USE OF GENE THERAPY IN THE TREATMENT OF RARE DISEASES

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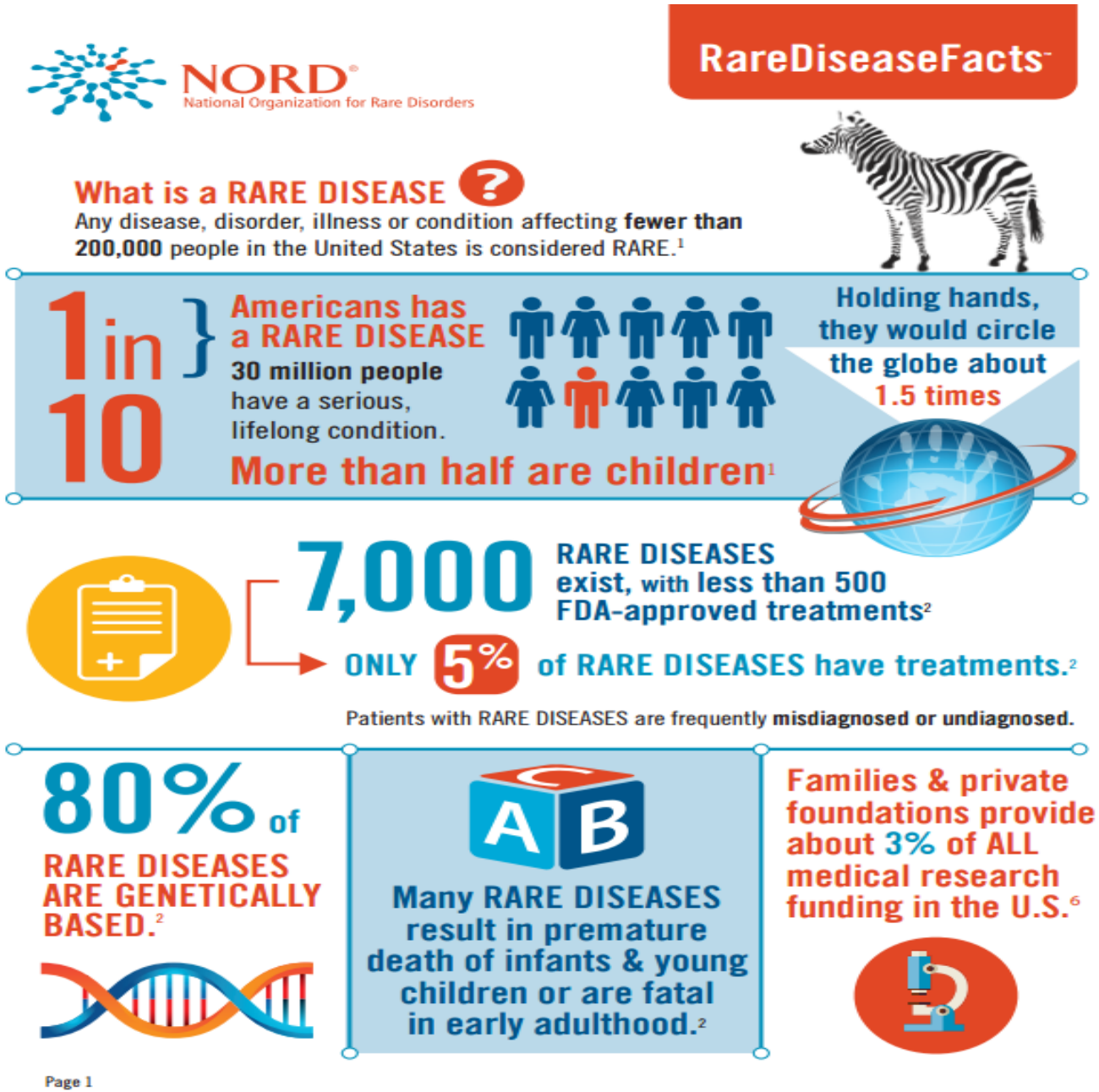
INTRODUCTION

RARE DISEASES

Rare Disease

- In USA, a rare disorder is defined as a disorder that affects **less than 200,000 people in the US**
- The characterization or description of a rare disorder differs in every country. In the **Europe (EU)** a disorder is deemed rare when it affects **less than 1 in 2,000 people**
- There are approximately **7,000 rare diseases in the world**. **While the number of individuals affected by a particular rare disorder are less, the total number of individuals affected by a rare disease is large**
- **Maximum number of rare diseases are known to be genetic which means they are usually caused by alterations in genes or chromosomes**
- Examples of rare diseases include : **Acute Hepatic Porphyria, Idiopathic Pulmonary Fibrosis, Scleroderma** etc.



Sources : 1.Genetic and rare diseases information center. FAQs about rare diseases [Internet]. National Center for Advancing Translational Sciences.
2. National Organization for Rare Diseases

