From Bench to Bedside: Current Trends, Advances, and Challenges in Gene Therapy: The Pharmacist's Role in Gene Therapy Management

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Disclosure

- Nothing to disclose

Learning Objectives

- At the end of this presentation, the participants should be able to:
- Describe
  - The basic concepts and mechanisms of gene therapy and how these therapies can be used to treat and prevent diseases.
- Discuss
  - The required infrastructure for proper handling and management of gene therapy products.
- Describe
  - The pharmacist's role in patient education, monitoring, and management of patients receiving gene therapy.

Prevalence of Genetic Disease

Abnormalities in individuals DNA	• Single gene – small mutations to larger chromosomal abnormalities
Monogenic Disorders	• Mutations in a single gene - Cystic Fibrosis, Sickle Cell Anemia, Huntington's disease; 1 in 100 births
Chromosomal Disorders	• Trisomy 21 (Down Syndrome) • 1 in 700 live births
Multifactorial Genetic disorders	• Common, multiple genes, environmental factors contributory e.g. Heart diseases, cancer, autism

Treatment Options for Genetic Disease

Medication

Lifestyle Modification

Surgery or Other Medical Interventions

Enzyme Replacement Therapy

What If We can?

REPLACE	***INACTIVATE***	***INTRODUCE A NEW OR MODIFIED***
a disease-causing gene with a healthy copy of the gene?	a disease-causing gene that is not functioning properly?	gene into the body to help treat a disease?

Yes we can!

FIRST SUCCESSFUL APPROVED GENE THERAPY SEPTEMBER 14, 1990 AT THE NIH

4 YEAR OLD ASHANTHI DESILVA

ADA-SCID (SEVERE COMBINED IMMUNODEFICIENCY)

RETROVIRAL VECTOR INFUSED GENE THERAPY

Types of Gene Therapy

Somatic Gene Therapy

Therapeutic genes transferred into somatic cells e.g. bone marrow, blood or skin cells

Not inheritable

All research directed to correct genetic defects in somatic cells

Germ Line Gene Therapy

Therapeutic gene is transferred to germ cells e.g. eggs or sperms

Inheritable

Ethical & safety issues

What is gene therapy & How does it work?

Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

Mechanisms:

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

Current studies on diseases treatment like; cancer, genetic diseases, and infectious diseases.

Types of Gene Therapy

Gene Addition/ Replacement

- A functional copy of a gene is inserted to replace a defective one, commonly delivered via viral vectors.
- Conditions: severe combined immunodeficiency (SCID) and Leber's congenital amaurosis (a form of inherited blindness).

Gene Editing

- Tools like CRISPR-Cas9 allow scientists to directly edit the DNA, correcting mutations.
- Conditions: Sickle Cell Anemia; Muscular dystrophy.

RNA-based Therapies

- Modifying/blocking the expression of a faulty gene using RNA technologies like siRNA and antisense oligonucleotides.
- Conditions: Spinal muscular atrophy (SMA) with the drug nusinersen.

Cell Therapy

Stem Cell Therapy: Stem cells develop into many different types of cells

Used replace damaged tissues or organs.

Conditions: e.g. Leukemia, hematopoietic stem cell transplants (HSCT) are used to restore healthy blood cell production.

CAR-T Cell Therapy:

Type of immunotherapy where T cells are modified to better recognize and attack cancer cells.

Conditions: certain types of blood cancers like B-cell acute lymphoblastic leukemia (ALL).

Regenerative Medicine:

