Cell and Gene Therapy, the Future of Precision Medicine

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- Pharm.D. from University of Washington in 2000
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- Certified pharmacogenomics specialist in 2024
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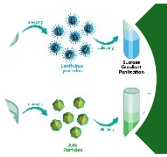
Agenda

Basics of Cell and Gene Therapy, and their Classifications



Current Cell and Gene Therapy Landscape

Review of FDA-Approved CGTs

Feasibility of CGT in the US Integrated Health System

Global CGT Research Pipeline Summary

Revolutions in Medicine

Exhibit 1: Progression of pharmaceutical technologies

	Small molecules Population treatment values volume and minimizes risk	**Biologics** High science brings targeted innovation and hope	**RNA therapeutics** Novel biologics with large population potential	**Cell & gene therapy** Paradigm disruption with high impact and low scale
Patient population	Mass market	Specialty	Specialty, Rare	Rare/ oncology
Cost	$1,000s or less / year	$10,000s/ year	$100,000s/ year	$100k -$1m+ per treatment
Clinical setting	Pharmacy	Clinic/ Specialty pharmacy	Specialist	Certified treatment center
Treatment journey	Primary care	Specialist	Specialist	Complex, multiple providers

Source: IQVIA Institute, Dec 2023.
Notes: Overall attributes are directional only and may vary by specific types of medicines within each category.

Unmet Needs in Inheritable Diseases and Cancer

Rare diseases burden in US: 997 billion annual costs, affecting 15.5 million patients

Poor Prognosis in many conditions. Many inherited disorders, cancers and other rare diseases would end in severe disability or premature death if left untreated

Earlier intervention vs delayed treatment. Gene therapy could help only if the patients received earlier in the course of disease, it has the potential to stop any damage before it occurs. Once the tissues and organs are damaged by the mutations, it will be difficult to reverse them

Targets the cause. Gene and cell therapies make it possible to design treatments that can target any of the thousands of genes in the body which causes cancer and other inheritable diseases

Cell and Gene Therapy Definitions

American Society of Gene and Cell Therapy:

- **Gene Therapy**: To repair, replace, activate, deactivate the dysfunction genetic material to treat or prevent disease
  - In vivo gene therapy (via transfer or editing of genetic material, thus redoes can be challenging)
  - Ex vivo gene-modified cell therapies
- **Cell Therapy**: To transfer of cellular materials into a patient to treat or prevent an illness
  - Autologous
  - Allogenic

