## **Genetic Testing and Gene Therapy**

 $\star$  Segal Consulting

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# **Genetic Testing**

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#### Genetic testing...

a process used in the medical field as a diagnostic and predictive tool. Genetic testing is available for over 10,000 rare and common conditions. Because the term "genetic testing" is constantly evolving, it is important to define the various types of tests for the purposes of this discussion.



# **Types of Genetic Tests Available Today\***

- Diagnostic testing: identifies a genetic condition or disease that is making, or in the future will make, a person ill. The results of diagnostic testing can help in treating and managing the disorder.
- Predictive and pre-symptomatic genetic testing: finds genetic variations that increase a person's chance of developing specific diseases. This type of genetic testing may help provide information about a person's risk of developing a disease, and can help in decisions about lifestyle and health care.
- **Prenatal testing:** is offered during pregnancy to help identify fetuses that have certain diseases.
- Carrier testing: tells people if they "carry" a genetic change that can cause a disease. Carriers usually show no signs of the disorder; however, they can pass on the genetic variation to their children, who may develop the disorder or become carriers themselves.
- Pre-implantation genetic testing: is done in conjunction with in vitro fertilization to determine if embryos for implantation carry genes that could cause disease.

- Newborn screening: is used to test babies one or two days after birth to find out if they have certain diseases known to cause problems with health and development.
- Pharmacogenetic testing: gives information about how certain medicines are processed in a person's body. This type of testing can help a healthcare provider choose the medicines that work best with a person's genetic makeup. For example, genetic testing is now available to guide treatments for certain cancers.
- Research genetic testing: helps scientists learn more about how genes contribute to health and disease, as well as develop gene-based treatments. Sometimes the results do not directly help the research participant, but they may benefit others in the future by helping researchers expand their understanding of the human body.



<sup>\*</sup>The National Institute of Health

- > Assessment of the costs associated with testing, screening, and treatment is challenging because technology and treatment approaches are changing rapidly.
- Senetic testing can cost less than \$50 for a simple blood screening for sickle cell anemia or cost in the \$10,000 range for a complicated pre- implantation genetic test for Tay-Sachs disease. These are two extremes of genetic tests with varying costs.
- Cost of testing for BRCA1 and BRCA2, the predictive genes for breast cancer, ranges from \$300 to \$3,000, depending on what type of testing is done and how extensive the test is.



## **Costs of Genetic Testing**

- In addition, before testing, a genetic consultation is recommended to help a patient understand and make decisions about genetic testing. This typically costs about \$150 per hour, and the length of time needed depends on the complexity of the situation.
- Due to this variation in pricing, it is virtually impossible to predict the total costs of genetic testing for a plan sponsor.



#### Treatment

- Senetic information can direct a physician toward appropriate treatments. For instance, cystic fibrosis and progressive muscular dystrophy are disorders that may be confirmed or ruled out by diagnostic genetic testing and thereby confirming what treatments should be used.
- Senetic testing for breast cancer and the BRCA genes look for changes or mutations in the BRCA1 and/or BRCA2 genes, which indicates an increased cancer risk.
  - The United States Preventive Services Task Force (USPSTF) has designated a Grade B recommendation for BRCA1/BRCA2 screening for women who have a family history of breast, ovarian, tubal, or peritoneal cancer (required testing for non-grandfathered plans)
- Senetic research has revealed that mutations of the gene for the epidermal growth factor receptor (EGFR) can predict treatment response for individuals with Non-small cell lung cancer (NSCLC).
  - This will eliminate waste due to patient non-response in cancer treatment



#### Drug Efficacy

Senetic testing can help a physician predict an individual's response to a specific drug therapy. This avoids the usual "trial-and-error" approach to drug treatment, resulting in eventual plan cost savings.

For example, genotype testing for the Human Leukocyte Antigen B (HLA-B\*5701) provides insights into medication treatments for patients infected with HIV-1, specifically Abacavir. Those patients that test positive for this antigen are not recommended to receive Abacavir treatments.