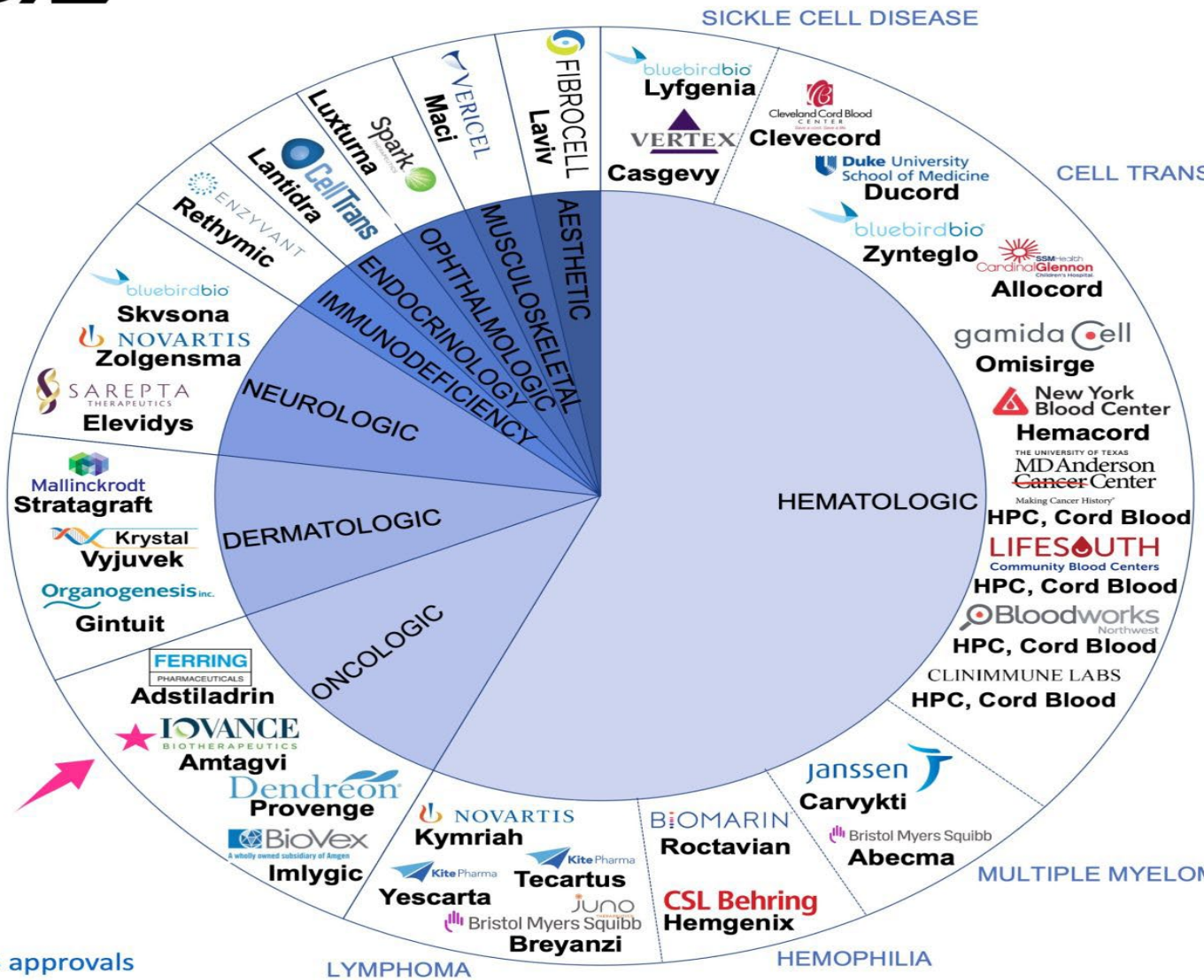
Disorders like Parkinson's or spinal cord injuries

Cell therapies aim to replace damaged neurons or other tissues, with the goal of restoring function or slowing disease progression.

Types of gene therapy products

- Plasmid DNA
- Viral vectors
- Bacterial vectors
- Human gene editing technology
- Patient-derived cellular gene therapy products

