Gene & Cell Services

A New Age of Medicine

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Walgreens

There are thousands of disease states that currently have no treatment or cure through traditional pharmacological means.

About 4,000 diseases have been linked to gene disorders alone.[1]

In recent years, gene and cell therapies have emerged as a new and exciting field to treat and, in many cases, cure diseases that previously have had no treatment options. Both gene and cell therapy have a similar ideology, which is to cure or treat diseases by introducing new cells or DNA to address the underlying cause of both genetic and acquired diseases.[2]

The gene and cell therapy pipeline is dominated by rare diseases and cancers, but many other more common diseases linked to gene disorders are all potential targets for cell and gene therapy as well.[3] Diseases such as Alzheimer's disease, HIV/AIDS, cardiovascular disease, arthritis and many more easily highlight the millions of people who could potentially benefit from these types of treatments.[1]

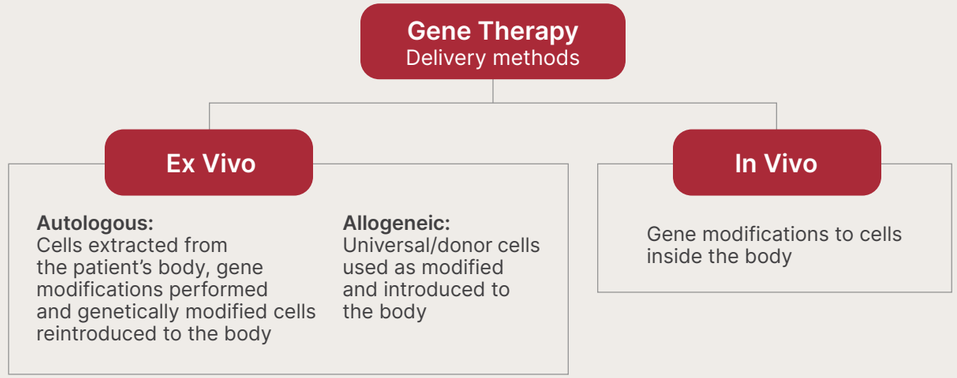
Genetic diseases are caused by spontaneous or inherited mutations in genes, which result in one or more proteins with limited or no function. While the goals of both cell therapy and gene therapy are the same, the mechanisms by which each work are decidedly different. In cell therapy, diseases are treated with cells grown or modified outside of the body and may originate from the patient or a donor.[2] Once prepared, these cells are injected into a patient to lessen the effects of or cure a disease. Most often, cells used for this therapy are stem cells, which may or may not be genetically altered and can mature into specialized types of cells targeted specifically to the needs of the patient.[4]

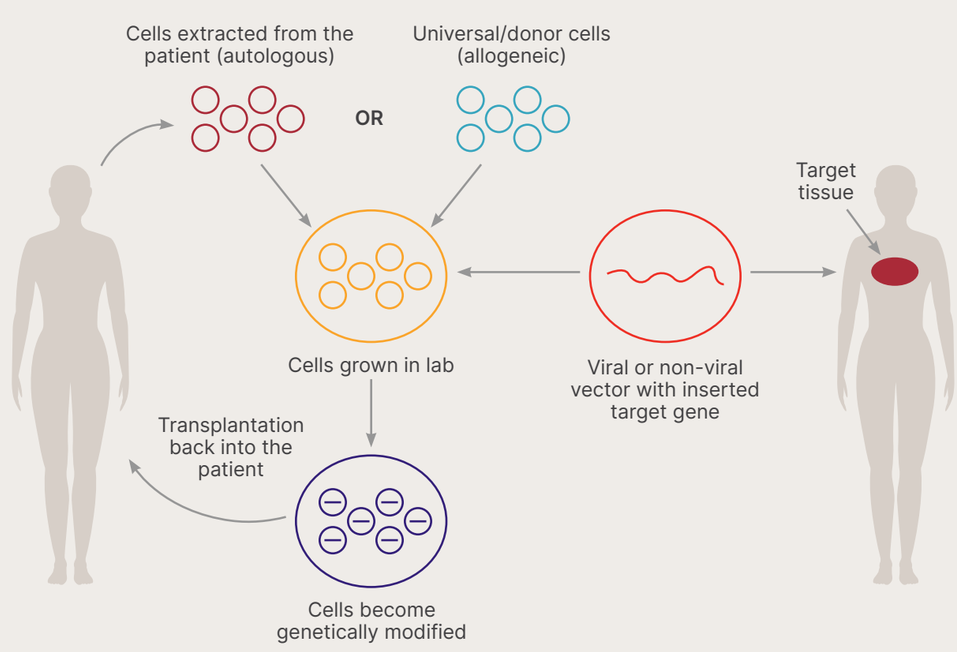
By contrast, gene therapy entails treating diseases at the genetic level by either replacing, deactivating or repairing the faulty DNA that is causing the disease.[1] Functional DNA is delivered into the patient's cells by a vector, usually of viral origin. These viruses, which are either not known to cause disease or have been attenuated in a lab, carry the DNA into the host cell and insert the material into the patient's DNA. Restoring gene function, in turn, allows for proteins to be properly produced. While in many cases this therapy can "cure" a patient of their disease, it does not fix the mutated DNA of their reproductive cells. Therefore, patients who are "cured" are still able to pass this genetic malady on to their children.[5,6]