## **Direct to Consumer Genetic Tests**

- > Additionally, there is an emerging trend of direct-to-consumer (or at-home) genetic tests marketed directly to consumers through advertising, such as:
  - 23&me
  - TellMeGen
  - AncestryDNA
  - DNAfit
- Individuals may purchase the genetic test from a manufacturer and complete the test by sending a sample back to the manufacturer's laboratory.
- Senetic counseling is key to interpreting the results of a test that imparts a probability of disease.
- Senetic counseling is often not included in direct-to-consumer testing products and can lead to patients misinterpreting results of a test.
- > At-home genetic testing kits such as 23&me are not covered by most plans.

# **Coverage of Genetic Testing**

- > Although many plan sponsors are silent about the coverage of genetic testing, many plans are beginning to provide guidance to its members regarding what genetic tests are covered, and in what circumstances.
- > Of those plans covering genetic tests, the following tests and/or restrictions are most prevalent:
  - Prenatal and newborn genetic testing
  - Testing for a genetic mutation in the BRCA
  - Those tests which will have a significant impact on a patient's treatment
  - Those tests which aid in the diagnosis of a specific condition
  - Other medically necessary tests which would improve a patient's diagnosis or treatment
- > Plan sponsors that choose to cover genetic tests may require pre-authorization for genetic tests (or certain categories of tests).



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# **Gene Therapy**





## What is Gene Therapy?

**Gene therapy** is treatment for a disease. It is not a diagnostic service. In some cases, genetic testing may need to be performed before gene therapy is initiated (e.g., in the case of Luxturna, covered later).

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> Gene therapy is different from genetic testing.

In general, gene therapy involves replacing a gene that causes a medical problem with one that does not, adding genes to help the body fight or treat disease, or turning off genes that cause medical problems.

## **CAR-T** Therapies

- CAR-T stands for Chimeric Antigen Receptor T-Cell Therapy. CAR-T therapy is a specific type of gene therapy (cell engineering) that adds a new receptor to the patient's own T cells (a type of white blood cell).
- CARs are designed to help the patient's immune system find and attack the cancer cells. With CAR-T therapy, the patient's own T cells are harvested, genetically modified in a laboratory and then later infused back into the same patient.
- CAR-T modified cells are directed to target and destroy cancer cells that have a specific antigen. In other words, the cancer patient's own cells are reprogrammed to attack and kill the patient's cancer.
- The procedure is complicated, is not always effective, and can have serious side effects (including death).



#### **CAR-T Therapies** *Kymriah*

- Novartis obtained FDA approval for Kymriah in August 2017 as a breakthrough therapy for relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) (a type of blood cancer) for those who have not responded to previous treatment.
- There are currently 20 approved medical centers in the U.S. that have been authorized by Novartis to provide treatment with Kymriah. There are plans to expand the number of treatment sites to 30 – 35 in the future.
- It has been estimated that about 600 patients would be eligible for Kymriah treatment each year.

**Kymriah...** a one-time treatment for children and young adult patients (up to 25 years of age) whose blood cancer is resistant to traditional treatment or who are in a second or later relapse.

The wholesale price of Kymriah is approximately **\$570,000** for a single course of therapy.

#### **CAR-T Therapies** *Yescarta*

- > Kite, a Gilead company, obtained FDA approval for Yescarta in October 2017 to treat certain types of non-Hodgkin's Lymphoma (a type of blood cancer) for those who have not responded to previous treatment.
- Initially, there will only be 16 approved U.S. medical centers authorized by Gilead to provide treatment with Yescarta. There are plans to expand the number of U.S. treatment sites to 30 in the future.
- It is estimated that up to 7,500 patients may be candidates for this therapy each year.

Yescarta... approved for the treatment of patients with relapsed or refractory aggressive B-cell non-Hodgkin's Lymphoma (NHL) who are ineligible for autologous stem cell transplant.