FDA APPROVED CELL AND GENE THERAPIES

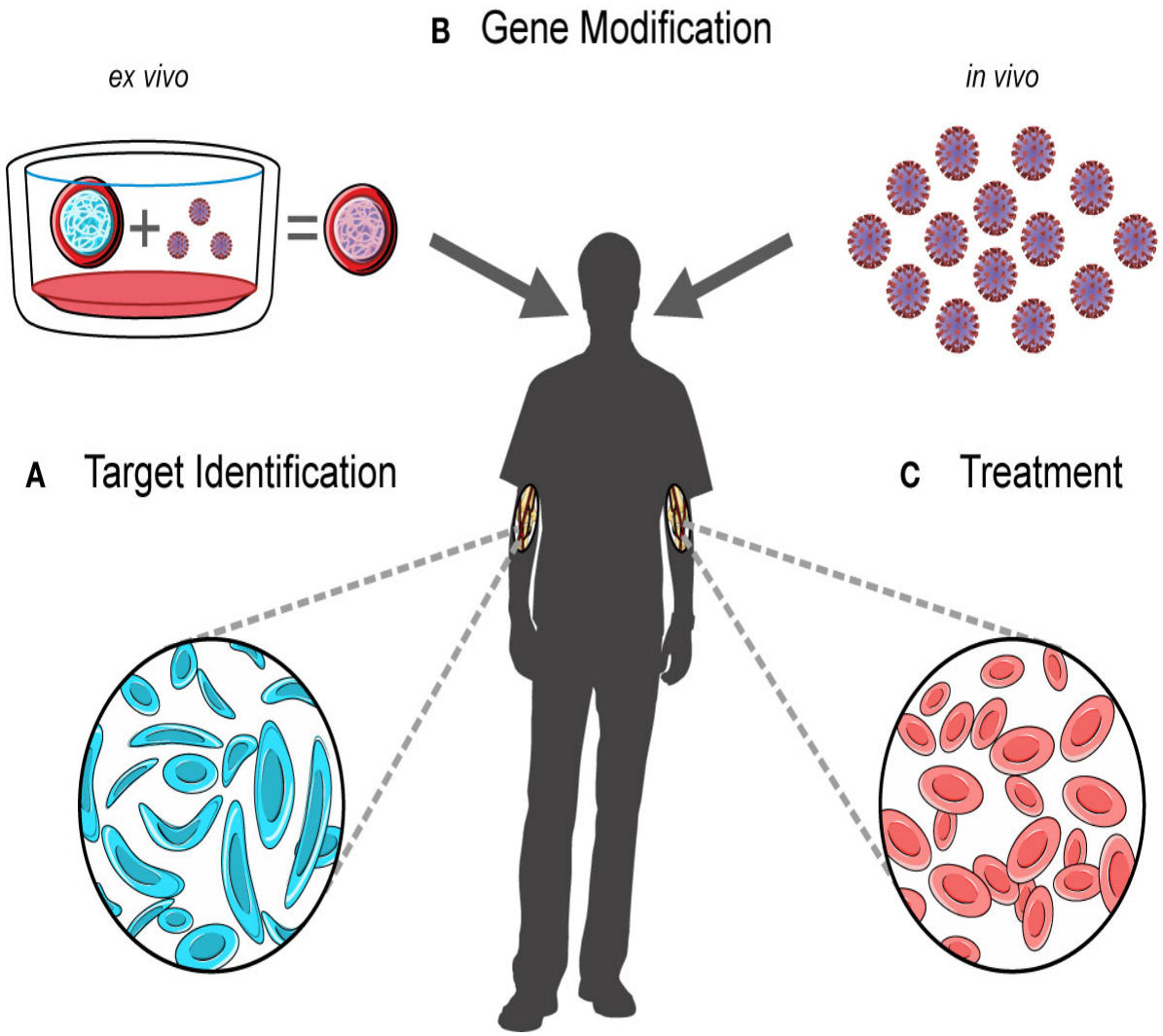


★ 2024 approvals

joanna-sadowska-phd @jmsadowska

Source: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

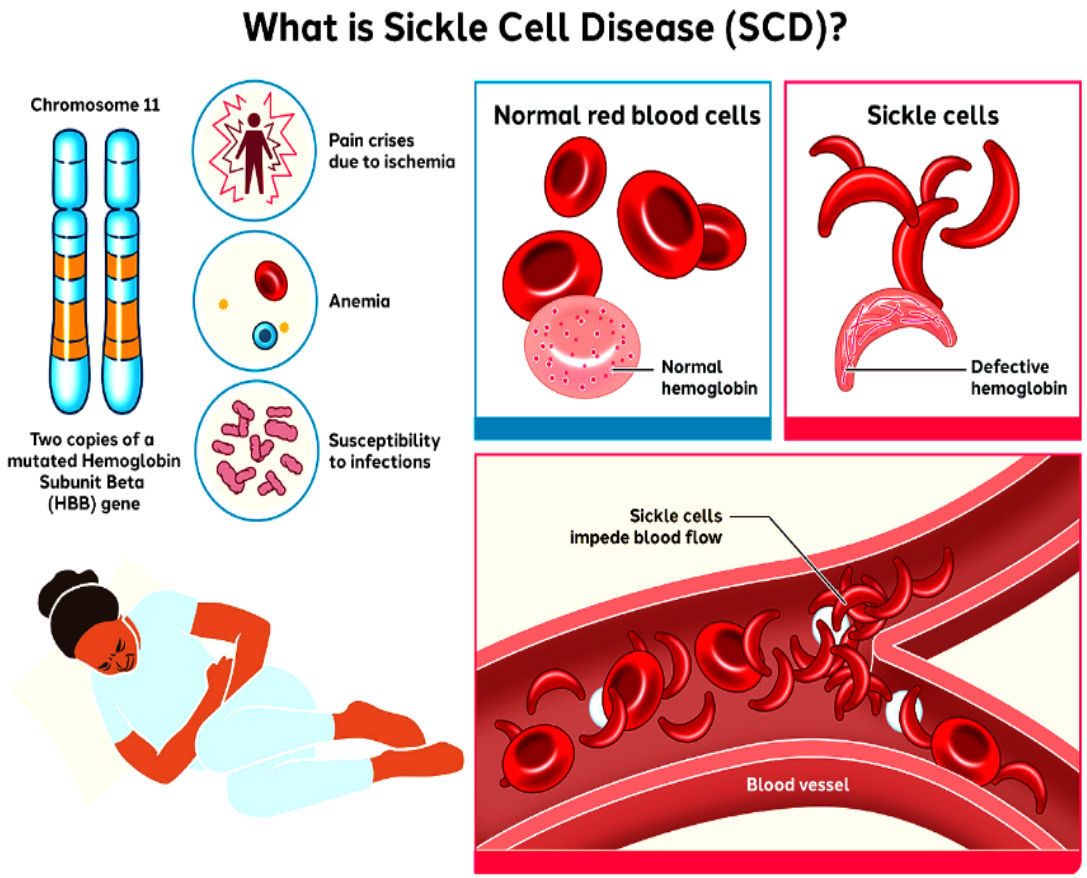
How does it work?