While potential applications of gene and cell therapies are vast, development is not without challenges. One issue is complexity. While some diseases are caused by the mutation of a single gene, many others are caused by mutations of two or more genes and are therefore not currently a candidate for treatment.[5] Another challenge of therapy development is disease population. The number of patients with a rare genetic disorder is very low and not only requires a specific tailoring of the therapy to each patient, but also provides a very small population of patients to participate in clinical trials. Arguably the most critical issue in developing these types of therapies is cost compared to value. It is estimated that by 2030, the global gene and cell therapy market size will reach $93 billion USD.[7] Funding for research of diseases and delivery methods in addition to clinical trials and regulatory documents make it more difficult to dedicate such large amounts of money to diseases with so few who are afflicted by them. This, in turn, can create extremely large price tags for patients and insurance companies for whom therapies are developed.

Approaches to gene & cell therapy

Gene and cell therapy can be divided into two approaches based on their delivery methods: in vivo and ex vivo.[8] While both approaches are used to deliver genes or genetically modified DNA into host cells, the techniques used differ between them. In vivo therapy entails the direct administration of DNA into cells already inside a patient, aiming to target affected cells. Ex vivo, on the other hand, involves the removal of cells from the host, genetically modifying them in a lab and reintroducing them back into a patient. An ex vivo approach can be autologous or allogeneic.





Source: Datamonitor Healthcare; adapted from Gene Therapy Net.com, 2017 and Kumar, 2017[8]

Autologous ex vivo therapy involves removing the patient's own cells to be modified and reintroduced. While auto-donation of cells is always advantageous from an immune response standpoint, the process is cumbersome and must be done on a patient-by-patient basis. Alternatively, allogeneic ex vivo therapy uses donor cells, genetically modifies them, and then introduces them into the patient. There are many redeeming qualities of an allogeneic approach, specifically the ability to treat many patients in a timelier manner and with reduced cost. However, as donor allogeneic cells are foreign to a patient, they can create undesirable immune reactions, which can limit their efficacy and viability.

Regardless of treatment type, in vivo or ex vivo, methods of delivery are required to perform these gene therapies. Direct insertion of a gene into a cell is not often functional.[9] In order for gene therapies to work, the replacement DNA, which will lessen or eliminate the phenotype of the disease, must be shuttled across the cell membrane and into the nucleus of cells.[10] As such, this delivery method is accomplished by the use of a vector. Multiple types of vectors are currently being used/investigated in gene therapy treatments, including viruses, plasmids, messenger RNA, liposomes and bacterial vectors.[8]

Due to their ability to infect cells, viruses are the most common vector of choice in both approved treatments and those currently in the pipeline, and account for approximately 59% of gene therapy prospects.[3] The genes for pathogenicity are typically removed from the genomes of these viruses and replaced with the targeted genes for a particular therapy, although viral features still make it possible to trigger an immune response.

Retroviruses allow for long-term expression of the gene; however, they have an increased risk of toxicity due to insertional mutagenesis and can't integrate into nondividing cells.[8,11] For therapies in the pipeline, the adeno-associated virus (AAV) has become the most commonly used vector. This virus offers many selective advantages. In addition to being nonpathogenic in humans, AAV demonstrates prolonged periods of continual transgene expression. Lentivirus, adenovirus, herpes simplex and others are also viral vectors currently being investigated in the pipeline. Nonviral vectors account for approximately 13% of pipeline therapies, with plasmids being the most prominently used.[3] While nonviral vectors are easier to produce, carry a lower risk of immunotoxicity and have the capacity to carry much larger genes, they do have some disadvantages. They are much less commonly used as they are often too large to enter the nucleus, demonstrate a much lower expression of transgenes and have substandard delivery efficiency.[8]

Currently, retroviruses are used in the highest volume of gene therapies on the market worldwide.

