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ISSUE BRIEF

Gene Therapy in 2019: Milestones and Challenges

For as long as medical researchers have been able to identify the genes responsible for particular diseases, they have set their sights on using that knowledge to devise gene therapies—ways to repair or circumvent the abnormal gene expression—to prevent or treat those diseases. What is the state of the science of gene therapy in 2019? What can we expect in the near future? And what gaps and challenges stand in the way of realizing our goals?

To address those questions, we reviewed the findings from completed trials of gene therapies and those ongoing trials that have completed recruitment. We also interviewed a diverse group of stakeholders, including clinicians, pharmaceutical industry representatives, patients and patient advocates, government and private insurers, and policy makers on the challenges and important issues as well as their hopes for gene therapy. This brief summarizes the findings of the report for policy makers.

KEY POINTS

- Gene therapy research has yielded 10 approved treatments so far, and dozens more are on the horizon. These therapies target both rare genetic diseases and more common diseases like some cancers.
- Both research and clinical care face technological, ethical, and especially financial challenges.
- Experts and stakeholders are exploring ways to tackle some of the most challenging issues, such as modifying the approval process and how to pay for treatment.

Gene Therapy Explained

We define gene therapies as products that replace or circumvent defective genes by a variety of mechanisms:

- Replacing a disease-causing gene with a healthy copy of the gene,
- Repairing, inactivating, or modulating a disease-causing gene that is not functioning properly, or
- Introducing a new or modified gene into the body to help treat a disease

Gene therapy products that replace defective genes or introduce new genes comprise the gene itself and a vector (delivery vehicle) that consists of a tiny piece of viral or bacterial DNA. These products may be administered to patients directly (to modify cells in the body) or they may be transferred to a patient's cells in the lab with the modified cells then being transferred back to the patient.

Since 2013, 10 therapies have successfully navigated the multi-phase Food and Drug Administration (FDA) approval process, for the treatment of 11 different diseases (Table 1). Only a few of the therapies are expected to cure the targeted disease with one treatment, while most other therapies require repeated—possibly lifelong—treatments. However, whether or not potentially curative treatments live up to that potential has yet to be seen. Treated patients have not yet been followed long enough to see if benefits persist, compared to the 10 or more years needed to see if cures have been realized and harms are avoided.

Table 1. Approved Gene Therapies as of 2019

Disease	Treatment (Generic names, Year approved)	Mechanism of Gene Therapy	Repeated Treatment Required?
Metabolic and Other Multi-Organ Diseases			
Homozygous familial hypercholesterolemia	Kynamro (Mipomersen sodium, 2013)	Antisense	Yes
Vision and Neuromuscular Diseases			
Biallelic RPE65 mutation-associated retinal dystrophy	Luxturna (Voretigene neparvovec, 2017)	Adeno-associated viral vector serotype 2 (AAV2)	No
Duchenne muscular dystrophy	Eteplirsen (Exondys 51, 2016)	Antisense	Yes
Spinal muscular atrophy	Spinraza (Nusinersen, 2016)	Antisense	Yes
Polyneuropathy of hereditary transthyretin amyloidosis	Tegsedi (Inotersen, 2018)	Antisense	Yes
Hereditary transthyretin amyloidosis with polyneuropathy	Patisiran (Onpattro, ALN-TTR02, 2018)	RNA interference (RNAi)	Yes
Spinal muscular atrophy	Zolgensma[1] (Onasemnogene abeparvovec-xioi, 2019)	Adeno-associated virus (AAV 9)	No
Cancer			
Melanoma (inoperable lesions such as those in organs)	Imlygic (Talimogene laherparepvec, 2015)	Genetically modified oncolytic viral therapy–replication-competent, attenuated derivative of herpes simplex virus type 1	Yes
Relapsed or refractory large B-cell lymphoma	Yescarta (Axicabtagene ciloleucel, 2017)	Chimeric antigen receptor (CAR)-T CD19-targeted cell immunotherapy	No
Adult relapsed or refractory large B-cell lymphoma	Kymriah (Tisagenlecleucel, 2018)	Chimeric antigen receptor (CAR)-T CD19-targeted cell immunotherapy	No
Pediatric refractory B-cell precursor acute lymphoblastic leukemia	Kymriah (Tisagenlecleucel, 2017)	Chimeric antigen receptor (CAR)-T CD19-targeted cell immunotherapy	No

1 Zolgensma was approved by the FDA after completion of the report on which this brief is based.

The approval process was designed to ensure, to the extent possible, that a medical intervention is effective, that all potential safety issues are considered, and that the benefit-to-risk ratio is acceptable. Gene therapy interventions may also be subject to ethical and social scrutiny, as well, to gain approval.

Our review identified dozens of seemingly promising therapies that have undergone testing in controlled trials, although at least one treatment has been approved without a placebo-controlled trial, because such trials are not always feasible for gene therapies targeted to extremely rare or devastating diseases. And even though some gene therapies appear promising and have been approved or are near approval, the evidence to support clear clinical effectiveness may be lacking.

Conditions for which Gene Therapies Have Been Approved

The interventions approved by the FDA thus far target a variety of diseases, ranging from metabolic disorders to neuromuscular disorders to cancer. The first gene therapy to be approved, Kynamro™ (Mipomersen sodium), treats familial (inherited) hypercholesterolemia; this condition results in significant suffering and decreases life expectancy by causing dangerously high blood cholesterol levels. The disease can be caused by a variety of defects in any of several genes that encode the proteins involved in forming and transporting cholesterol throughout the body.

The approved therapy appears to work in many but not all patients, highlighting the vital importance of knowing the precise genetic cause of a patient's disease. In addition, this treatment must be administered via repeated injection (contrary to the single-treatment "cure" that has been a prime goal of gene therapy), and it has the potential to cause severe liver damage.