The cost of Yescarta is approximately **\$373,000** for a single course of therapy.

#### Ocular Gene Therapy Luxturna

- Sparks Therapeutics received FDA approval for Luxturna, a type of gene therapy, in December 2017.
- This is the first treatment approved in the U.S. that targets a disease caused by mutations in a person's specific gene.
  - The manufacturer is offering free genetic testing to determine if a patient has the correct mutation.
- Luxturna works by delivering a normal copy of the gene to the retinal cells, causing these retinal cells to produce the normal protein that converts light to an electrical signal, thus restoring the patient's vision loss.
- There are only eight treatment centers that can administer this therapy in the U.S. at this time.

Luxturna... approved to treat (in children and adults) a rare form of inherited blindness called confirmed biallelic RPE65 mutationassociated retinal dystrophy.

Analysts expect the cost to be approximately **\$1 million** for both eyes. Again, the cost does not include facility fees, professional fees and complications.

# Spinal Muscular Atrophy (SMA) Type 1

SMA is a genetic disease that affects voluntary muscle movement and weakens physical strength.

SMA Туре	Severity	Age of onset	Highest function	Life expectancy
I (Werdnig-Hoffmann disease)	Severe	0-6 months	Never sits	<2 years
II	Intermediate	7-18 months	Sits but never stands	>2 years
III (Kugelberg-Welander disease)	Mild	>18 months	Stands and walks	Adult
IV (adult form)	Mildest	Second and third decade	Walks	Adult

- > 1 in 10,000 live births are diagnosed with SMA Type 1, and without treatment, approximately 90% of children die before 24 months of age.
- > Babies with SMA Type 1 have difficulty breathing, eating, sitting, or walking.
- > SMA Type 1 is the number one genetic cause of death for infants.



#### **SMA Type 1 Gene Therapy** *Zolgensma*

- > AveXis, a Novartis Company, received FDA approval for Zolgensma in May, 2019.
- Novartis has set the cost of the drug at around \$2.1 million.
- > Zolgensma is a gene therapy.
  - Zolgensma uses intravenous (IV) delivery for infants diagnosed with SMA Type 1.
  - Zolgensma is a one-time infusion, not a chronic medication, and is typically indicated in patients who are less than 2 years of age.
- Spinraza, which is currently approved to treat all types of SMA, is dosed repeatedly in order to improve motor function for patients with SMA.
  - Spinraza is not gene therapy.

**Zolgensma...** differs from Spinraza by replacing the patient's dysfunctional SMN-1 gene through a single dose of the therapy, ultimately treating the underlying cause of the condition for infants 6 months of age and younger. Both products demonstrate a positive impact on the mortality rate for the most severely affected infants with type I SMA.

## **Gene Therapy Trends**

- There are currently about 300 gene therapies in development with more than 100 focused on cancer.
- > Other promising areas for gene therapy include eye disorders, cardiovascular, neurological (i.e., Alzheimer's, Parkinson's), and blood disorders (i.e., Hemophilia).





## **Action Steps for Plan Sponsors**

- Initially, plan sponsors should determine whether they will cover these novel therapies.
- > Absent clear language excluding them, it is likely that they would be covered by the terms of most plans because they have been FDAapproved, they are no longer experimental, and they will be considered medically necessary for a rare subset of patients.
- > While the number of people needing these therapies is small, the costs are extremely high.
- If a plan sponsor wishes to exclude coverage, consultants and analysts should work with the health compliance practice and legal counsel to draft an appropriate exclusion for the plan.
- For plan sponsors that decide to cover these therapies, there are several implementation concerns that should be addressed.



## Some Plans Exclude Zolgensma Coverage

- To date, some multiemployer plans have decided not to allow coverage for Zolgensma under the plans.
  - This is due to the fact that the drug is so new and long-term results are unavailable, and that the prevalence rate is so low.
  - They've decided to approach claims, if any, on an appeal basis and utilize possible government or manufacturer's assistance programs at that time to bring down the cost.