An emerging concept of genetic therapy that can't be ignored is gene editing, which is set apart from classical gene therapy in three ways.[12] First, rather than introducing new genes into cells, gene editing modifies existing genes. Second, gene editing is capable of silencing expression of disease-causing proteins. And third, changes made by gene editing are preserved through cell division, whereas classic gene therapies may not integrate into a genome. Gene editing technologies include CRISPR, zinc finger nuclease, TALEN and MegaTAL. These technologies can be employed both in vivo and ex vivo. While gene editing is relatively new compared to traditional gene and cell therapy, it is the fastest growing with respect to drug development, outpacing all other forms of gene, cell or RNA therapy.

Gene & cell therapy development

Gene and cell therapies are being developed for a large variety of diseases, including musculoskeletal, immunological, blood and clotting disorders, rare disease, neurological, cardiovascular and more. The largest demographic of the gene and cell therapy pipeline is oncology and rare disease, each accounting for a third of the candidates in development. However, it should be noted that 54% of rare diseases being focused on in the pipeline are for rare oncological diseases.[3,13] This makes cancer, by far, the most targeted disease state. While this may be attributed to the vast amount of people globally with oncological afflictions, it also may be related to the current success of chimeric antigen receptor T cell (CAR-T) therapy.

CAR-T therapy has been a major breakthrough in the treatment of certain types of cancers, particularly hematological malignancies.[14] This ex vivo cell therapy involves removal of healthy immune system T cells from a patient (autologous or allogeneic), modifying them in the lab to fight cancer and reintroducing them back into the patient. Specifically, this is done by engineering T cells to produce an artificial receptor on its surface. This receptor gives T cells the ability to bind to a specific protein that is expressed on a tumor, which activates the immune system to destroy them. The targeted tumor cell protein is not normally expressed in healthy cells, allowing the CAR-T cells to only bind to and destroy tumor cells.

The path to gene and cell therapy development has not been fast or simple. Although the concept of gene therapy to treat diseases was first proposed by Theodore Friedmann and Richard Roblin in 1972, it wasn't until 1990 that the first gene therapy trial was conducted at the National Institutes of Health in a young girl with severe combined immunodeficiency (SCID).[15,16] While that patient had a successful outcome, the death of a teenage boy in 1999 following an experimental gene therapy for ornithine transcarbamylase deficiency at the University of Pennsylvania brought pause to the entire gene therapy development landscape in the United States.[16] Drug developers went on to improve the safety of viral vectors and other delivery methods, and by 2011 PROVENGE® became the first personalized, cellular immunotherapy approved in the U.S.[17] There are now 30 gene or cell-based therapies approved for use in the United States (see Table 1), ranging from cord blood therapies for hematopoietic cell transplantation, to a gene therapy to treat blindness, and even personalized treatments for cosmetic enhancement.