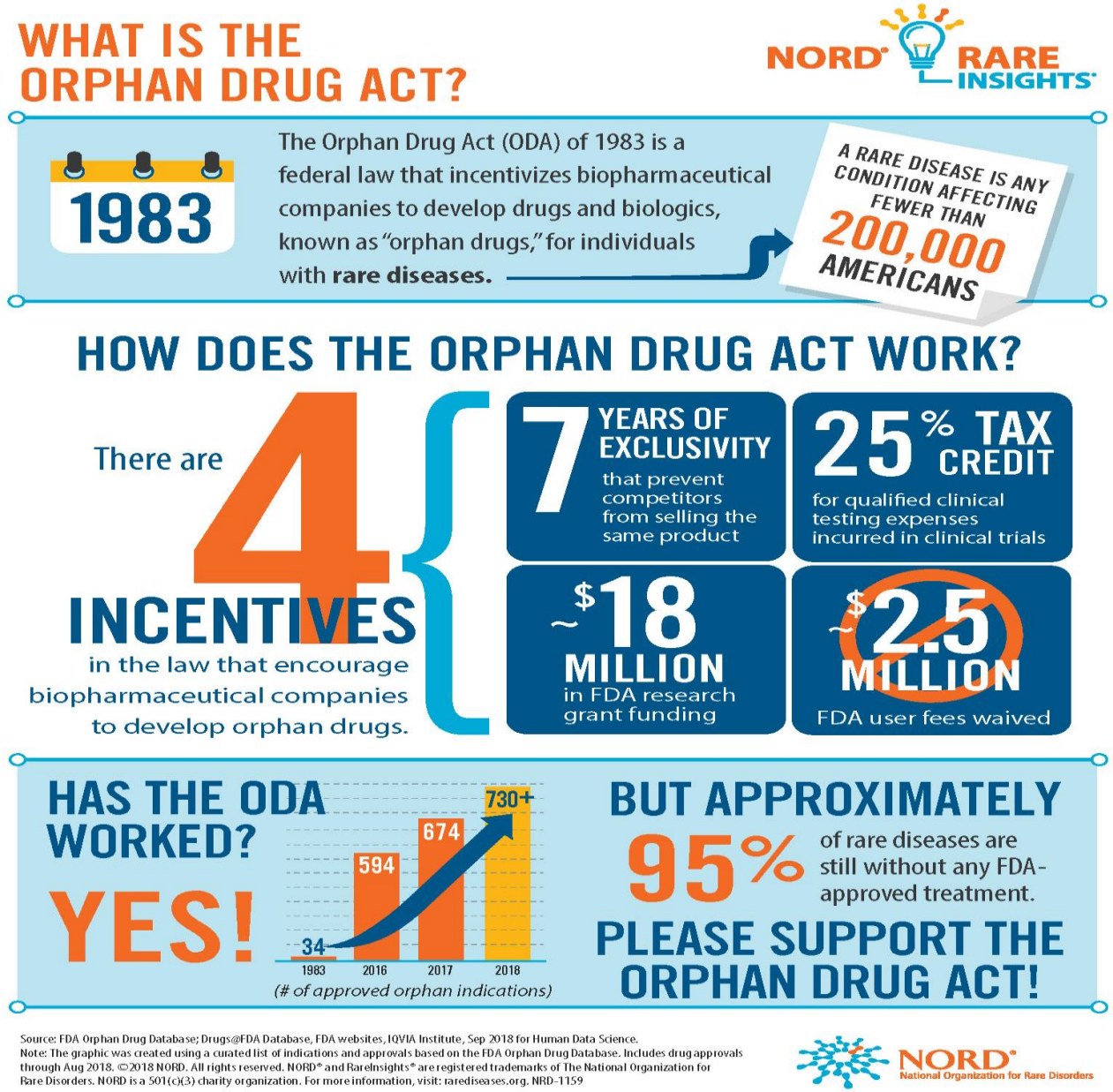
ORPHAN DRUG ACT (ODA)

Orphan Drug Act

- Orphan Drug Act (also known as ODA) was passed on January 4, 1983. Since the enactment of ODA, there has been a significant shift in orphan drug development
- ODA was passed to give an impetus to the pharmaceutical companies and lead to an increase in the manufacturing of drugs for treatment of orphan diseases

Incentives provided by ODA

- **A major incentive provided by ODA is that the pharmaceutical companies receive marketing exclusivity of 7 years**
- ODA also made available various grants which will be granted to academic based researchers or pharmaceutical companies annually and a tax credit of 50% will be incurred for expenditures when orphan drugs are assessed for their curative potential
- Since the passing of ODA, there has been a tremendous increase in marketing approvals of orphan drugs



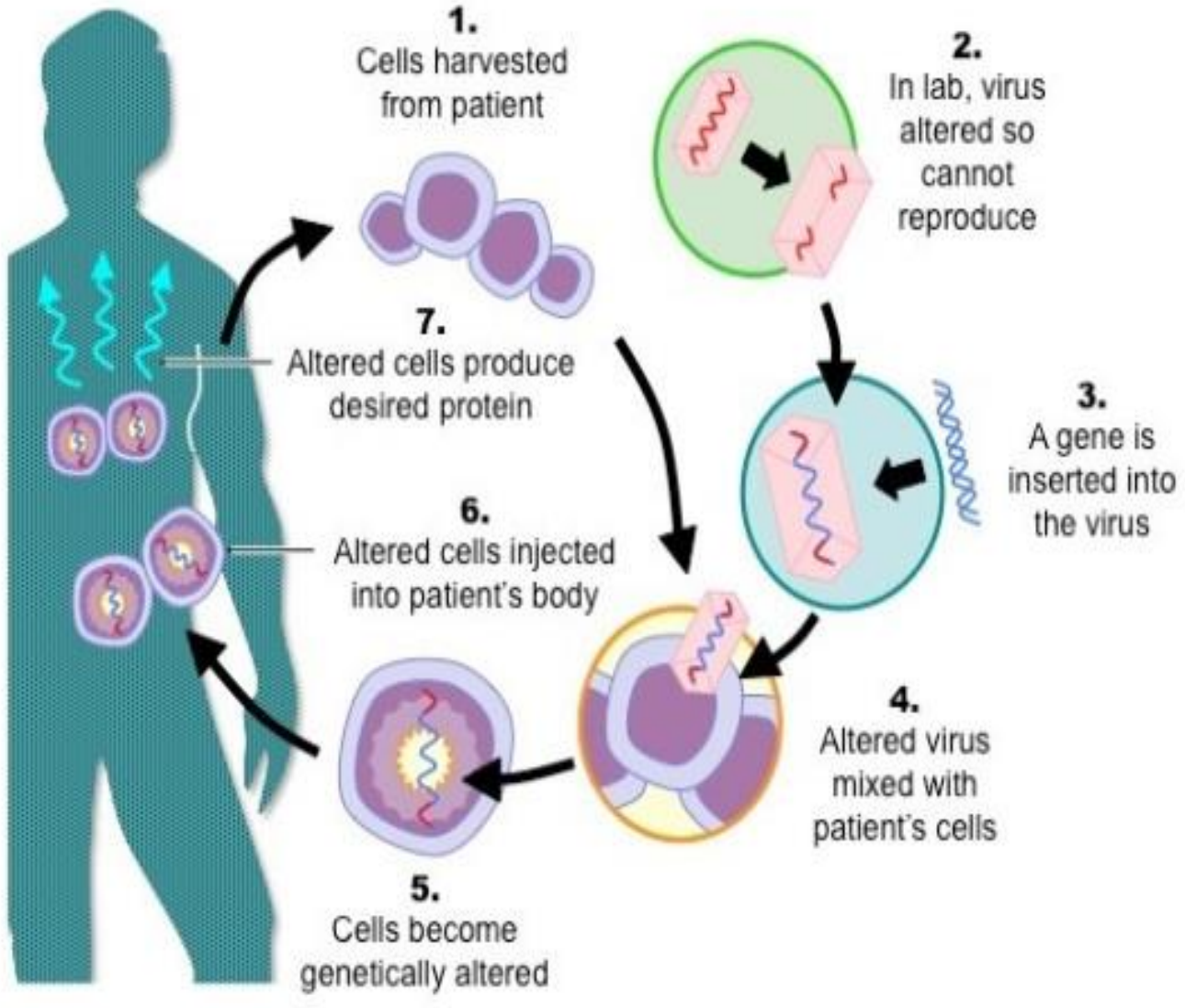
Sources : 1. Laura Joszt. 5 Things About the Orphan Drug Act. American Journal of Managed Care; 2019. 2. National Organization of Rare Diseases

