Insightsfeature

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Gene Therapies: Promising, Costly, Complex

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With novel treatments for aggressive cancers, as well as hereditary conditions like cystic fibrosis, ocular disorders and hemophilia, gene therapies bring new hope to patients with conditions that previously had few or no treatment options, and required a lifetime of management.

These treatments use genetic engineering to replace or repair mutated genes, effectively treating the patient's medical condition. Some have been granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA), which is intended to expedite the development and review of drugs for serious or life-threatening conditions, which may demonstrate substantial improvement over existing therapies.

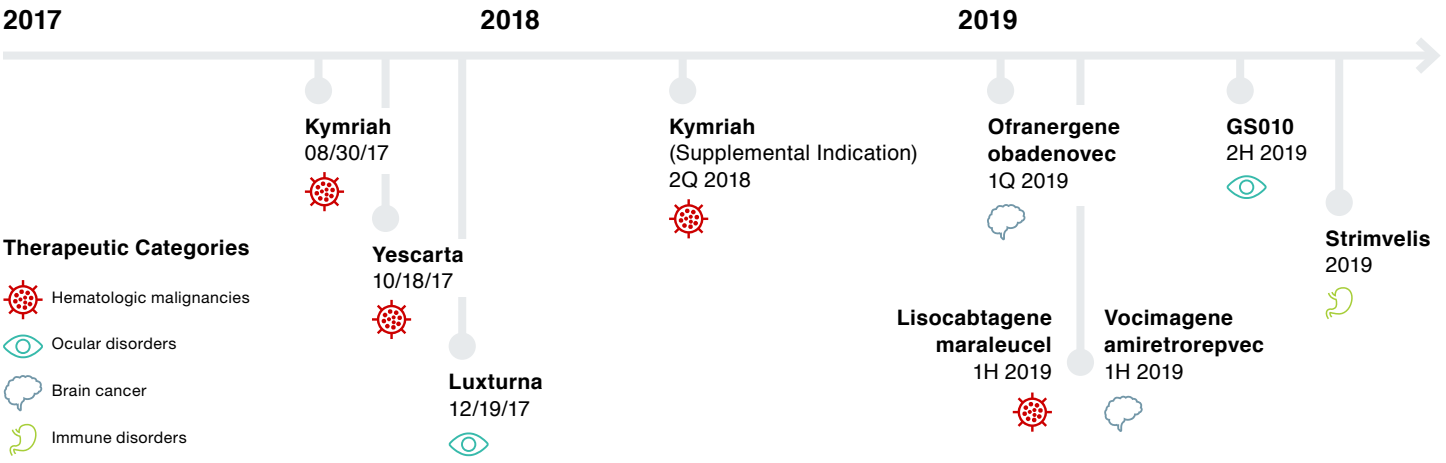
Gene therapies are highly complex and, thus far, have targeted small patient populations with rare conditions. The initially approved agents require highly specialized care and administration in a hospital or medical setting. Along with the hope for effective treatment, or even a cure, come other considerations including understanding the safety and side effect profiles, durability of response, utilization management requirements, and how to ensure access to treatment centers qualified to administer them. Careful patient monitoring is also important. Combined with the high cost of gene therapies, these factors heighten the complexity for payors, consumers, and the health care system for these much anticipated therapy options.

What are Gene Therapies?

Gene therapies work by utilizing different mechanisms to alter an individual's genes or modify the expression of a gene product in order to prevent, treat, or cure a disease. Some vector-based gene therapies may use a virus to deliver genetic material directly into a cell to replace a missing or defective gene to treat single-gene disorders. The material may be administered directly into an organ, such as an eye. Gene therapies take advantage of the fact that all viruses introduce genetic material into the host cell, as part of their replication cycle, by binding to their hosts.

The FDA recently approved Luxturna, a vector-based gene therapy that is injected directly into a patient's retina (back of the eye) to help reverse vision loss in pediatric and adult patients with a specific type of progressive blindness due to a mutate gene (RPE65). Vector-based gene therapies are also in development for the treatment of ocular and immune disorders, cystic fibrosis, certain forms of brain cancer, sickel cell disease, and hemophilia.

Approved and In-Development Gene Therapies*



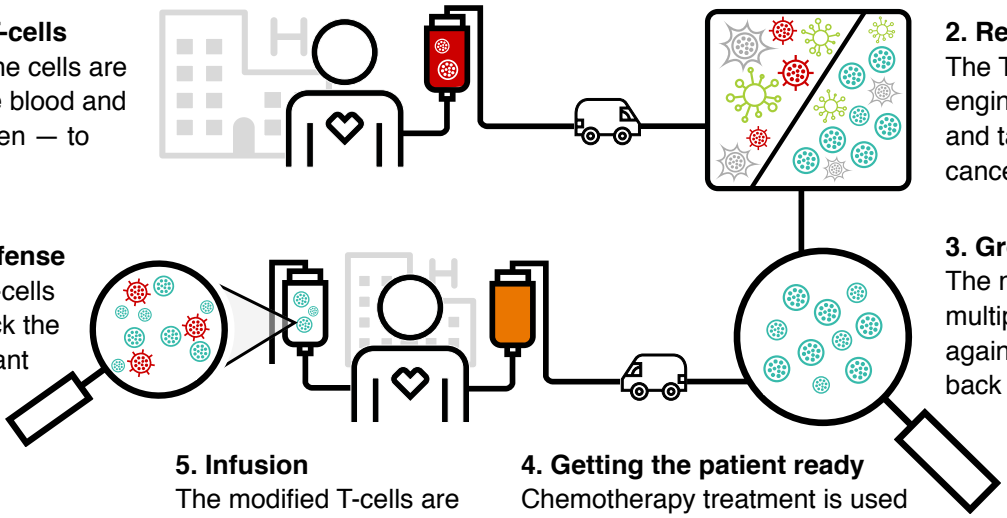
*This is a sample of the gene therapies in development, not a complete list of all therapies

CAR T-Cell Therapies

The first gene therapies to be approved, Kymriah and Yescarta, are a type known as chimeric antigen receptor (CAR) T-cell therapies. They are used for the treatment of patients with certain aggressive forms of blood cancer that have relapsed or were not responsive to previous treatment.