Table 1. U.S.-approved gene & cell therapies

Product	Manufacturer	Technology	First Approval Date	Indication(s)	Cost[a]
PROVENGE® (sipuleucel-T)	Dendreon Pharmaceuticals, LLC	Autologous dendritic cells	4/29/2010	Prostate cancer	$225,369.06[b]
HEMACORD (HPC, cord blood)	New York Blood Center, Inc	Cord blood	11/10/2011	Unrelated donor hematopoietic progenitor cell transplantation	N/A
HPC, Cord Blood	Clinimmune Labs, University of Colorado Cord Blood Bank	Cord blood	5/24/2012	Unrelated donor hematopoietic progenitor cell transplantation	N/A
DUCORD (HPC, cord blood)	Duke University School of Medicine	Cord blood	10/8/2012	Unrelated donor hematopoietic progenitor cell transplantation	N/A
ALLOCORD (HPC, cord blood)	SSM Cardinal Glennon Children's Medical Center	Cord blood	5/30/2013	Unrelated donor hematopoietic progenitor stem cell transplantation	N/A
HPC, Cord Blood	LifeSouth Community Blood Centers, Inc.	Cord blood	6/13/2013	Unrelated donor hematopoietic progenitor cell transplantation	N/A
IMLYGIC® (talimogene laherparepvec)	Amgen, Inc.	Herpes Simplex Virus Type 1 vector	10/27/2015	Melanoma	$304.16 (initial dose) $30,414.28 (subsequent doses)
HPC, Cord Blood	Bloodworks	Cord blood	2/24/2016	Unrelated donor hematopoietic progenitor cell transplantation	N/A
CLEVECORD (HPC, cord blood)	Cleveland Cord Blood Center	Cord blood	9/1/2016	Unrelated donor hematopoietic progenitor cell transplantation	N/A
MACI® (autologous cultured chondrocytes on a porcine collagen membrane)	Vericel Corporation	Autologous cellularized scaffold product	12/13/2016	Repair of knee cartilage defects	$134,810.40[c]
KYMRIAH® (tisagenlecleucel)	Novartis AG	CAR-T	8/30/2017	• Pediatric ALL • Adult DLBCL-NHL	$652,593 (pediatric) $512,457.24 (adult)
YESCARTA® (axicabtagene ciloleucel)	Gilead Sciences, Inc.	CAR-T	10/18/2017	• DLBCL-NHL • FL	$508,800
LUXTURNA® (voretigene neparvovec-rzyl)	Spark Therapeutics, Inc.	AAV2 vector	12/19/2017	Leber's congenital amaurosis	$1,020,000 (both eyes)
HPC, Cord Blood	MD Anderson Cord Blood Bank	Cord blood	6/21/2018	Unrelated donor hematopoietic progenitor cell transplantation	N/A
ZOLGENSMA® (onasemnogene abeparvovec-xioi)	AveXis, Inc.	AAV9 capsid	5/24/2019	SMA type I	$2,705,294.40[d]
TECARTUS™ (brexucabtagene autoleucel)	Gilead Sciences, Inc.	CAR-T, First Approval	7/24/2020	• MCL-NHL • ALL	$508,800
BREYANZI® (lisocabtagene maraleucel)	Bristol-Meyers Squibb	CAR-T	2/5/2021	DLBCL-NHL	$536,672.40
ABECMA® (idecabtagene vicleucel)	Bristol-Meyers Squibb	CAR-T	3/26/2021	Multiple myeloma	$548,706
StrataGraft® (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen – dsat)	Mallinckrodt plc	Cell-based tissue	6/15/2021	Thermal burns	$4,800[e]
RETHYMIC® (allogeneic processed thymus tissue-agdc)	Enzyvant Therapeutics, Inc.	Allogeneic cell therapy	10/8/2021	Congenital athymia	$3,275,400
CARVYKTI™ (ciltacabtagene autoleucel)	Janssen Biotech, Inc.	CAR-T	2/28/2022	Multiple myeloma	$574,740

Product	Manufacturer	Technology	First Approval Date	Indication(s)	Cost[a]
ZYNTEGLO® (betibeglogene autotemcel)	bluebird bio	BB305 lentiviral vector	8/17/2022	β-thalassemia	$3,360,000
SKYSONA® (elivaldogene autotemcel)	bluebird bio	Lentiviral vector	9/16/2022	Cerebral adrenoleukodys-trophy	$3,600,000
HEMGENIX® (etranacogene dezaparvovec-drlb)	CSL Behring	AAV5 vector	11/22/2022	Hemophilia B	$4,200,000[d]
ADSTILADRIN® (nadofaragene firadenovec-vncg)	FKD Therapies Oy	Ad5 vector	12/16/2022	Bladder cancer	$72,000[f]
OMISIRGE® (omidubicel-onlv)	Gamida Cell Inc.	Cord blood	4/17/2023	Neutrophil recovery following umbilical cord blood transplantation	$405,600
VYJUVEK™ (beremagene geperpavec-svdt)	Krystal Biotech, Inc.	HSV-1 vector	5/19/2023	Dystrophic epidermolysis bullosa	$29,100[g]
ELEVIDYS (delandistro-gene moxeparv-ovecrokl)	Sarepta Therapeutics, Inc.	AAV vector	6/22/2023	Duchenne muscular dystrophy	$3,840,000[d]
LANTIDRA™ (donislecel-jujn)	CellTrans, Inc.	Allogeneic cell therapy	6/28/2023	Type 1 diabetes	Unknown
ROCTAVIAN™ (valoctocogene roxaparvovec-rvox)	BioMarin Pharmaceutical, Inc.	AAV5 vector	6/29/2023	Hemophilia A	$2,936,250[h]