GENE THERAPY

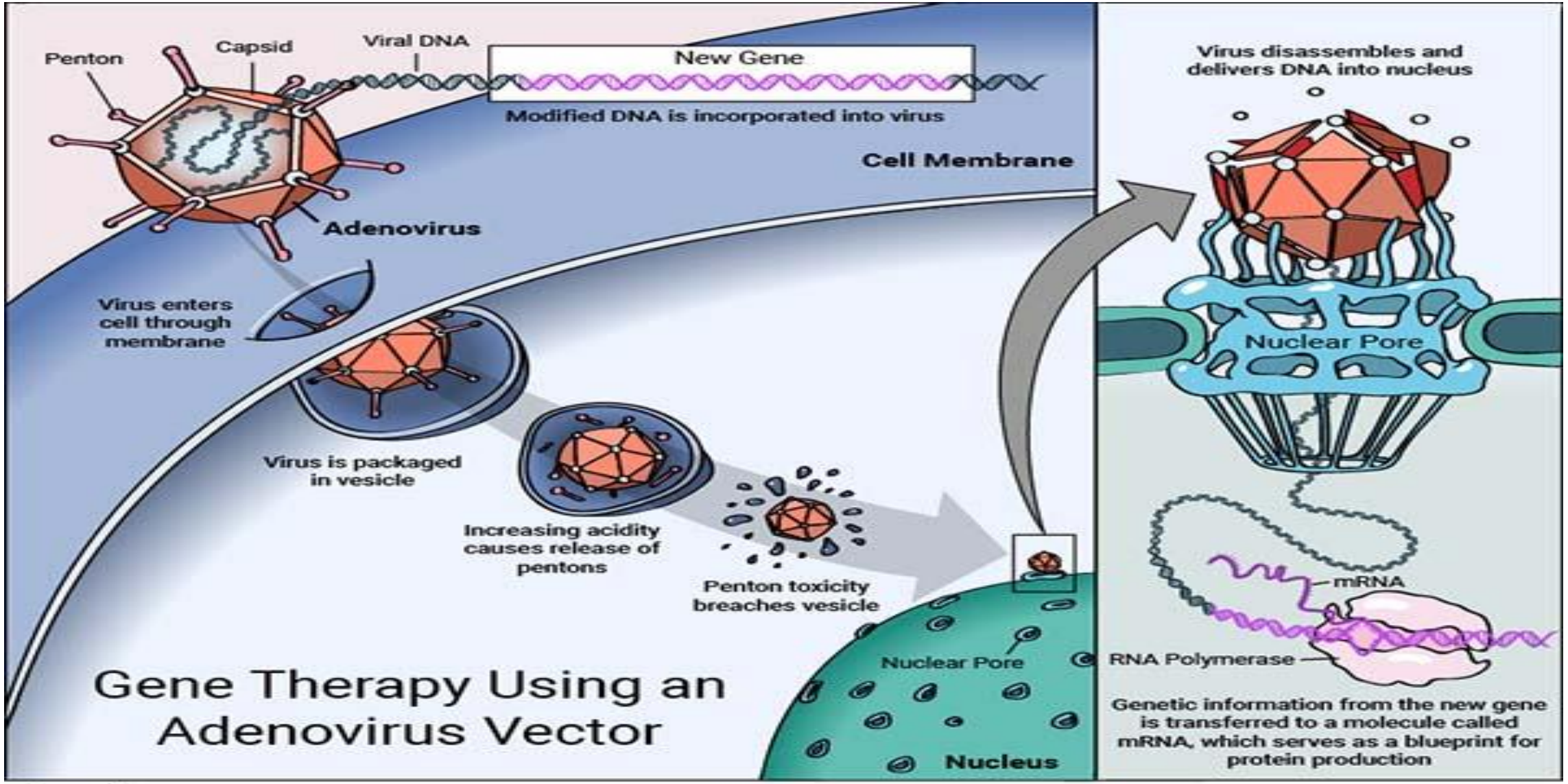
Gene therapy is a technique which **uses genes either to prevent a disease or to treat it**. Several approaches to the use of gene therapy are being established by scientists, including:

- **Replacing an altered or mutated gene** that leads to the development of a disease
- **Inactivating an altered gene,** which is a defective gene
- **Introducing a corrected or functional gene** into the human body to cure the disease

Gene therapy is used to introduce a corrected gene into the cells to either produce a beneficial protein or to replace defective genes