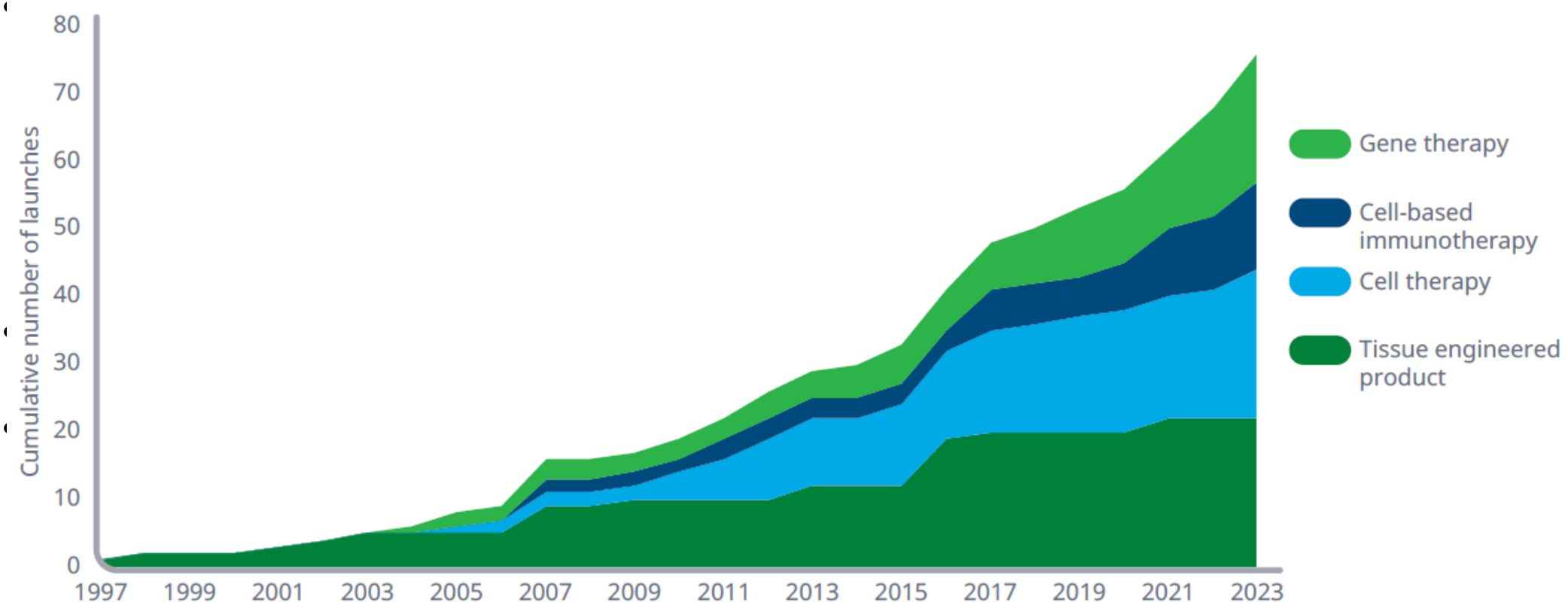
Risks and Challenges of CGTs

- **Challenges:**
  - Single Gene based treatment
  - Rare diseases focus = limited participants
  - High precision requirement
  - limited size of the delivery system.
  - R&D time requirement
  - Funding

- **Risks:**
  - Unintended gene modifications
  - Off-target editing
  - over-expression
  - Limited long term outcome data
  - Treatment related toxicities & immune response

Global Cell, Gene and RNA Therapy Availability

Exhibit 15: Global cumulative cell and gene therapy launches by type



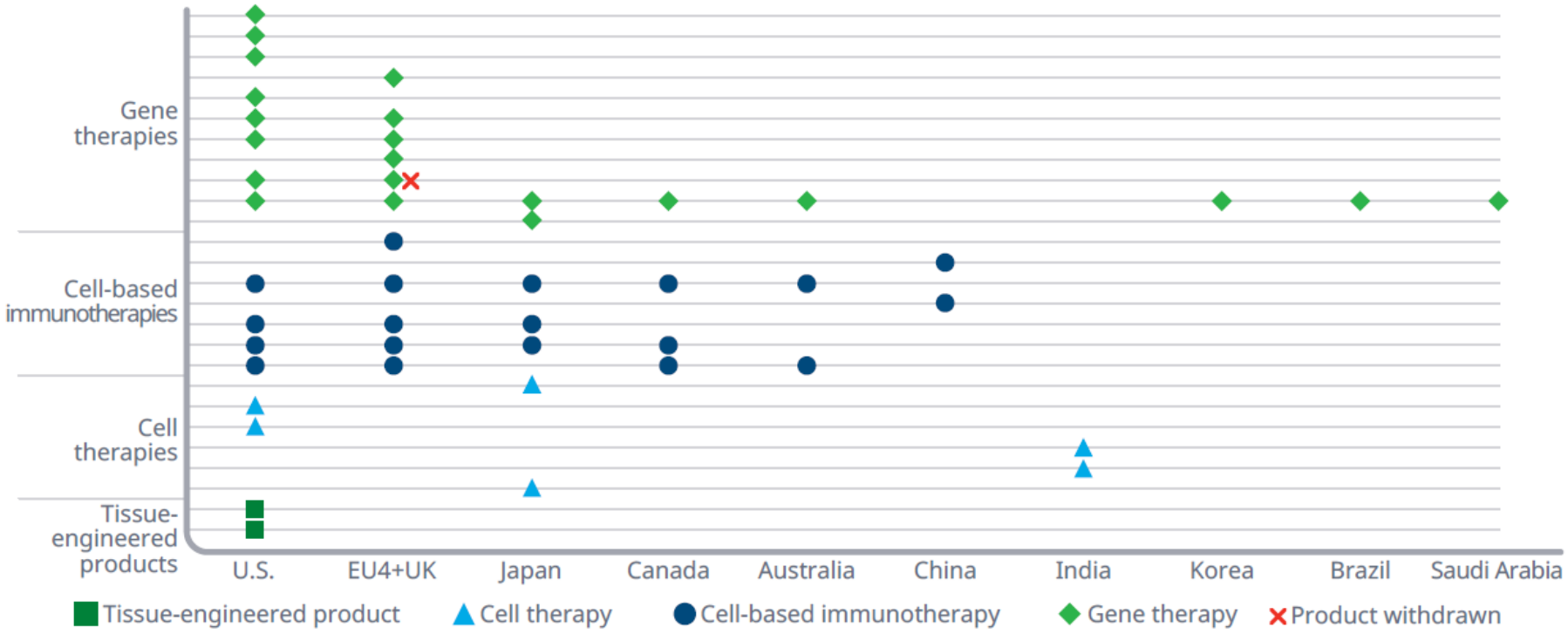
Source: Alliance for Regenerative Medicine, Sep 2023; IQVIA Institute, Oct 2023.