CAR T-cell therapies use the patient's own T cells — cells in the immune system that fight infections — to target and kill cancer cells. The cells are harvested in a clinical setting — usually a hospital — and genetically engineered to incorporate a chimeric antigen receptor, which contains protein receptors that enable the modified T-cells to identify and target cancer cells. The modified cells are reintroduced into the patient to help fight the disease. The cells continue to multiply and persist over time providing ongoing cancer-fighting ability and help prevent a recurrence.

1. Extracting T-cells
Patient's immune cells are filtered from the blood and shipped — frozen — to manufacturer.



2. Reprogramming
The T-cells are genetically engineered to recognize and target the malignant cancer cells.

3. Growth
The modified T-cells are multiplied in the lab, once again frozen and shipped back to the hospital.

4. Getting the patient ready
Chemotherapy treatment is used to kill some white blood cells so the body will accept the modified T-cells.

5. Infusion
The modified T-cells are returned into the patient through an infusion.

6. Targeted defense
The modified T-cells target and attack the specific malignant cancer cells.

Yescarta was approved to treat adults with certain forms of relapsed or refractory large B-cell lymphoma, who have failed previous therapies. In a clinical trial, 51 percent of patients achieved complete remission three months after treatment.

Kymriah has been shown to be effective in patients up to 25 years old with a specific form of acute lymphoblastic leukemia (ALL) that have relapsed or do not respond (refractory) to conventional therapies. In a clinical trial, 83 percent of patients achieved complete remission three months after treatment.** Kymriah is also pending FDA approval for a type of B-cell lymphoma, an indication for which Yescarta is already approved.

Patient Considerations

There are several unknowns when it comes to gene therapy. It is too early to tell how long the effects of the treatments — regained vision, remission, etc. — will last. There isn't enough patient follow-up data yet to know whether they will truly be "cures," or if the diseases will eventually return.

CAR T-cell therapies have significant safety issues including risk of neurological toxicity and cytokine release syndrome (CRS). Common neurological symptoms include headache, encephalopathy (brain disease, damage or malfunction), tremors, and confusion. Patients are advised to refrain from driving or operating heavy machinery for eight weeks after CAR T-cell therapy. Mild CRS may present with flu-like symptoms, while severe cases may lead to life-threatening cardiac and respiratory distress, and multi-organ failure that requires intensive care unit admission and may even lead to death. Due to the potential for such side effects, patients are advised to stay within two hours of the treatment center for at least four weeks after receiving therapy. Additional treatment may be required to treat the side effects. For instance, Actemra was recently approved by the FDA for the treatment of CAR T-cell induced CRS. Luxturna carries the risk of intraocular inflammation, cataracts, increased intraocular pressure and retinal tears.

Gene therapies are highly personalized and the routes of administration are complex. Given the risks, logistics, and potential for adverse events, they would be administered in a hospital setting under medical supervision. So far, the therapies that have been approved are only available at select treatment centers across the country which have trained professionals, and have been certified by the manufacturer in the handling and administration of these treatments. Patients must travel to a certified center to receive treatment.

Payor Considerations

If the trend observed for therapies approved so far holds true, most gene therapies are likely to carry price tags of hundreds of thousands of dollars for a one-time treatment.

Kymriah is priced at $475,000, Yescarta at $373,000, and Luxturna at $850,000 (for both eyes). However, there may also be significant costs associated with the administration and required patient monitoring. In addition to the direct cost of the treatment, payors will need to consider the total cost of care, including hospitalization and ancillary services, as well as side effect management and supportive care. Patients may also need costly treatment for significant adverse events and complications resulting from the therapy. In addition, most gene therapies are likely to be covered under the medical benefit, where payors have historically had lower visibility into their drug spend.

Some of these therapies may be administered in an inpatient hospital setting instead of as an outpatient service. This means payors will need ways to ensure appropriate utilization to effectively manage costs because typical utilization management programs do not apply to inpatient services. For outpatient treatments, medical benefit management programs can assist with ensuring appropriate utilization.

Longer Term Gene Therapy Pipeline

Treatment Name	Projected Launch	Therapeutic Category
Lenti-D	1Q 2021	Cerebral adrenoleukodystrophy
Lentiglobin	1Q 2021	Transfusion-dependent B-thalassemia; severe sickle cell disease
Valoctocogene roxaparvovec	2024	Hemophilia
SPK9001	TBD†	Hemophilia
SPK8011	TBD†	Hemophilia

†Projections not yet available due to mid-phase status.

There are several other therapies in the pipeline that could be approved and launched in 2019. Yet others are in earlier stages of development and could be launched in later years. The pipeline for gene therapies is robust. We will continue to provide updates and perspective on this new class of treatments.

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**Or complete remission with incomplete blood count recovery (CRi).

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