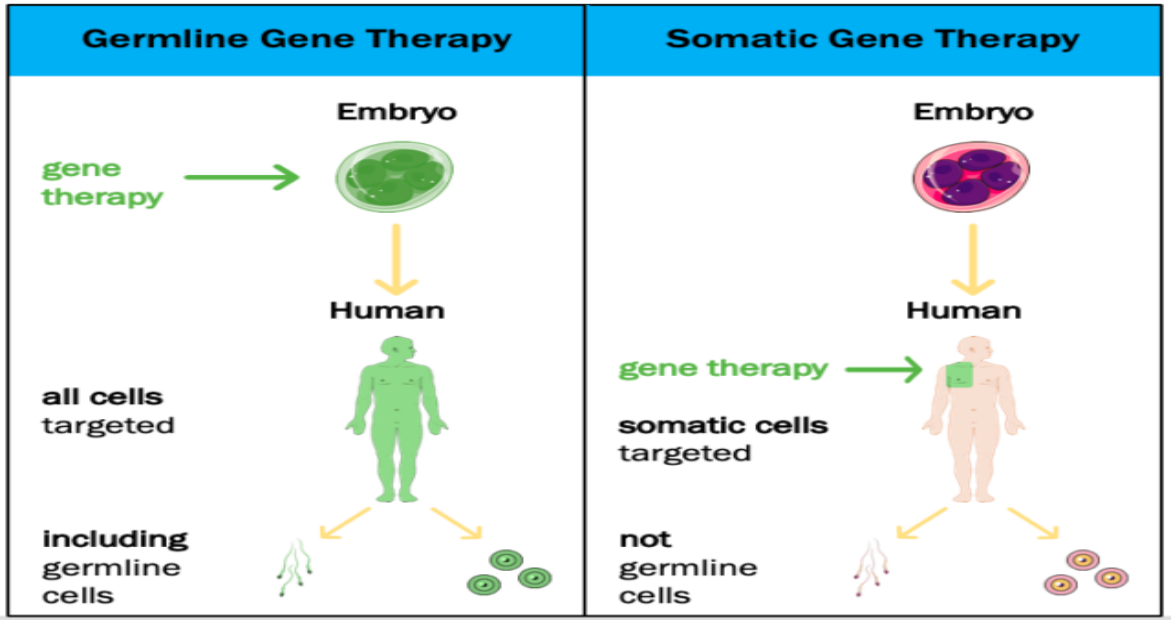


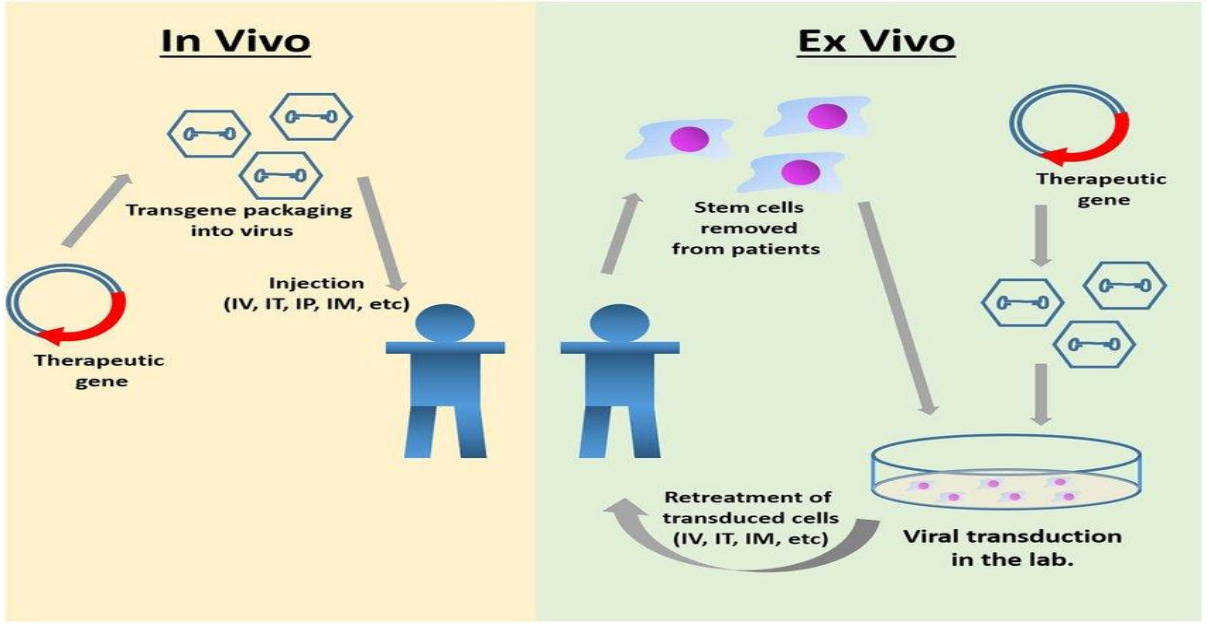
Sources : 1. Genetics Home Reference. What is gene therapy. U.S. National Library of Medicine. 2. Genetics Home Reference. How does gene therapy work. U.S. National Library of Medicine.



NIH U.S. National Library of Medicine

Source : NIH (US National Library of Medicine)





TYPES OF GENE THERAPY

Source : Types of gene therapy [Internet]. Gene Therapy Net.com.

PROJECT REPORT

AIM

To study the use of gene therapy in treatment of rare diseases

OBJECTIVES

1. To review the strengths and weaknesses of gene therapy in treatment of rare diseases
2. To determine present approved gene therapy treatments for treatment of rare diseases
3. To determine the scope of gene therapy in the treatment of rare diseases

LITERATURE REVIEW

- Gene therapy has shown significant potential in the treatment of rare diseases. Most gene therapy trials today are focused on gene replacement, gene correction or knockdown of gene products for monogenetic or single gene diseases via viral vectors that cure or slow down progression of disease
- Gene therapy for rare diseases demonstrates tremendous potential as is evident from the success of clinical trials in several diseases till date
- To use gene therapy for other disorders will depend on various factors. Diseases such as hemophilia in which the severe clinical manifestations can be improved by administering low levels of protein, are feasible options for gene therapy
- There is a need for efficient and effective models for development of gene therapy which should be scalable and sustainable so that all the patients affected by rare diseases can be treated
- Such models must quicken and augment processes and timelines, promote platform approaches, stimulate innovation in development of treatment, timely regulatory approvals and feasible trial design
- All these factors must be taken into consideration along with fostering greater collaboration among the different stakeholders who are required to successfully develop new treatments for rare diseases

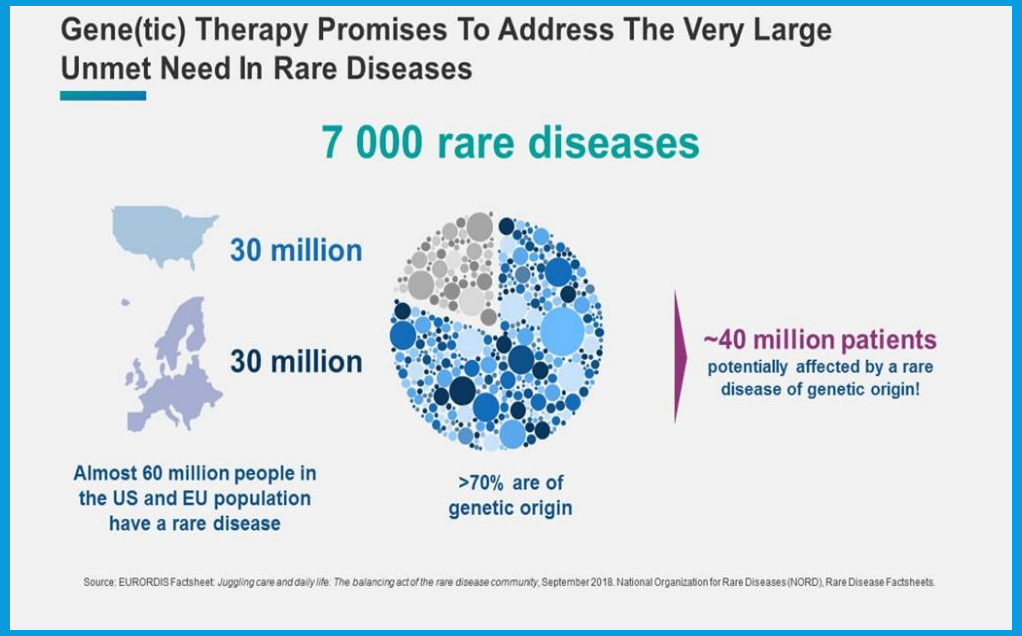
Sources : 1. M Ian Phillips and Andrew B Burns on 'The emergence of gene therapy for rare diseases' (Taylor & Francis Online; 2014) 2. Marina O'Reilly et al. titled 'Gene Therapy for Rare Diseases: Summary of a National Institutes of Health Workshop, September 13, 2012' (National Center for Biotechnology Information; 2013) 3. Petra Kaufmann, Anne R. Pariser and Christopher Austin on 'From scientific discovery to treatments for rare diseases – the view from the National Center for Advancing Translational Sciences – Office of Rare Diseases Research' (Orphanet Journal of Rare Diseases; 2018)