## **Medical vs. Pharmacy Benefit?**

- In general, gene therapy benefits should be administered by the medical plan, not under the pharmacy benefit (except Express Scripts).
- > Although sometimes referred to as products or drugs, they are best described as prescribed therapies administered by medical professionals.
- Some PBMs have advised plan sponsors to exclude these treatments under the pharmacy benefit so that everyone understands that they are not covered through the pharmacy benefit.
  - This makes sense because many people in the news media and elsewhere often inaccurately refer to these therapies as new FDA-approved drugs.
- > As each therapy comes to market, the Plan will need to evaluate coverage of the therapy and whether to cover under the medical plan or the pharmacy benefit



## **Precertification/Prior Authorization**

- > Precertification/prior authorization for any of these new therapies is important to assure use of these expensive therapies meets at least the FDA approved indications.
- > Where possible, the patient should be directed to a network provider.
- If the plan provides a travel benefit, that should also be subject to precertification.
- The Plan will want to make sure that its precertification/prior authorization company is up to date with their screening criteria and is ready to precertify these new therapies.
  - Major insurers are just beginning to publish their screening criteria.



## **Zolgensma Distribution and Administration**

- > Zolgensma will be distributed through Express Scripts subsidiary Curascript. The dispensing process is exactly the same regardless of the medical or pharmacy benefit.
- > Zolgensma dispensing is limited to two specialty pharmacies:
  - One pharmacy is Orsini.
  - The other pharmacy is Accredo an Express Scripts' specialty pharmacy business.
- Any doctor prescribing Zolgensma must submit to the United BioSource HUB to determine eligibility and processing.
  - It's our understanding that at this point the proper channel for coverage will be determined per the benefit, and a coverage review will be performed.
  - If coverage criteria are met, the HUB then routes the prescription to either Accredo or Orsini for dispensing.



## Zolgensma / Pharmacy Benefit Coverage / Express Scripts

- Since Express Scripts/Accredo is one of the two dispensers, it has the ability to provide coverage to their PBM clients.
  - Other PBMs don't have this ability.
- > Express Scripts pricing for Zolgensma is AWP 14.7%.
  - On the medical side the pricing for Zolgensma can range from AWP 12% to AWP – 14.5% depending on the arrangement the medical provider has with Accredo.
- Solution > Given that the dispensing of the drug is exactly the same regardless of the medical or pharmacy benefit, and there is opportunity for a larger discount for Zolgensma directly through Express Scripts, it makes sense for Zolgensma to be covered under the Plan's pharmacy benefit if the PBM is Express Scripts.

## Luxturna / Pharmacy Benefit Coverage / Express Scripts

- The manufacturer has confirmed that Luxturna is not considered a drug and is better described as a "therapy."
- It will be provided to treatment centers exclusively by one specialty pharmacy - Express Script's specialty pharmacy (CuraScript Specialty Distribution/Accredo Specialty Pharmacy).
  - It appears that Luxturna will only be dispensed to retinal surgeons/treatment centers trained by the manufacturer.
- Solven that Express Scripts can offer a discount for Luxturna, it may make sense for Luxturna to be covered under the Plan's pharmacy benefit if the PBM is Express Scripts.
  - Express Scripts can provide prior authorization under most Plan's Pharmacogenomic Prior Authorization clinical program list.



### **Other Considerations**

- > Network provider issues
- Travel benefits
- > Stop loss coverage



## In Conclusion

 Plan sponsors that do not want to cover gene therapy should consider excluding coverage for gene therapy treatment, as existing plan documents may not provide a sufficient basis for exclusion

The exclusion should be drafted in coordination with Plan legal counsel and Segal's compliance practice

> Plan sponsors that want to cover gene therapy should consider a variety of factors as they design their benefits for this new treatment