This data is accurate as of August 1, 2023.
a. Average wholesale price accessed on August 1, 2023, via Medi-Span PriceRx Pro
b. Cost for complete 3-dose series
c. AWP for 2-sheet pack
d. Dose is based on patient's weight, but all doses are priced the same
e. Cost per sheet
f. Cost per treatment; therapy to be administered once every 3 months
g. Cost per treatment; therapy to be administered weekly until wound is closed
h. Dose based on weight; each vial is priced at $108,750 (accessed August 1, 2023) and price above assumes 70kg adult

While initial development of gene and cell therapies may have gotten off to a slow start, there are no signs of slowing down. The American Society of Gene + Cell Therapy's most recent quarterly data report on gene and cell therapy estimates there are now 2,800 candidates in clinical development ranging from preclinical through pre-registration, with oncology and rare diseases as the top two targeted therapeutic areas for pipeline gene and cell therapies.[13]

There are also at least nine therapies currently under review for FDA approval by the end of 2024 (see Table 2).

Table 2. Gene & cell therapies in late-stage development (BLA or Phase III)[a,b]

Product	Manufacturer	Delivery Method	Phase	Indication(s)
RYONCIL™ (remestemcel-L)	Mesoblast Limited	Allogeneic adult mesenchymal stem cells (MSC)	BLA PDUFA: 8/2/2023	Steroid-refractory acute graft vs. host disease (SR-aGVHD)
lifileucel	Iovance Biotherapeutics, Inc.	Autologous tumorinfiltrating lymphocyte cell product	BLA PDUFA: 11/25/2023	Advanced melanoma
Exa-cel (exagamglogene autotemcel)	Vertex Pharmaceuticals	CRISPR-Cas9 gene editing	BLA PDUFAs: 12/8/2023 3/30/2024	• Sickle cell disease • β-thalassemia
NurOwn (debamestrocel)	BrainStorm Cell Therapeutics	Autologous cultured mesenchymal bone marrow stromal cells secreting neurotrophic factors (MSC-NTF)	BLA PDUFA: 12/8/2023	Amyotrophic lateral sclerosis (ALS)
Lovo-cel (lovotibeglogene autotemcel)	bluebird bio	LentiGlobin vector	BLA PDUFA:	Sickle cell disease
HPC-Cord Blood Therapy	StemCyte Inc.	Allogeneic umbilical cord blood hematopoietic stem cells	BLA PDUFA: 2023	Ischemic stroke
Fidanacogene Elaparvovec	Pfizer Inc.	AAV vector	BLA PDUFA: Q2 2024	Hemophilia B
OTL-200 (atidarsagene autotemcel)	Orchard Therapeutics Limited	Lentiviral vector	Rolling BLA PDUFA: 1H 2024	Metachromatic leukodystrophy (MLD)
Afami-cel (afamitresgene autoleucel)	Adaptimmune Therapeutics plc	Autologous Specific Peptide Enhanced Affinity Receptor (SPEAR) T-cells	Rolling BLA PDUFA: TBD	Synovial sarcoma

Product	Manufacturer	Delivery Method	Phase	Indication(s)
AB-205	Angiocrine Bioscience, Inc	Allogeneic E4ORF1+ human umbilical vein endothelial cells (E-CEL® cells)	III	Multi-organ repair in patients with lymphoma undergoing hematopoietic transplant[c]
Autologous Muscle Derived Cells	Cook Group, Inc.	Autologous musclederived cells (AMDC)	III	Urinary incontinence
Botaretigene sparoparvovec	Johnson & Johnson	AAV5 vector	III	X-linked retinitis pigmentosa (XLRP)
CAP-1002	Nippon Shinyaku Co., Ltd.	Allogeneic cardiospherederived cells (CDCs)	III	Duchenne Muscular Dystrophy (DMD)
Cx601 (darvadstrocel)	Takeda Pharmaceutical Co. Ltd.	Allogeneic expanded adipose-derived stem cells	III	Complex perianal fistulae in Crohn's disease
D-Fi (dabocemagene autoficel)	Castle Creek Biosciences, Inc.	Autologous genetically modified dermal fibroblasts transduced with lentiviral vector	III	Dystrophic Epidermolysis Bullosa (DEB)
DB107 (vocimagene amiretrorepvec)	Denovo Biopharma LLC	Retroviral replicating vector (RRV)	III	Glioblastoma (GBM)
DCVax-L	Northwest Biotherapeutics, Inc.	Autologous dendritic cells (DC)	III	Glioblastoma (GBM)
DTX301 (avalotcagene ontaparvovec)	Ultragenyx Pharmaceutical Inc.	rAAV vector serotype 8	III	Ornithine transcarbamylase (OTC) deficiency
DTX401 (pariglasgene brecaparvovec)	Ultragenyx Pharmaceutical Inc.	AAV vector serotype 8	III	Glycogen storage disease type IA (GSDIa)
EB-101	Abeona Therapeutics Inc.	Retroviral vector (RVV)	III	Recessive dystrophic epidermolysis bullosa (RDEB)
Engensis (donaperminogene seltoplasmid)	Helixmith Co., Ltd.	Plasmid DNA	III	Chronic diabetic foot ulcers (DFU) Diabetic peripheral neuropathy (DPN)
ExoFlo	Direct Biologics, LLC	Allogeneic bone marrow mesenchymal stromal/ stem cells (BM-MSCs)	III	COVID-19 associated Acute Respiratory Distress Syndrome (ARDS)