Case Presentation

- James is a 16-year-old African American male Diagnosed with sickle cell disease (SCD) at birth through newborn screening. James has experienced frequent vaso-occlusive crises, leading to seven hospitalizations in 2023 and three in 2024. He has also developed chronic anemia and has had one episode of acute chest syndrome. His organs function normally; one episode of viral infection in 2023. He is treated with Hydroxyurea, blood transfusions, and various pain management cocktails. He is a candidate for a bone marrow transplant but no donor has been found yet.

Sickle Cell Disease



Genetic disease

Atypical hemoglobin molecules called hemoglobin S

Distorts RBC into a sickle or crescent shape

Slows or blocks blood flow in smaller vessels

Prevelance

- 50 million Globally. 4-6 million Nigerians; 1 in 4 Nigerians (trait)
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- 300,000 infants/year (100-150k in Nigeria)
- Approximately 5% of the world's population carries the sickle cell trait (HbAS)
- Affects approximately 100,000 individuals in the USA. 1 in 365 AA
- Sub-Saharan Africa, India, the Middle East, and the Mediterranean region.

https://www.panafrican-med-journal.com/content/article/41/161/pdf

Current Treatments and Their Challenges

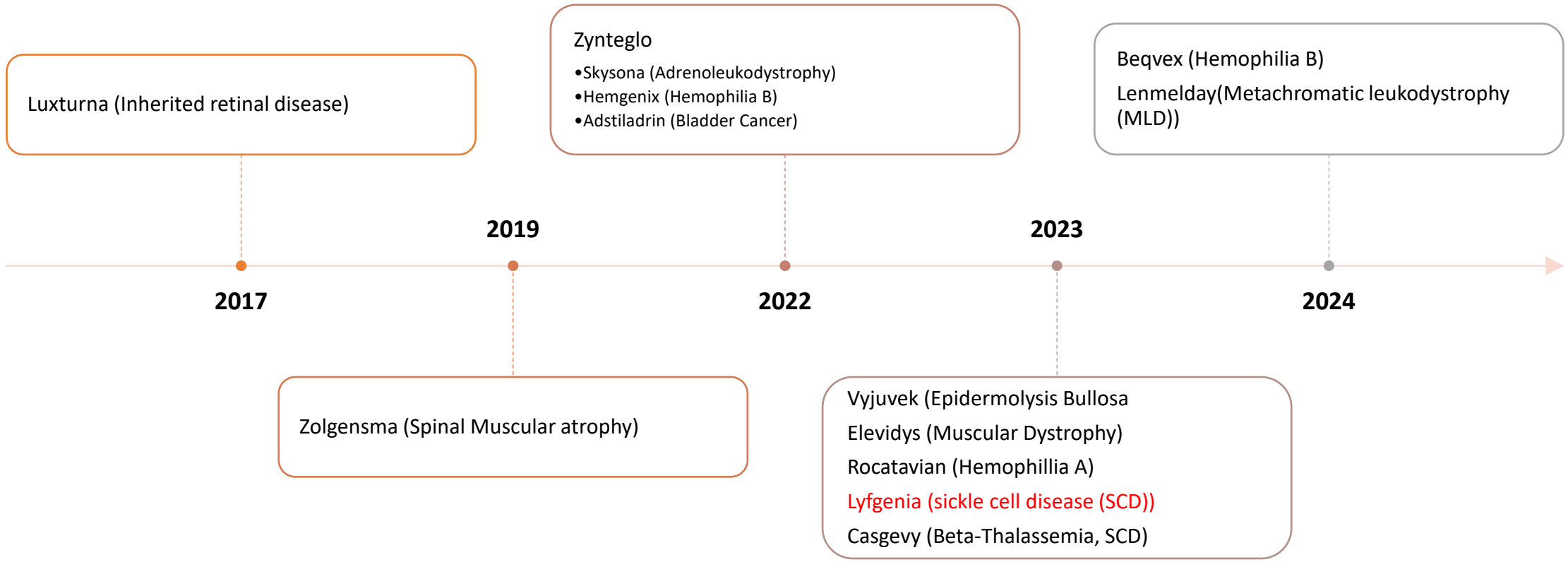
Standard Treatments:

- Hydroxyurea
- Blood Transfusions
- Pain Management.
- Bone Marrow Transplant

Challenges:

- Chronic disease
- Limited curative options.
- High treatment burden.
- Risk of complications (from iron overload, infection, and organ damage).

