence.informa.com/IV123560/Partnering-In-Cell-And-Gene-Therapy-Is-A-Unique-Endeavor> [Accessed October 2, 2018].

19. Personal correspondence (2018) Telephone interview with Morrie Ruffin, co-founder and senior advisor at Alliance for Regenerative Medicine. Conducted on July 16, 2018.

**Table 2. In-house and external cell and vector manufacturing efforts by select Big and Mid Pharma companies**

Company name	In-house gene therapy manufacturing capabilities	External gene therapy manufacturing capabilities/partners
AveXis (now owned by Novartis)	Fully operational GMP 50,000 sq ft manufacturing facility in Libertyville, Illinois to support clinical and commercial activities for pipeline; plans to build 170,000 sq ft plant in Durham, North Carolina to produce drug substance	AveXis has indicated it may partner with CMOs
Celgene/Juno	135,000 sq ft cellular immunotherapy facility being built in Summit, New Jersey, with \$130m investment to support development and commercialization of CAR-T therapy bb2121 (bluebird bio); separate 68,000 sq ft manufacturing operation in Bothell, Washington to develop and commercialize CAR-T therapies (Juno)	n/a
GlaxoSmithKline	n/a	Bluebird bio (non-exclusive rights to lentiviral vector platform for development of gene therapies for Wiskott-Aldrich syndrome and metachromatic leukodystrophy [agreement likely transferred to Orchard Therapeutics as part of asset sale])  Miltenyi (integration of Miltenyi's high-tech processing technology into cell and gene therapy R&D manufacturing capabilities)  MolMed (implementation of production process development for Strimvelis [transferred to Orchard Therapeutics]; and lentiviral development, manufacturing, and supply for oncology programs)
Kite Pharma/Gilead	43,000 sq ft plant in El Segundo, California to produce CAR-T cell and T-cell receptor therapies for clinical trials and commercialization; 117,000 sq ft cell and gene therapy manufacturing facility in Amsterdam, Netherlands; Santa Monica, California plant that will expand clinical manufacturing capabilities for cell therapies	GE Global Research (development of fully integrated and fully automated manufacturing process for engineered T-cell therapy)
Novartis	Dedicated 173,000 sq ft cell manufacturing facility in Morris Plains, New Jersey for Kymriah and other CAR-T therapies	Oxford BioMedica (supply of lentiviral vectors)  Fraunhofer Institute for Cell Therapy and Immunology (cell processing and manufacturing in Germany)  CELLforCURE (clinical and commercial manufacturing of CAR-T therapies in France)  Cellular Biomedicine Group (Kymriah manufacturing process in China)
Pfizer	11,000 sq ft facility in Chapel Hill, North Carolina, acquired in Bamboo Therapeutics transaction, that specializes in suspension cell-based technique to generate AAV vectors; Sanford, North Carolina facility is undergoing \$100m expansion	n/a
AAV = adeno-associated virus; CAR-T = chimeric antigen receptor T-cell; CMO = contract manufacturing organization; GMP = good manufacturing practices		

Source: AveXis, 2017; BusinessWire, 2018; Celgene, 2018; CELLforCURE, 2018; FiercePharma, 2016, 2017, 2018; Genetic Engineering & Biotechnology News, 2017; GlaxoSmithKline, 2016, 2018; Kite Pharma, 2015, 2016; Marketwired, 2011; MolMed, 2018; Novartis, 2018; Pfizer, 2018; PR Newswire, 2018; Reuters, 2017

## Future outlook for gene therapies

The expansion of the gene therapy pipeline in recent years, followed by key US and EU approvals for the next generation of gene therapies, are important reasons for developers to be optimistic about the future prospects of this market, and for patients to have hope that a disease that was previously not addressable may now even be cured. The reality is that these therapies will have high prices – they are expensive to develop and expensive to manufacture – and over the next few years

payers in the major world markets will be forced to value gene therapies through a new lens, and also to adopt payment mechanisms that may be completely novel. Given recent examples, such as the outcomes-based agreements established by Novartis and Spark Therapeutics, it is clear that payers and pharmaceutical companies are willing to work together, and that is a positive sign for all stakeholders in this class of products.

## Editor's note

This analysis is derived from several reports published by Informa's Datamonitor Healthcare, including Gene Therapy Pipeline and Portfolio Analysis, Gene Therapy Deal-Making Trends, 2012–17, and Gene Therapy Commercialization – Opportunities and Barriers. Certain sections are

based on data from several of Informa's databases including Pharmaprojects, Medtrack, and Strategic Transactions.

Access more information at: <https://pharmastore.informa.com/gene-therapy-reports/>

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Accurate and timely intelligence about the drug development pipeline is vital to understanding the opportunities and risks in today's biopharmaceutical marketplace – whether you are targeting an unmet medical need, investigating promising new therapies or researching drug development historical trends and treatment patterns. If you are providing contract research or other services in the pharma industry, you need to stand out. A solid understanding of your potential clients' pipelines and competition will help you leave a lasting impression.