Notes: Includes products with regulatory approval and launch determined based on desk research. Evidence of launch includes sales data, company statements, or availability of patient support websites. When launch evidence is not available, products are assumed launched at approval unless otherwise stated publicly. Year of launch determined by earliest global launch. Includes products which launched and were subsequently withdrawn from the market.

Global CGT Recent Launch Comparison

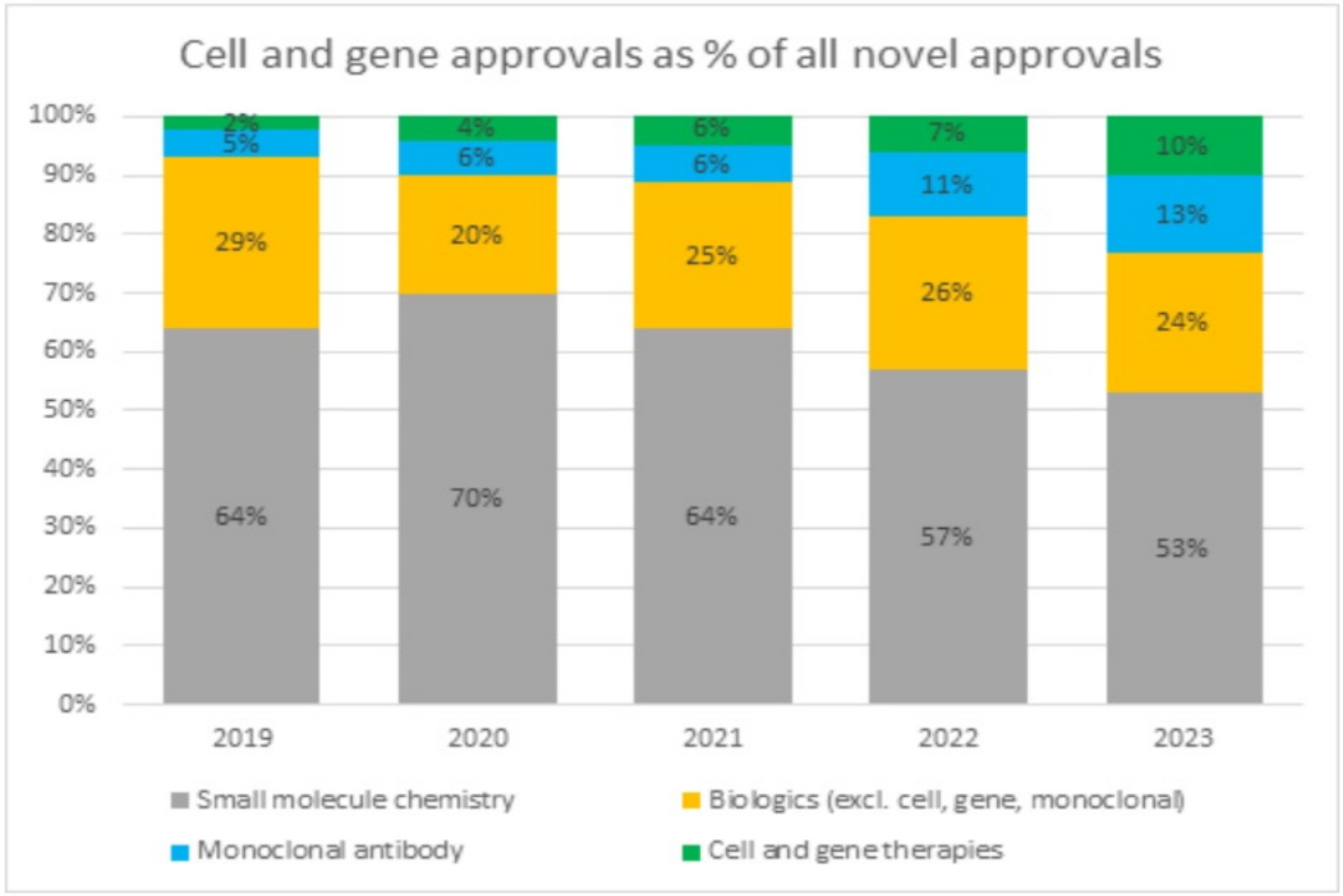
- US and EU lead CGT availability

Exhibit 16: Availability across select markets of cell and gene therapies launched globally 2019–2023



Source: Alliance for Regenerative Medicine, Dec 2023; IQVIA Institute, Jan 2024.
Notes: Each line represents a single therapy and symbols represent availability in that geography. Products available by country reliant on company announcements and publicly available information as of December 31, 2023. Products sorted within type by launch year (earliest on bottom).

CGT Approval Increased in the Past Five Years



Source: Evaluate; RSM US LLP

US FDA Approved CGT by Therapeutic Class

1. **Ten** Oncology agents (6 CAR-T)
2. **Nine** Human Cord Blood and blood products
3. **Seven** Hematology agents
    A. 2 SCD agents
    B. 3 Hemophilia B agents (Epidemiology: 38,000 people worldwide)
    C. 1 hemophilia A agent (Epidemiology: 400000 males worldwide)
    D. 1 ß-thalassemia
4. **Seven** rare disease agents
5. **Two** Topical
6. **One** ophthalmic product
7. **One** cosmetic product
8. **One** diabetes cell therapy (transplant)

CGTs for Cancers

Name	Year Approved	Type	Description