Product	Manufacturer	Delivery Method	Phase	Indication(s)
Fordadistrogene Movaparvovec	Pfizer Inc.	rhAAV vector	III	Duchenne Muscular Dystrophy (DMD)
Generx (alferminogene tadenovec)	Gene Biotherapeutics Inc.	Adenovirus serotype 5 vector	III	Refractory angina
Giroctocogene Fitelparvovec	Pfizer Inc.	rAAV vector	III	Hemophilia A
Invossa (tonogenchoncel-L)	Kolon TissueGene, Inc.	Allogeneic chondrocytes	III	Knee osteoarthritis (OA)
JadiCell	Therapeutic Solutions International, Inc.	Mesenchymal stem cells (MSC)	III	COVID-19 associated Acute Respiratory Distress Syndrome (ARDS)
LUMEVOQ® (lenadogene nolparvovec)	GenSight Biologics S.A.	rAAV2/2-ND4	III	Leber Hereditary Optic Neuropathy
MDR-101 (sizavaleucel)	Medeor Therapeutics, Inc.	Allogeneic organ donor-derived CD34+ hematopoietic stem and progenitor cells and CD3+ T cells	III	Graft vs. host disease: HLA-matched living donor kidney transplant (LDKT)
MPC-06-ID (rexlemestrocel-L)	Mesoblast Limited	Allogenic mesenchymal precursor cells (MPCs)	III	Chronic low back pain (CLBP) due to degenerative disc disease
MultiStem® (invimestrocel)	Athersys, Inc.	Allogeneic multipotent adult progenitor cells (MAPCs)	III	Ischemic stroke
NeoCart	Ocugen Inc.	utologous chondrocytederived neocartilage	III	Articular cartilage defects in the knee
Orca-T	ORCA Bio Inc.	Allogeneic regulatory T cells, conventional T cells and CD34+ stem cells	III	Conditioning for allogeneic hematopoietic stem cell transplant (alloHSCT) in hematologic cancers
PLX-PAD	Pluri Inc.	llogeneic mesenchymal-like adherent stromal cells (ASCs)	III	Muscle recovery following surgery for hip fracture

Product	Manufacturer	Delivery Method	Phase	Indication(s)
Viralym-M (posoleucel)	Allovir, Inc.	Allogeneic multi-virusspecific T cells	III	Adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), JC virus (JCV) in allogeneic hematopoietic cell transplant (HCT)
ReACT	ProKidney LP	Autologous selected renal cells (SRCs)	III	Diabetic kidney disease
realSKIN™	Alexis Bio	Non-autologous live biotherapeutic, nonhuman skin transplant[d]	III	Severe and extensive deep-partial and fullthickness thermal burn wounds
REVASCOR® (rexlemestrocel-L)	Mesoblast Limited	Allogenic mesenchymal precursor cells (MPCs)	III	Chronic Heart Failure - Reduced Ejection Fraction (Chronic HFrEF)
Ryoncil (remestemcel-L)	Mesoblast Limited	Allogeneic adult mesenchymal stem cells (MSC)	III	Crohn's disease
SkinTE	PolarityTE, Inc.	Autologous heterogenous skin construct (AHSC)	III	Chronic diabetic foot ulcers (DFU)
SPK-8011 (dirloctocogene samoparvovec)	Roche Holding AG	Bio-engineered AAV capsid	III	Hemophilia A
Tabelecleucel	Atara Biotherapeutics, Inc.	Allogeneic Epstein-Barr virus-specific T cells	III	Relapsed or refractory EBV-positive post-transplant lymphoproliferative disorder (PTLD)[e]
Vigil® (gemogeno-vatucel-T)	Gradalis, Inc.	Autologous tumor cell vaccine using bi-shRNA DNA based plasmid[f]	III	Ewing's sarcoma