Gene Therapy Landscape



Gene Therapy for Sickle Cell Disease

Casgevy from CRISPR/Vertex (Gene editing first of its kind)

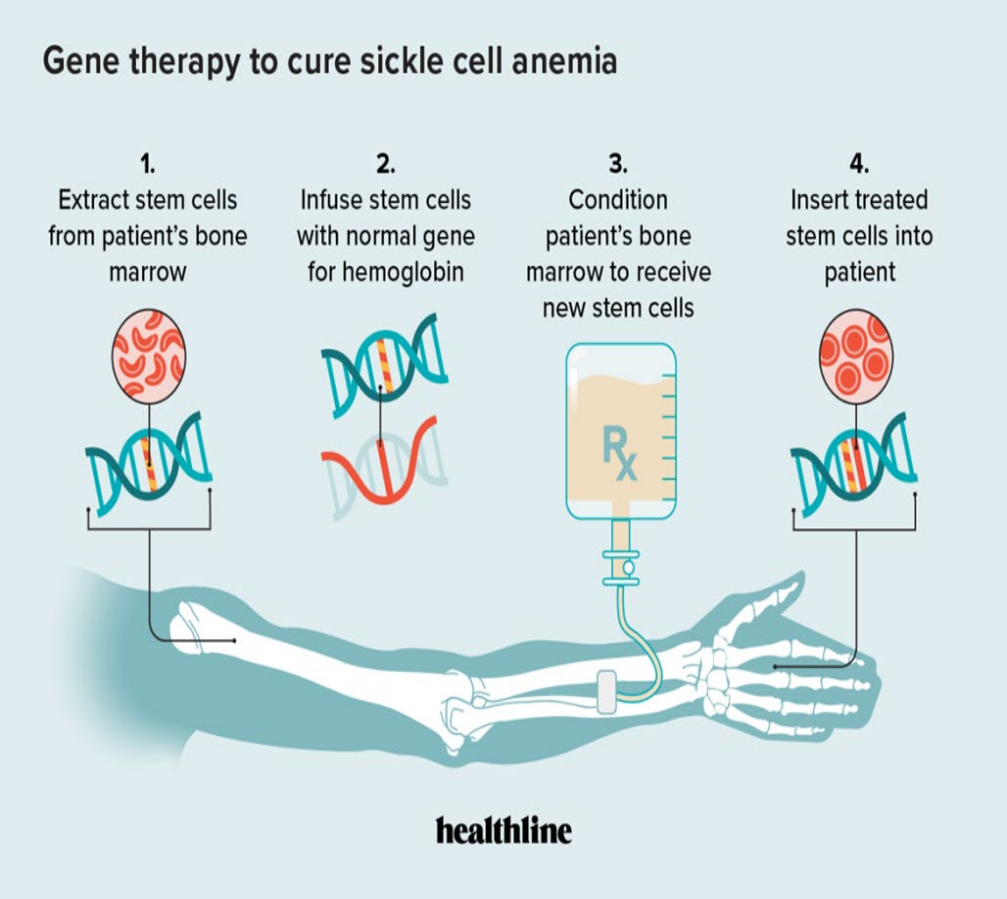
- CRISPR/Cas9 can be directed to cut DNA in targeted areas, enabling the ability to accurately edit (remove, add, or replace) DNA where it was cut.

Lovotibeglogene autotemcel (Lovo-cel) Lyfgenia

- Bluebird bio (gene addition)
- Lentiviral vector (gene delivery vehicle) for genetic modification
- Ex-vivo - Lyfgenia, the patient's blood stem cells are genetically modified to produce HbAT87Q, a gene-therapy derived hemoglobin that functions similarly to hemoglobin A
- RBCs containing HbAT87Q have a lower risk of sickling and occluding blood flow. These modified stem cells are then delivered to the patient.

Dec. 8, 2023, the Food and Drug Administration (FDA) approved two cell-based gene therapies for sickle cell disease (SCD),

Gene Therapy in Sickle Cell Disease



- Patients' own stem cells are collected
- Patient undergo high-dose chemotherapy removes cells from the bone marrow
- Replaced with the modified cells - Lyfgenia.
- SE: stomatitis; Decr. Platelets, WBC, Febrile neutropenia (consistent with Chemo/SCD)
- Hematologic malignancy has occurred in patients treated with Lyfgenia – Black box warning.
- Patients - long life monitoring for these malignancies & effectiveness

Patient Qualification Criteria

Age:	• Patients must typically be 12 years or older.
Disease Severity:	• History of severe SCD-related complications (e.g frequent vaso-occlusive crises (2 or more per year), acute chest syndrome, or stroke).
Treatment History:	• Failed or exhausted hydroxyurea • Chronic transfusions or • Unsuitable for above treatment.
Organ Function:	• Adequate organ function
Informed Consent:	• Patients and/or their guardians must provide informed consent.