sipuleucel-T	**2010**	**Cell (autologous, activated/expanded)**	**Antigen presenting cells are activated and used to treat certain types of prostate cancer.**
Talimogene laherparepvec	2015	HSV-1	Recombinant HSV-1 delivers GM-CSF to treat patients with certain unresectable melanoma lesions.
tisagenlecleucel	2017	Cell (autologous, modified)	**CAR T** cells engineered to treat patients with certain kinds of relapsed or refractory follicular lymphoma.
axicabtagene ciloleucel	2017	Cell (autologous, modified)	**CAR T** cells engineered to treat patients with certain kinds of relapsed or refractory large B-cell lymphoma.
brexucabtagene autoleucel	2020	Cell (autologous, modified)	**CAR T** cells engineered to treats patients with certain kinds of relapsed or refractory mantle cell lymphoma.
idecabtagene vicleucel	2021	Cell (autologous, modified)	**CAR T** cells recognize the B-cell maturation antigen (BCMA) and kill BCMA-expressing tumor cells.
Lisocabtagene maraleucel	2021	Cell (autologous, modified)	**CAR T** cells engineered with lentivirus to attack CD19-expressing tumor cells. Treats patients with certain kinds of large B-cell lymphoma.
nadofaragene firadenovec-vncg	2022	Adenovirus	A recombinant adenovirus (rAd-IFNa/Syn3) delivers **human interferon alfa-2b cDNA** into the bladder epithelium. Treats patients with certain types of bladder cancer.
Ciltacabtagene autoleucel	2022	Cell (autologous, modified)	**CAR T** cells engineered with lentivirus to treats patients with certain kinds of relapsed or refractory multiple myeloma.
Lifileucel	2024	Cell (modified)	Engineered T cells for the treatment of adult patients with unresectable or metastatic melanom. a