METHODOLOGY

- **Material and methods :** Articles and journals on the internet (13 articles and journals)
- **Study design :** Descriptive cross-sectional study
- **Duration of study :** April to May 2020
- **Data collection procedure :** Secondary research based on available literature on the internet

RESULTS

GENE THERAPY FOR RARE DISEASES



Patients affected by rare diseases have limited number of treatment options. In total there are about 7,000 known rare diseases. Out of which, less than 5% have an approved therapy by FDA

- Approximately 85% of the known rare diseases are caused due to an alteration or mutation in the gene. This makes them ideal disorders for treatment using gene therapy
- In order to approve gene therapies, an all-inclusive and robust understanding of designs of clinical trials and their execution, along with awareness of the regulatory scenario with regard to rare disorders is necessary
- Adeno-associated virus (AAV) is the most often used viral vector for administering gene therapies
- Most advancements in research of gene therapy are taking place with regard to hemophilia and ocular diseases
- Within a span of 3 years (2016-2019), the number of clinical trials concerned with gene therapy for ocular diseases rose more than 200 percent
- The development of a gene therapy for the treatment of biallelic RPE65 mutation associated retinal dystrophy is one of the most successful stories in rare ocular diseases

Source : Candice Tang. Gene Therapies in Rare Disease: From R&D to Regulatory Approval [Internet]. Xtalks; 2019.

True to their name, rare diseases are indeed very ‘rare’. Researchers must take into consideration the natural history of a disease for an improved understanding of the prognosis of a disease

Researchers can use this strategy and can determine the endpoints expected to be accomplished by the gene therapy which is being examined. As the burden of disease of rare diseases is low, authentication of these outcome measures is difficult.

Rare disease trials present a unique set of the following challenges:

- **There is limited knowledge of disease etiology of rare diseases**
- **There are few or non-validated biomarkers or clinical endpoints**
- **There are significantly fewer patients with a high degree of geographical dispersion**
- **There are a less number of experienced or well versed clinical investigators**

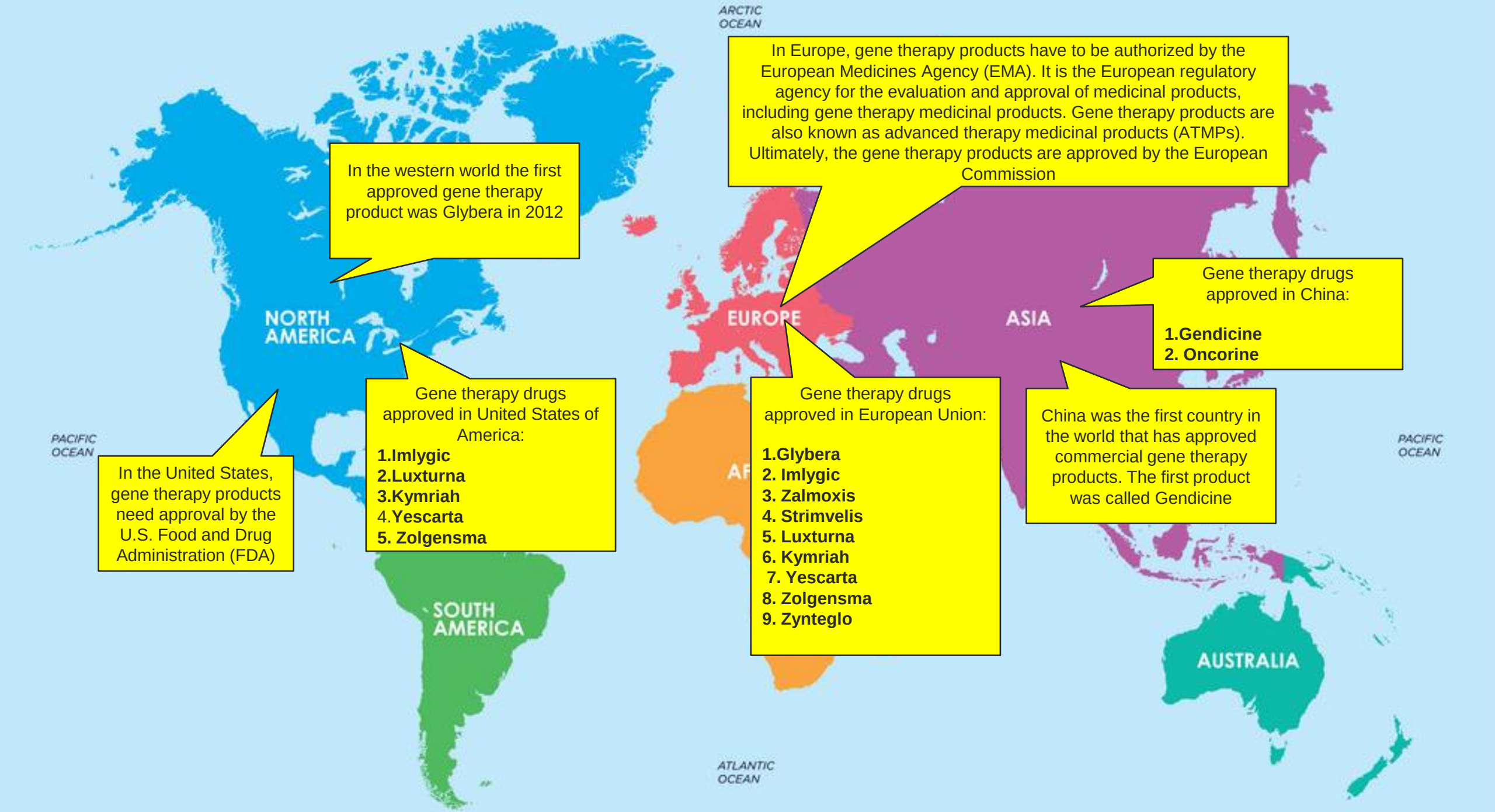
Source : Candice Tang. Gene Therapies in Rare Disease: From R&D to Regulatory Approval [Internet]. Xtalks; 2019.