This data is accurate as of August 1, 2023.

a. Biomedtracker

b. IPD Analytics

c. Angiocrinebioscience.com/pipeline/

d. Businesswire.com/news/home/20221215005998/en/U.S.-FDA-Designates-Alexis-Bios-realSKIN-Regenerative-Medicine-Advanced-Therapy

e. Atarabio.com/pipeline/tabelecleucel/

f. Globenewswire.com/news-release/2023/03/14/2626549/0/en/Gradalis-Announces-Publication-in-Clinical-Cancer-Research-Featuring-Positive-Results-from-a-Study-Evaluating-Vigil-in-Combination-Therapy-for-Patients-with-Recurrent-Ewing-s-Sarco.html

Barriers to gene & cell therapies

Clinical applications in the gene and cell therapy markets have opened doors never before seen for patients with rare or unique medical maladies. The potential for treatment or cure of so many disease states with little or no current therapy options elicits hope for a tremendous amount of people. This hope is both real and cautionary. Despite the long and difficult medical and pharmaceutical journey to create these treatment solutions, some of the largest barriers to these lifesaving and life-altering treatments are pricing, reimbursement and manufacturing.

Pricing in the gene and cell therapy line is often extraordinarily high. Many of these therapies are developed to cure or treat very rare diseases. With such a large expenditure in research for each disease state, combined with a limited number of patients per disease, a large price tag is often required for manufacturers to receive return on investment.[18] For payers, large price tags for many gene and cell therapies raise red flags. There are currently eight FDA-approved gene and cell therapies that cost over $1 million (see Table 1). The huge, one-time, upfront nature of these payments presents economic challenges.

For instance, the estimated annual per patient drug costs for the treatment of hemophilia are $300,000 to $500,000.[19] This amount does not account for the clinic visits, hospitalizations and frequent lab tests hemophilia patients undergo.[19] In November 2022, CSL Behring gained FDA approval for its one-time, potentially curative therapy for hemophilia B, HEMGENIX® (etranacogene dezaparvovec-drlb). Its $4.2 million (AWP) makes it the highest-priced drug in the world (see Table 1).[20] But the long-term savings over the course of the life of a patient cured by this treatment is potentially significant.[18] However, in the United States, the frequency at which patients change insurers in a private insurance-based market is common.

As a result, the long-term savings resulting from a large, upfront payment may not be realized by that particular payer if and when the patient changes insurers.[1] Another payer concern is a reservation about such high costs for purported cures whose long-term effects of treatment are unproven and efficacy largely unknown at the current time.[18] Additionally, approvals for some of these therapies that profess a cure or long-term benefit can be based on single-arm trials with a small number of patients.[3] This raises doubt for payers regarding the true length of therapeutic benefit and whether a one-time treatment would actually be sufficient or would require one or more additional treatments over the course of any given patient's life.[3]

Manufacturers posit the upfront cost is worth the long-term savings in many cases.

Given these factors, alternative financing and payment options will most likely be sought out by payers in lieu of large, upfront payments. Many options and strategies have been suggested to thwart traditional payment models, which are likely unsustainable, to address the high cost of gene and cell therapy. The figure below briefly describes numerous financing and payment options currently being discussed for gene and cell therapies. Every option has its own set of pros and cons with each yielding varying levels of benefit and risk to patients, payers and manufacturers.

Table 3. Proposed payment models

Annuity	Payments broken up into multiple payments over a given period of time
Consumer mortgage	Paid by a loan taken by the patient who pays back the loan over a given period of time
Direct payment/ distribution	Treatments are purchased by payers directly from the manufacturers
Discounts/revenue caps	Therapy price reduced by discounts that apply when manufacturer surpasses revenue benchmarks
Patient assistance/ subsidy	Financial aid for patients for their gene and cell therapy related expenses
Pay for performance/ outcomes	Performance-based payment system where manufacturers are paid based on results of treatment and clinical peformance over set periods of time
Reinsurance	Catastrophic insurance coverage of high-cost therapies
Risk pools	Dedicated payer funds where higher-cost patient premiums are offset by lower cost patient premiums
Supplier credit	Third parties purchase therapies directly from the manufacturer and negotiate cost with the payers

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

An additional challenge for reimbursement is defining value.