Preparation for Gene Therapy

Pre-treatment Evaluation:

- Complete Medical Assessment
- Discontinuation of Concomitant
- Hematopoietic Stem Cell Collection

Production:

- Gene Editing:
  - Duration:10 to 15 weeks up to 22 weeks
- Quality Control

Production, Storage, and Transport

Storage:	Cryopreserved at ultra-low temperatures (-196°C)
Transportation:	Shipped in specialized containers at very low temperatures to ensure the cells remain viable.
Conditioning Regimen:	Chemotherapy (Myeloablative Conditioning) with busulfan
Administration	LYFGENIA is given by an IV infusion
	Post Infusions: patients stay at the treatment center for approximately 3-6 weeks for close monitoring

Assessing Efficacy

Reduction in Symptoms

Hemoglobin Levels

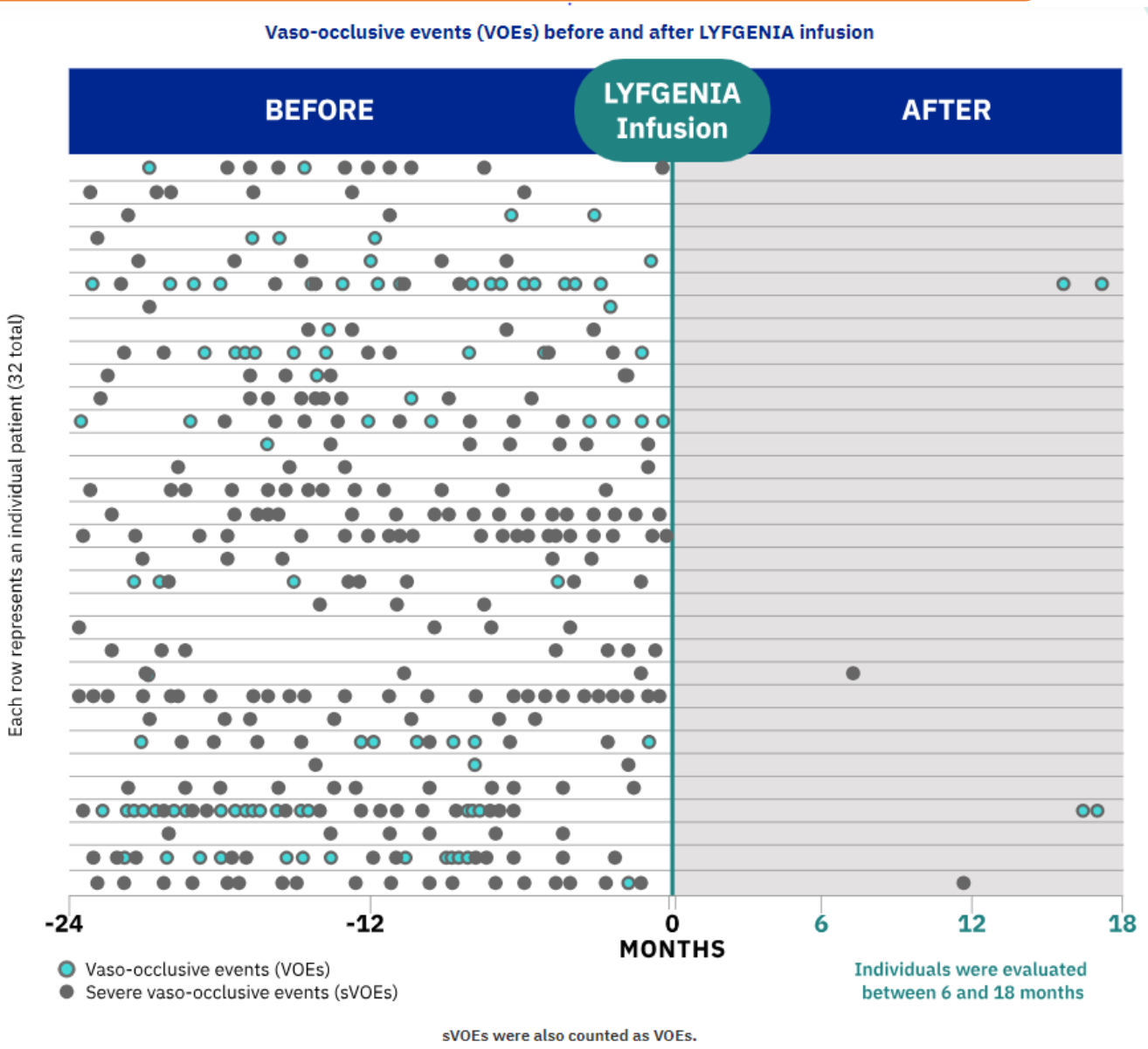
Long-term Outcomes

Efficacy of Lyfgenia

The efficacy of LYFGENIA was studied in 36 individuals. 32 individuals were evaluated for the number of vaso-occlusive events (VOEs) they experienced between 6-18 months after treatment.

88% of individuals did not experience any **vaso-occlusive events (VOEs)** (28/32 individuals)

94% of individuals did not experience any **severe vaso-occlusive events (sVOEs)** (30/32 individuals)



https://www.lyfgenia.com/clinical-trial-results

Potential Side Effects

Short-term

- Conditioning-related Toxicity: Includes nausea, vomiting, and an increased risk of infections due to bone marrow suppression.
- Infusion Reactions: Possible but generally mild, such as fever or chills.