SWOT ANALYSIS

STRENGTHS	WEAKNESSES
▪ Gene therapy offers the possibility of correction of genetic defect ▪ The scope and potential of gene therapy is humungous ▪ Gene therapy is a viable treatment option for rare diseases ▪ The gene therapy can possibly lead to permanent changes ▪ Several products in the pipeline ▪ Gene therapy can work in combination with cell therapy techniques	▪ Adverse events or immune reactions can be common ▪ Gene therapy methods can sometimes target the non-target cells ▪ The viral vector may become pathogenic and can cause disease ▪ Gene therapies could lead to the development of a tumor ▪ Uncertainty about the outcome of gene therapy ▪ New genes may be incompatible with the patients ▪ Possible development of resistance to gene therapy by patients ▪ Exorbitant cost of gene therapy ▪ The existence of ethical concerns about gene therapy ▪ Gene therapy is predominantly suited for monogenic mutation ▪ Gene therapy requires huge investment
OPPORTUNITIES	**THREATS**
▪ Extensive research on what causes rare diseases in humans ▪ Availability of affordable genetic and genomic analyses for research and diagnosis ▪ Evolution of new technologies such as gene disruption and modification, ex vivo and in vivo gene therapy	▪ Extremely high cost of development and production ▪ Very long development and research timelines ▪ Presence of a large number of diseases which affect few patients

Source : Keith Miller. 20 Advantages and Disadvantages of Gene Therapy[Internet].Future of working.com

MARKETED PRODUCTS



Source : Gene therapy products on the market [Internet]. Gene Therapy Net.com

LIST OF MARKETED PRODUCTS

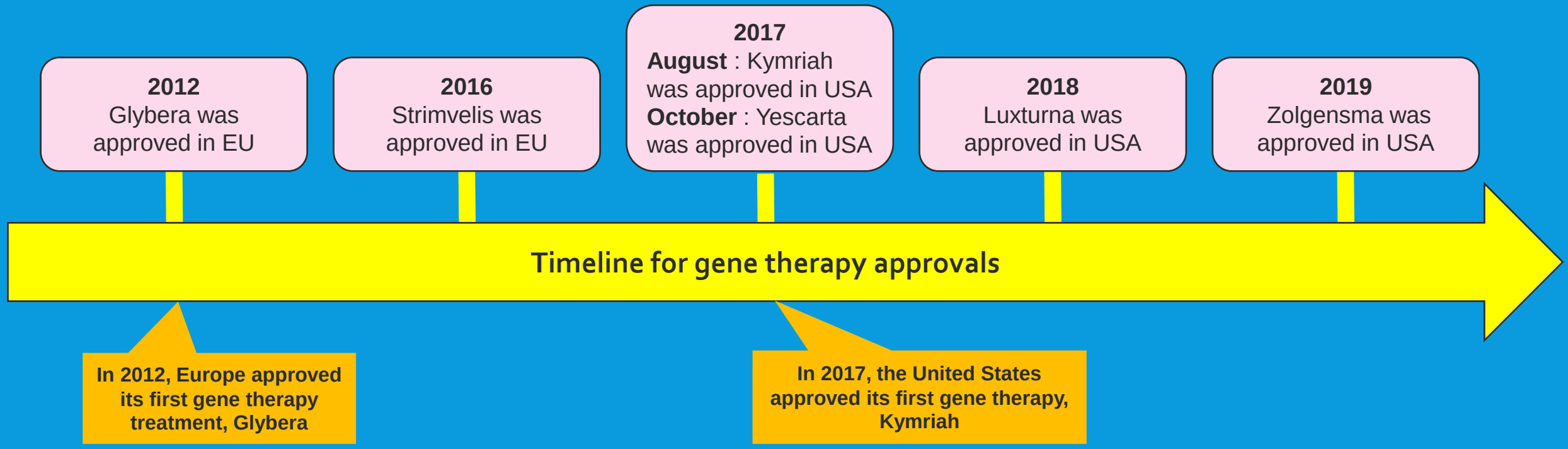
S.No.	Gene Therapy	Indication	Developer	Countries
1.	**Gendicine**	Head and neck squamous cell carcinoma	SiBionoGeneTech Co	China
2.	**Oncorine**	Late stage refractory nasopharyngeal cancer	Shanghai Sunway Biotech Co. Ltd	China
3.	**Glybera**	Lipoprotein lipase deficiency (LPLD)	Amsterdam Molecular Therapeutics (AMT) (acquired by UniQure)	EU
4.	**Imlygic**	Melanoma	BioVex /Amgen	USA, EU
5.	**Zalmoxis**	Add on treatment in adults who have received a Haematopoietic stem cell transplant (HSCT)	MolMed S.p.A	EU

S.No.	Gene Therapy	Indication	Developer	Countries
6.	**Strimvelis**	ADA-SCID (Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency)	GlaxoSmithKline (GSK)/ Orchard Therapeutics Ltd.	EU
7.	**Luxturna**	Inherited form of retinal dystrophy	Spark Therapeutics/Novartis	USA, EU
8.	**Kymriah**	B-cell acute lymphoblastic leukemia (ALL)	Novartis	USA, EU
9.	**Yescarta**	Large B-cell lymphoma	Kite Pharma (acquired by Gilead Sciences)	USA, EU
10.	**Zolgensma**	Spinal muscular atrophy	AveXis (a subsidiary of Novartis)	USA, EU
11.	**Zynteglo**	Beta thalassaemia	bluebird bio	EU

Source : Gene therapy products on the market [Internet]. Gene Therapy Net.com

DISCUSSION

TIMELINE FOR GENE THERAPY APPROVALS (USA AND EU)



Source : Kevin Curran. The gene therapy sector is experiencing an acceleration [Internet]. Rising tide bio.com;2020.