Another gene therapy, Luxturna™ (Voretigene neparvovec), approved in 2017 for the treatment of a rare eye disease, was the first approved to make use of a—theoretically—benign viral vector to transport genetic material into human cells. Localized side effects are observed in about two-thirds of recipients.

Gene therapies have also been approved for five neuromuscular disorders. While Spinraza™ (nusinersen) has been approved to treat a rare condition called spinal muscular atrophy with repeated administration, Zolgensma™ (Onasemnogene abeparvovec-xioi) has just been approved to treat this condition with a single administration, which may cost over $2 million.

Though much of the initial promise of gene therapies lay in their potential to treat rare, incurable conditions, science is discovering that these therapies can successfully treat much more common diseases such as cancer and blood disorders.

Therapies on the Horizon

More than 75 additional gene therapies have shown promise in clinical trials and may be close to approval to treat patients. These therapies are being tested for their ability to treat multiple disease types, from the exceedingly rare (like cerebral adrenoleukodystrophy, commonly known as Lorenzo's Oil disease) to the far more common diseases like mesothelioma and Parkinson's (a sample of conditions is shown in Table 2). As Table 2 shows, some diseases are the targets of multiple therapeutic efforts, partly because of the many different mutations that can have the same clinical presentation.

Table 2. Examples of Diseases for which Gene Therapies Are in Clinical Trials (Number of Unique Therapies)

Metabolic and Other Multi-Organ Diseases ▶ Amyloidoses (5) ▶ Familial amyloidotic neuropathies (1) ▶ Cerebral adrenoleukodystrophy or Lorenzo's Oil disease (1) ▶ Mucopolysaccharidosis I, II, IIIa, b (1)	**Cancer** ▶ Adult solid tumors (16) ▶ Pediatric neuroblastoma (1) ▶ Leukemia and lymphoma (20)
Immune Disorders ▶ HIV (2)	**Vision Diseases** ▶ X-linked retinitis pigmentosa (2)
Blood Diseases ▶ Hemophilia A and B (5)	**Neuromuscular Diseases** ▶ Alzheimer's disease (1) ▶ Huntington's disease (1) ▶ Limb-Girdle muscular dystrophy, type 2B, 2D, 2E (4)

Realizing the Promise of Gene Therapy: Challenges and Opportunities

The potential promise gene therapy holds for treating a broad variety of heretofore untreatable diseases must be tempered by the many challenges moving forward. We present here some of the unknowns for which answers will be most useful for policy makers.

LONG-TERM BENEFITS AND HARMS

As stated earlier, most recipients of gene therapies have not yet been followed long enough to ensure a cure or even persistent effectiveness. Likewise, some studies have shown that gene therapies can have adverse health outcomes, such as triggering immune responses or organ failure. Therapies that introduce a new copy of a gene into a patient's cells also have the potential to disrupt the genome, with possible consequences to future generations. Some experts propose forming patient registries to track both the long-term effectiveness and the risks of treatments in various patient populations.

A related challenge is that patients may lack sufficient science literacy to understand the risks of gene therapy and to provide truly informed consent to treatment. Improving provider and patient education might help address this concern.

DEVELOPMENT CHALLENGES AND COSTS

Another challenge lies in the considerable time and cost involved in the development, testing, and approval of gene therapies. Advocates have suggested some ways to streamline the currently lengthy approval process.

For example, some have suggested allowing approval based on shorter-term outcomes (like changes in biomarkers, as was true for Exondys), rather than waiting for longer-term outcomes like a complete cure or disease prevention. Research will be needed to assess the effects of such regulatory changes on costs and time to approval as well as on patient outcomes.

PRODUCTION AND TREATMENT

Manufacturing and regulating the administration of gene therapies also present numerous quality challenges. Some of these challenges may be addressed by creating centers of excellence for gene therapy manufacturing and delivery, but many challenges remain.

PAYMENT

One of the greatest challenges may be how to pay for treatment—both for single-administration therapies with large upfront costs and for those that require repeated, often lifelong, administration—and how equitable access to treatment will be assured. Prices can range from the thousands to the millions and per person lifetime costs for some approved therapies can reach well over $1 million, with the prevalence of the conditions varying from rare to common.

Novel public-private research and cost-sharing partnerships have been proposed. Other proposed solutions include long-term loans and risk sharing—linking payments to treatment outcomes. One suggestion has been to make the costs of developing gene therapies more transparent. Research aimed at predicting the effects of various payment models on access to care might also be illuminating. Hopefully, the benefits of gene therapies will someday vastly outweigh the costs and challenges of bringing those therapies to patients.

ETHICAL CHALLENGES

While drug pricing presents ethical issues that are not unique to gene therapy, there may be significant ethical concerns for expensive gene therapies. Also, without improving science education, patients may not have a strong enough understanding of the potential risks of undertaking certain therapies to provide fully informed consent. For example, gene therapy could change the genome of subsequent generations without the possibility for consent.

Many unknowns remain about the promise and reality of gene therapies. We have listed some of the unknowns above for which the answers would be useful to policy makers. Finally, given the rapid rate at which gene therapy research is advancing, an automated clearinghouse is needed to track the evidence of effectiveness and safety and make the evidence available to researchers, policy makers, payers, providers, and patients.

This issue brief is based on a two-volume report. For more information, see:

Richardson A, Apaydin E, Baxi S, Vockley J, Akinniranye O, Larkin J, Motala A, Hempel S. (2019). Landscape Review and Evidence Map of Gene Therapy. The full reports may be accessed at: *www.pcori.org/emerging-tech*

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