Immune related side effects

- Cytokine Storm
  - Prevention and management
    - Pre-treatment with immunosuppressive drugs, such as corticosteroids,.
    - Vector Design
    - Close Monitoring of Patients during and after the therapy
    - Anti-inflammatory

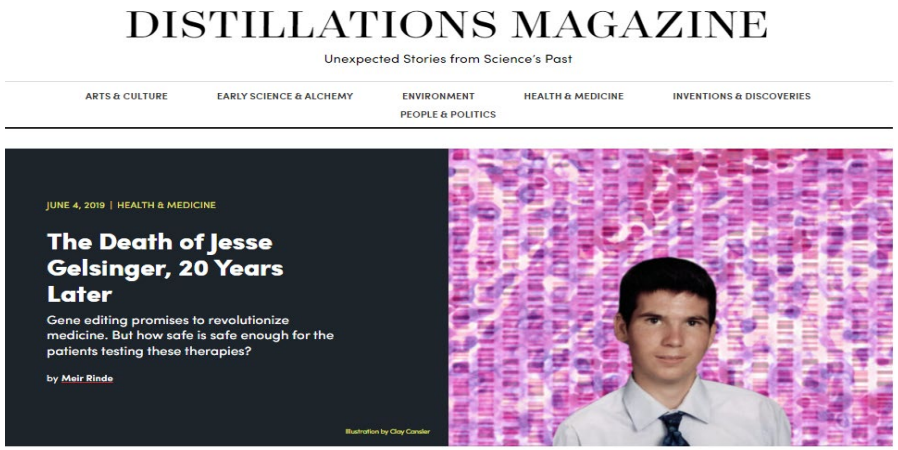
Toxicity from Vector Components

- Some components of viral vectors, such as proteins or DNA, can be toxic to cells.
- High doses of viral vectors may lead to organ toxicity, particularly in the liver

Long term Side Effects

- Adverse Reactions to Gene Therapy Components
- Inefficacy or Loss of Therapeutic Effect
- Insertional Mutagenesis (if the new gene is inserted into the patient's DNA)
- Off-Target Effects (in Gene Editing e.g. CRISPR/Cas9),
- Unintended Germline Modifications (If gene therapy inadvertently affects the germline cells (sperm or eggs))
- Graft Failure

Ethics, Informed Consent, Conflict of Interest



Case presentation

- Seventeen-year-old Jesse Gelsinger had a genetic disease called ornithine transcarbamylase (OTC) deficiency. OTC deficiency prevents the body from breaking down ammonia, a metabolic waste product. Gelsinger volunteered for a gene therapy experiment designed to test possible treatments; A vector carrying a normal OTC gene was injected into his liver. The vector being used to deliver the OTC gene was adenovirus, a modified version of the virus that causes the common cold.He had negative reaction to the injection, and four days later, on September 17, 1999, he died.

- Ethics, Informed Consent, Conflict of Interest
  - He was healthy but wanted to help
  - Previous reports of deadly reactions to the vector
  - Lead Scientist had financial interest in development in the development of adenovirus vector

https://www.sciencehistory.org/stories/magazine/the-death-of-jesse-gelsinger-20-years-later/

Impact on Pharmacy Practice

Logistics, Access, Coverage, Patient Care

Gene therapy: A glimpse at the future

- Rare and Complex Disease States
  - Muscular Dystrophy
  - CALD
  - Epidermolysis bullosa
  - Spinal muscular atrophy (SMA)
  - Hemophilia
  - Bet Thalassemia
  - Sickle Cell Disease
  - Metachromatic leukodystrophy
  - Non-muscle invasive bladder cancer
- New Targets – Coming soon
  - Angina Pectoris
  - Osteoarthritis
  - Diabetic foot Ulcer
  - Diabetic peripheral neuropathy
  - Peripheral artery disease

Considerations for Pharmacy & Pharmacists

Access	• Qualified Treatment Centers
Operations	• Cold Chain Storage • Biohazard and safety Precautions
Cost	• Extremely expensive – up to $4.5 million/treatment
Reimbursement	• Single-case agreements • Outcome-based agreements
Clinical Expertise	• Pre-treatment, intra-treatment; post treatment care

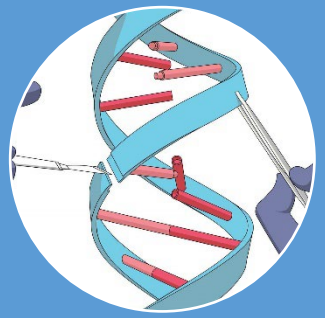
Considerations from the Payer's Perspective

Benefit Assessment	• Medical vs. Pharmacy
Contract Assessment	• Cost Reimbursements, Rates
Clinical Assessment	• Prior Authorization Use, Ancillary Services/site of care
Utilization Notification Process	• Gene therapy usage communication, established utilization review
Management and Monitoring	• Ongoing Treatment and Outcomes
Affordability/Risk Assessment	• Utilization likelihood, Financial Stability (eye on budget/allocation)