CGTs in Hematology Therapeutic Class

- **Hemophilia A**: valoctocogene roxaparvovec-rvox
- **Hemophilia B**:
  - voretigene neparvovec-rzyl
  - etranacogene dezaparvovec-drlb
  - Fidanacogene elaparvovec-dzkt
- **ß-Thalassemia**: betibeglogene autotemcel
- **Sickle Cell Disease**:
  - exagamglogene autotemcel (exa-cel)
  - lovotibeglogene autotemcel (lovo-cel)

Expanding CGTs in Therapeutic Areas

- First approval: 2010, Sipuleucel-T, Oncology
- 2010 to 2022: Most CGTs are Human cord blood, and Chimeric Antigen Receptor (CAR) T-cell (oncology)
- 2022: new direction for previously unmet needs for rare diseases
- December 2022: new supply method, first off-the-shelf product
- 2023: route of administration expansion (Topical products)
- December 2023: first CRISPR/Cas9 platform curative for Sickle Cell Diseases

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Factors that Influence the Success of CGTs

- Durability of long-term efficacy
- Sufficient patient population size
- Availability of alternate therapies
- Cost: would the price be more competitive in the future?
  - R&D simplification
  - More competition
  - More government funding

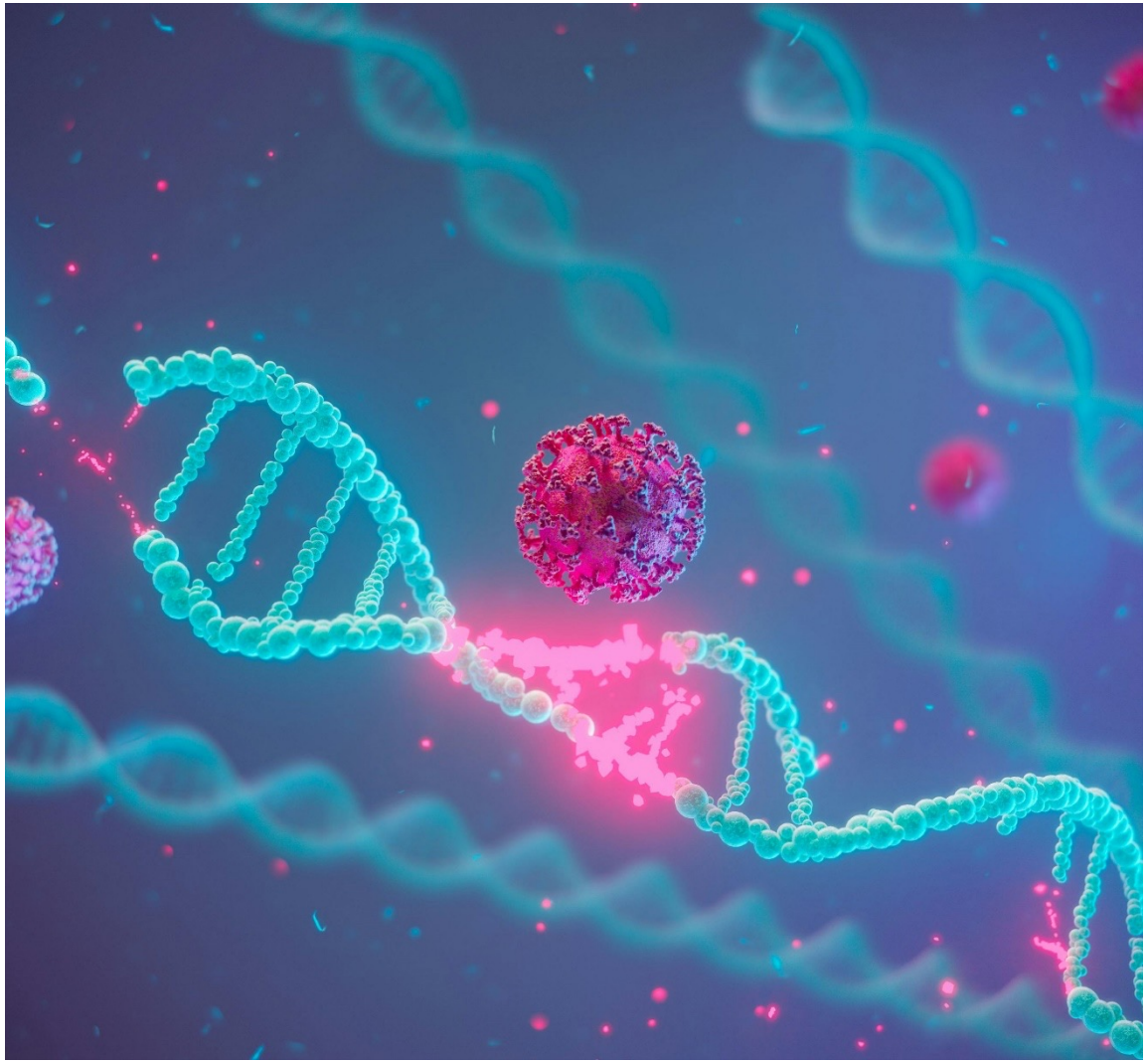
Establishing Teams to Provide CGTs

- CGTs can revolutionize healthcare by shifting the focus from managing chronic diseases to preventing or curing them.
- However, CGTs require highly coordinated teams to successfully process the complicated CGT treatment.
- Each element of the process:
  - ordering the product,
  - specialized storage and handling requirements,
  - operational logistics,
  - administration of the CGT to the patient,
  - extended patient monitoring,
  - payer and reimbursement issues,

  may take months of planning and require complex coordination across a health system.

IDNs are Uniquely Prepared for CGTs

- Existing Bone Marrow Transplant Programs
- Well trained staff to handle treatment related adverse events and Post transplant care
- Established Facilities with negative and positive pressure rooms for patients
- Policies and procedures for storage and handling of cellular materials and other human products
- Treatment Center Policy and Procedures to guild



Cost Considerations

5 out of the 10 most expensive drugs in 2023 were CGTs