APPROVALS IN EUROPE AND USA (2000-2020)

- The European Union's first gene therapy drug or treatment option was approved in 2012. The EMA (European Medicines Agency) authorized a viral treatment, Glybera, to cure a type of pancreatitis
- **In 2015, Glybera's cost was $1 million dollars. Hence, with such an exorbitant price, Glybera was touted as the most expensive treatment of 2015**
- UniQure was the pharmaceutical company that manufactured Glybera and it has already halted the manufacturing of this drug after treating a very less number of patients. Till 2018, **Glybera was no longer included in the pipeline of UniQure's products**
- In 2016, the EMA approved another gene therapy called Strimvelis. Strimvelis was developed by GalaxoSmithKline (GSK), which is a stem cell gene therapy to treat ADA-SCID patients
- The gene therapy was at first priced at $665,000 (it was believed that a single treatment of Strimvelis could cure ADA-SCID). Till 2017, only 2 patients had been provided with a treatment of Strimvelis and GSK was aiming to put on sale this gene therapy
- Strimvelis was sold to Orchard Therapeutics from GSK in 2018. At the point of this agreement, approximately 5 patients had been provided treatment with Strimvelis (it was later priced at $730K)

Strimvelis

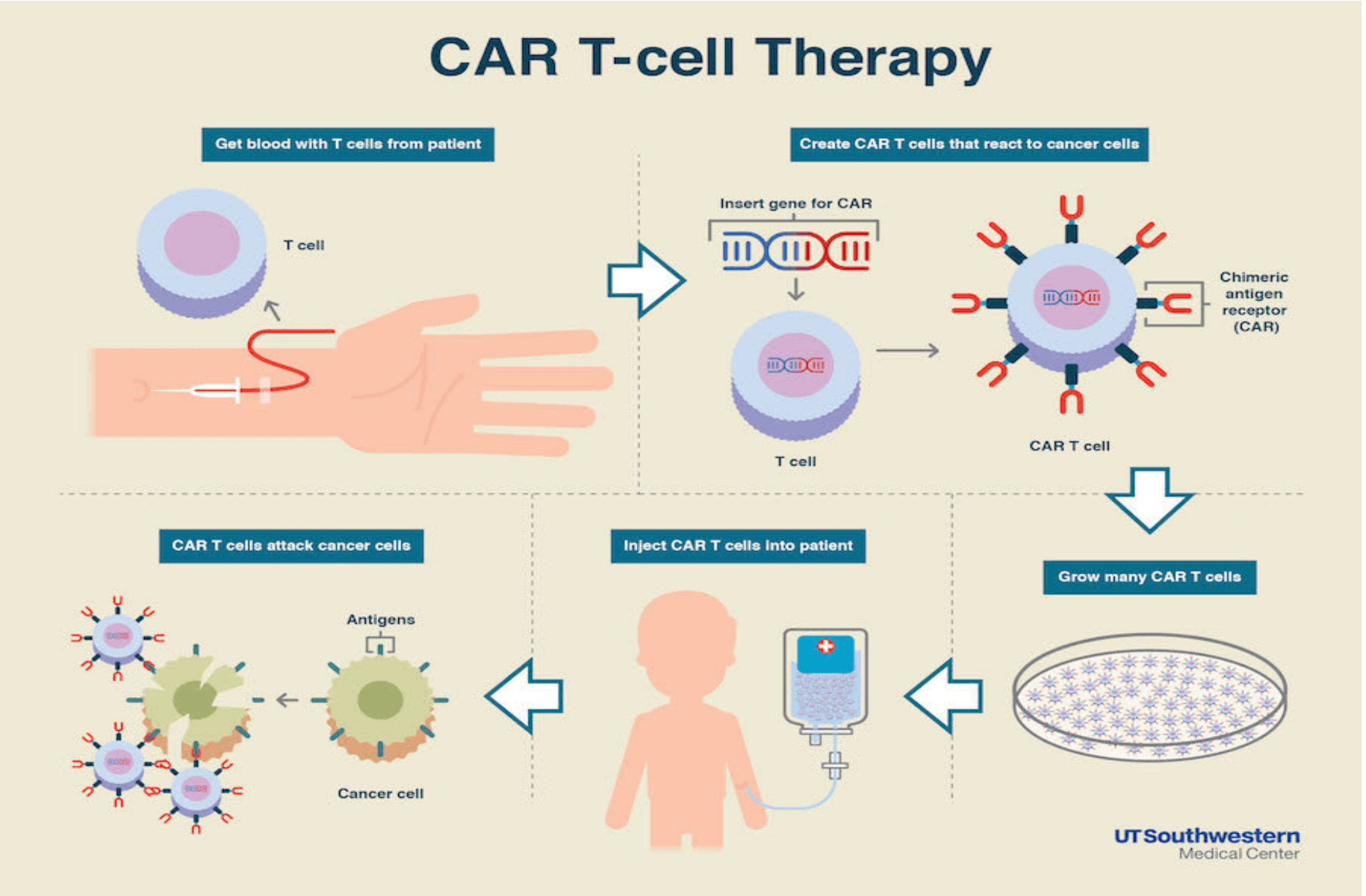
Source : Kevin Curran. The gene therapy sector is experiencing an acceleration [Internet]. Rising tide bio.com;2020.

APPROVALS IN EUROPE AND USA (2017)

- **The United States of America authorized its foremost gene therapy drug, a CAR-T, in 2017**
- **FDA authorized the use of the foremost gene therapy, a CAR-T therapy called Kymriah for the treatment of ALL (acute lymphoblastic leukemia) in August of 2017.** Kymriah was developed by Novartis
- **FDA authorized the use of Yescarta, which is another CAR-T therapy in October of 2017 for treatment of adults affected with diffuse large B-cell lymphoma.** Yescarta was manufactured by Kite Pharma and it was acquired by Gilead for US $11.9 billion in August 2017

YESCARTA®
(axicabtagene ciloleucel) Suspension for IV infusion

Source : Kevin Curran. The gene therapy sector is experiencing an acceleration [Internet]. Rising tide bio.com;2020.



Source : UTSouthwestern Medical Center

APPROVALS IN EUROPE AND USA (2018)

- **Luxturna was approved by FDA in 2018. Luxturna is developed by Spark Therapeutics.** Luxturna is used as a curative option for RPE65 mutation-associated retinal dystrophy
- **Since Luxturna is injected directly into the patient's body (also known as in vivo gene therapy), this gene therapy is touted as the first true (or actual) gene therapy**
- In, Kymriah and Yescarta , the affected cells are removed from the body before treatment. The new gene is delivered to the removed cells and the treated cells are transferred back to the body (ex vivo gene therapy)

Source : Kevin Curran. The gene therapy sector is experiencing an acceleration [Internet]. Rising tide bio.com;2020.