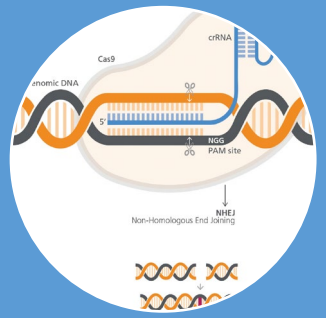
Challenges and Opportunities

Cost:	• These therapies can be extremely expensive (e.g., Zolgensma for SMA costs several million dollars), limiting accessibility.
Long-term Safety:	• Since gene editing and viral vectors modify a patient's DNA, there is concern about unintended effects, like off-target mutations or immune responses.
Delivery:	• Ensuring that the therapeutic genes or cells reach the correct tissue or organ is still a challenge in some diseases.
Supply Chain:	• Production, transportation, administration, education
Future:	• personalized and affordable, curative for many previously untreatable genetic conditions.

Conclusion



Potential permanent solution for genetic diseases



Several complexities – cost and accessibility to patients

Potential for almost every disease having a gene therapy

Revolutionizing the practice of medicine

More Gene and Cell Therapies

- ABECMA (idecabtagene vicleucel)
  Celgene Corporation, a Bristol -Myers Squibb Company
- ADSTILADRIN (nadofaragene firadenovec-vcng)
  Ferring Pharmaceuticals A/S
- ALLOCORD (HPC, Cord Blood)
  SSM Cardinal Glennon Children's Medical Center
- AMTAGVI (lifileucel)
  Iovance Biotherapeutics, Inc.
- BEQVEZ (fidanacogene elaparvovec-dzkt)
  Pfizer, Inc.
- BREYANZI (lisocabtagene maraleucel)
  Juno Therapeutics, Inc., a Bristol -Myers Squibb Company
- CARVYKTI (ciltacabtagene autoleucel)
  Janssen Biotech, Inc.
- CASGEVY (exagamglogene autotemcel [exa-cel])
  Vertex Pharmaceuticals Incorporated
- CLEVECORD (HPC Cord Blood)
  Cleveland Cord Blood Center
- Ducord, HPC Cord Blood
  Duke University School of Medicine
- ELEVIDYS (delandistrogene moxeparvovec-rokl)
  Sarapeta Therapeutics, Inc.
- GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen)
  Organogenesis Incorporated
- HEMACORD (HPC, cord blood)
  New York Blood Center
- HEMGENIX (etranacogene dezaparvovec-drlb)
  CSL Behring LLC
- HPC, Cord Blood
  Clinimmune Labs, University of Colorado Cord Blood Bank
- HPC, Cord Blood - MD Anderson Cord Blood Bank
  MD Anderson Cord Blood Bank
- HPC, Cord Blood - LifeSouth
  LifeSouth Community Blood Centers, Inc.
- HPC, Cord Blood - Bloodworks
  Bloodworks
- IMLYGIC (talimogene laherparepvec)
  BioVex, Inc., a subsidiary of Amgen Inc.
- KYMRIAH (tisagenlecleucel)
  Novartis Pharmaceuticals Corporation
- LANTIDRA (donislecel)
  CellTrans Inc.
- LAVIV (Azficel-T)
  Fibrocell Technologies
- LENMELDY (atidarsagene autotemcel)
  Orchard Therapeutics (Europe) Limited
- LUXTURNA (voretigene neparvovec-rzyl)
  Spark Therapeutics, Inc.
- LYFGENIA (lovotibeglogene autotemcel [lovo-cel])
  bluebird bio, Inc.
- MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane)
  Vericel Corp.
- OMISIRGE (omidubicel-onlv)
  Gamida Cell Ltd.
- PROVENGE (sipuleucel-T)
  Dendreon Corp.
- RETHYMIC (allogeneic processed thymus tissue – agdc)
  Enzyvant Therapeutics GmbH
- ROCTAVIAN (valoctocogene roxaparvovec-rvox)
  BioMarin Pharmaceutical Inc
- SKYSONA (elivaldogene autotemcel)
  bluebird bio, Inc.
- STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat)
  Stratatech Corporation
- TECARTUS (brexucabtagene autoleucel)
  Kite Pharma, Inc.
- TECELRA (afamitresgene autoleucel)
  Adaptimmune LLC
- VYJUVEK (beremagene geperpavec)
  Krystal Biotech, Inc.
- YESCARTA (axicabtagene ciloleucel)
  Kite Pharma, Incorporated
- ZYNTEGLO (betibeglogene autotemcel)
  bluebird bio, Inc.
- ZOLGENSMA (onasemnogene abeparvovec-xioi)
  Novartis Gene Therapies, Inc.

Dalu Nuooo!!

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