CGT cost was $3.7 Billion in 2023, and is expected to reach $30 Billion by 2030

Research and development, complicated manufacturing processes, and individualized, sometimes patient specific products, drive up the cost of CGTs

Complex patient care associated with administration, supportive care, and facility requirements (including certification processes), drive up hospital and IDN expenses.

In the balance: Single treatment cost vs lifetime cost of disease management

Payment Models in the US are Complicated

- Prior authorizations
- Financial investigation
- Individual case contract
- Value based contract
- Payment schedule (over time)

Challenges and Solutions for Implementing CGTs

- **Access:** commercial availability; IDN must have certified treatment center
- **Cost:** IDNs should work with payers for individual contracts to assure financial feasibility
- **Reimbursement**: Lack of product-specific ICD-10, CPT, HCPCS codes and payers' policies. Reimbursement is thus handled case-by-case.
- **Operations**: Safe preparation and handling guidance is unclear, with package inserts only recommending **universal biohazard precautions**. Most approved therapies, including CAR-T agents, need to be stored at **ultra-low or cryogenic** temperatures.
- **Value-Based Contract**:, valoctocogene roxaparvovec-rvox is offering an outcomes-based agreement, in which it will reimburse payers up to **100% of WAC** if the patient doesn't respond. betibeglogene autotemcel also offer outcome-based contracts
- **Accelerated approval** may complicate payer willingness to cover these agents.

The Zelenska Success Story

- Onasemnogene abeparvovec-xioi
  - One-time treatment
  - Indicated to treat Spinal Muscular Atrophy (SMA)
  - Cost per treatment: $2.1 Million
  - > 3,000 children treated
  - Total 2023 global sale exceeded $1.2 Billion
  - R&D was Supported by Miracle for Madison and Friend Fund, Cure SMA, Sophia's Cure (patient organizations) and AveXis (Physician funded) all contributed significant amount of support.
  - We ALL can help saving children like Madison Reed

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Thank you and stay in touch

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