APPROVALS IN EUROPE AND USA (2019)

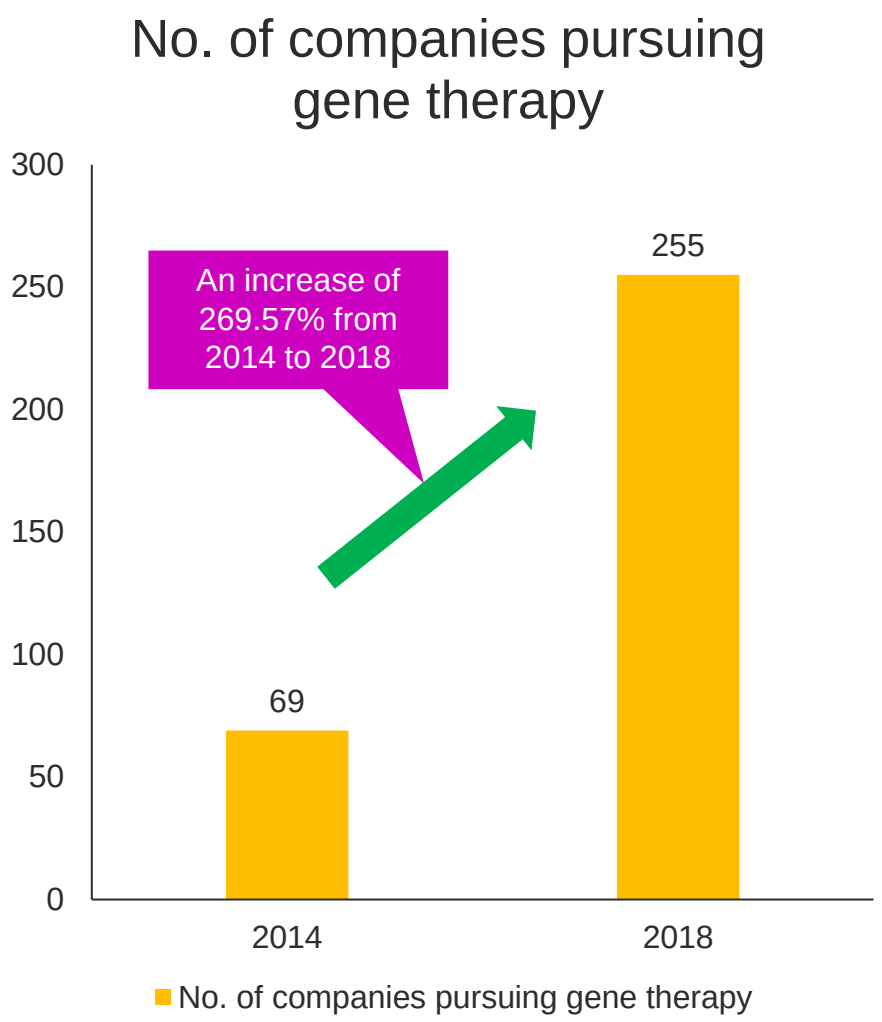
- **FDA approved Zolgensma in 2018. Zolgensma is being developed by Avexis**
- Novartis is the owner of Avexis. Zolgensma acts as an AAV9 viral vector
- This vector only target motor neurons. The SMN gene is injected by AAV9 virus into the nucleus of the motor neurons of the Spinal Muscular Atrophy patients
- Zolgensma has a unique mechanism of action as it is an IV injected AAV gene therapy and its therapeutic effect reaches neurons effectively

Source : Kevin Curran. The gene therapy sector is experiencing an acceleration [Internet]. Rising tide bio.com;2020.

THE FUTURE AND SCOPE OF GENE THERAPY

- It is expected that more number of gene therapies will reach the market in the subsequent years. **An approval for a gene therapy for hemophilia is being expected soon**
- **Many pipeline products are in Phase III or have demonstrated efficacy in Phase I/II trials**
- However, pharmaceutical companies are focused on addressing two major challenges at the present moment, **reducing cost of manufacturing** and **determining the quickest and most feasible path to approval** via clinical trials
- The FDA is keeping up with the rapidly changing scenario in the development of gene therapies
- The FDA is adjusting its policies and structure to meet the requirements of a clinical trial for gene therapy. For instance, 50 clinical trial reviewers were hired by the FDA to review the increasing number of gene therapy applicants (as of 2020)

Source : Kevin Curran. The gene therapy sector is experiencing an acceleration [Internet]. Rising tide bio.com;2020.



There has been a rapid increase in the number of pharmaceutical companies which are pursuing the development of gene therapies. The Alliance for Regenerative Medicine estimated that 69 companies were pursuing gene therapy in 2014. This number had risen to 255 in 2018

Source: Kevin Curran. The gene therapy sector is experiencing an acceleration [Internet]. Rising tide bio.com;2020.

ONGOING GENE THERAPY TRIALS

At present, gene therapy trials are ongoing for the following rare diseases:

- Human Immunodeficiency Virus
- Sickle cell anemia
- Choroideremia
- ADA-SCID

Many pipeline products are in Phase III or have demonstrated efficacy in Phase I/II trials

Source: Kevin Curran. The gene therapy sector is experiencing an acceleration [Internet]. Rising tide bio.com;2020.

CONCLUSION

- Due to the RMAT designation by FDA, clinical activity with regard to development of gene therapy, is expected to continue to increase
- A **Regenerative Medicine Advanced Therapy (RMAT)** term was added by the FDA to the 21st Century Cures Act on December 13, 2016
- **Incentives are provided by FDA for pharmaceutical companies to pursue gene therapies**
- **These incentives include recurrent and regular interactions with FDA and the possibility to deliberate intermediate endpoints or outcomes for clinical trials of gene therapies**
- Clinical efficacy of gene therapy has been determined for various rare diseases, using different vectors
- The advancement in technology is unparalleled in current times.Yet, there is a lack of treatment for **more than 90% of rare diseases**
- **Undoubtedly, gene therapy is a viable treatment option to cure rare diseases as these diseases are genetic in nature**
- Gene therapy is the future of treatment of rare diseases and a step to eliminating prevalence and incidence of rare diseases in the population

Source : Kevin Curran. The gene therapy sector is experiencing an acceleration [Internet]. Rising tide bio.com;2020.

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APPENDIX - Abbreviations

AAV	Adeno-associated virus
ADA-SCID	Adenosine deaminase-severe combined immunodeficiency
ALL	Acute lymphocytic leukemia
AMT	Amsterdam Molecular Therapeutics
ATMPs	Advanced therapy medicinal products
CAR-T	Chimeric T cell receptor
CDFA	China State Food & Drug Administration
DLBL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
FDA	Food and Drug Administration
FIX	Clotting factor IX
GSK	GlaxoSmithKline
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplant
IV	Intravenous therapy
LPL	Lipoprotein lipase
LPLD	Lipoprotein lipase deficiency
ODA	Orphan Drug Act
RPE65	Retinal pigment epithelium 65 gene
R&D	Research and Development
RMAT	Regenerative Medicine Advanced Therapy
SMN	Survival motor neuron