From a payer perspective, it is easy to only look at cost savings over time. In other words, how much would a one-time treatment save them compared to the collective lifetime annual costs to treat a disease with the current available therapies? However, people will define value differently, and payers, as a result, may have to include novel metrics that may not normally be applied. Due to the high cost paid at the onset of treatment, additional metrics to consider may include severity of disease, age of disease onset and lifetime burden of illness.[1] As these therapies emerge with greater frequency to cover a broader spectrum of diseases, societal pressure may play a role in valuating therapies. Can society place extra value on therapies that can cure life-threatening diseases compared to other treatments with significantly lower medical impact?[1] Will benefits of return to work, reductions in the burden of care and increases to societal productivity play a role?[1] Several gene therapies will be targeting young patients with severe conditions. Will treatments for children be given increased value over adult treatments? It is unknown which, if any, metrics or societal expectations will affect reimbursements; however, given the dramatic impact these new therapies will present, it seems likely that the traditional valuation models will need adjustment.

In an ideal world, where pricing and reimbursement weren't factors, there are still logistical impediments to the mass commercialization of these treatments. The manufacturing process for these therapies is quite arduous, requiring significant investment and time. Most therapies are generated in a patient-specific manner, which eliminates manufacturers' ability to produce in bulk.[1] Additionally, the production of viral vectors used to deliver these therapies can seriously delay treatments, as many manufacturing facilities creating them have long waits, between 12-24 months.[3] Without reliable vector production, patient access to gene and cell therapies is reduced. With more manufacturers looking to invest in their own in-house development processes, vector supply issues should gradually lessen with commercial demand.

Although gene and cell therapies are usually one-time treatments requiring healthcare provider administration, specialty pharmacies can still play an important role in the distribution of these cutting-edge products. Today, the manufacturers of LUXTURNA® and ZOLGENSMA® both rely on specialty pharmacies to provide their products to patients in a process that is not unlike the dispensing of more conventional medications. Under current arrangements, the contracted specialty pharmacies purchase product from the manufacturer, handle distribution of product for individual patients to healthcare providers and bill the patient's insurance plan for reimbursement for the drug product.[21] In the case of ZOLGENSMA, the specialty pharmacy pays the manufacturer in full, up front, for the cost of product, but accepts payment for the $2 million therapy from the health plan over time.[21] Payments to healthcare providers for administration, hospital stays and other care and services related to the therapy are made directly by the health plan. The model for LUXTURNA is very similar to that of ZOLGENSMA, except that health plans reimburse the dispensing pharmacy for the product in a one-time full payment instead of a pay-over-time schedule.[21] Due to a breadth of experience in areas that may be key to successful deployment of a gene or cell therapy, specialty pharmacies are well-positioned to remain part of the gene and cell therapy distribution model as more products are approved.

The role of specialty pharmacy

One area where specialty pharmacy could play a role is in the management and handling of the physical gene or cell therapy product. A specialty pharmacy's history of managing limited distribution medications, including any unique reporting, purchasing or dispensing requirements, may give a gene or cell therapy manufacturer confidence in that pharmacy's capability to handle these ultra high-touch products. Additionally, special storage, handling and shipping requirements are commonplace for drugs dispensed via the specialty pharmacy channel. The physical capacity in specialty pharmacy facilities, as well as the experience in these unique storage and handling requirements, may relieve some burden from a manufacturer.

Experience in billing for medications will be increasingly important due to the high cost of gene and cell therapies. Depending on the benefit designated by a health plan, pharmacies have capabilities to submit online claims, whereas healthcare providers generally do not. Instantaneous submission through a PBM claim could prevent billing errors and streamline the process for reimbursement. If pharmacy claim submission is not an option, many specialty pharmacies are still well-versed in requirements for medical claim submission.

Clinical management programs, technological platforms to provide clinical management and reporting capabilities are all fundamental to the specialty pharmacy business. An established, validated clinical management platform could be harnessed to track the outcome measures that may be key to value-based contracts utilized to pay for gene and cell therapy products. Specialty pharmacies have the experience needed to effectively communicate with patients suffering from rare diseases and their healthcare providers in order to obtain outcomes-focused data. Collection and reporting of outcomes data from a single specialty pharmacy provider, rather than multiple individual patients and healthcare providers, would simplify the value-based contracting model for the manufacturer and health plans.

Potentially the most valuable attribute of a specialty pharmacy with respect to participating in gene and cell therapy distribution is experience in clinical management of patients with complex diseases.

Regardless of distribution models used, gene and cell therapy promises to continue shifting paradigms for manufacturers, patients, healthcare providers and pharmacies alike. These impressive technologies offer hope and promise to millions of patients for the future.

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