SHIELDS HEALTH SOLUTIONS

Introduction to the Gene and Cellular Therapy Era

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Learning Objectives

- List the current gene and cellular therapies FDA approved and mechanisms of action
- Discuss operational and payer considerations unique to gene and cellular therapy program implementation
- Describe innovative payment models under consideration for cell and gene therapy
- Understand gene therapies expected to launch in the next year

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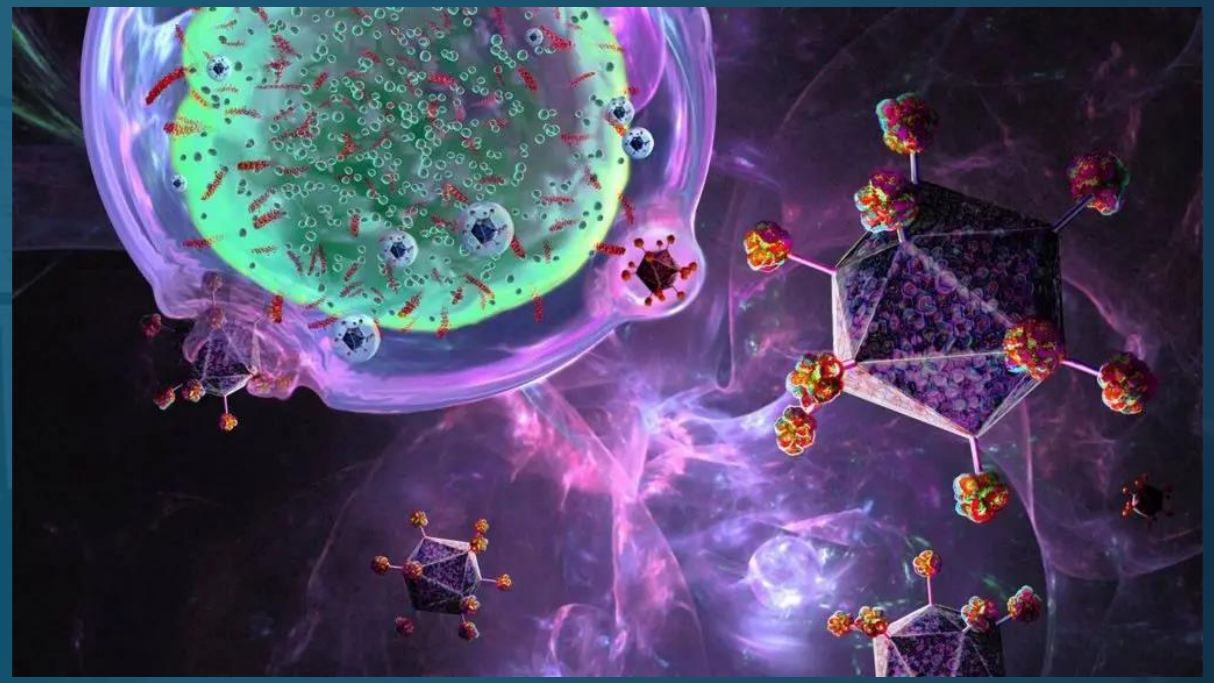

Defining Gene and Cellular Therapy - GCT

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GENE & CELL THERAPY TERMINOLOGY AND DEFINITIONS

GCT: Agent intended to treat, cure, or prevent a disease or medical condition caused by things like gene mutations (can be inherited or acquired-healthy genes that mutate over time).

Cell Therapy

Transfer of whole "living" cells with relevant function into a patient.

Can be created from autologous (own) or allogeneic (donor) cells

Examples: BMT, SOT

Gene-Modified Cell Therapy

Overlap of cell and gene therapies

Blood, bone marrow or other tissues isolated, cells are genetically engineered & modified to express new gene, expanded, and reintroduced into a patient.

Examples: CAR-T, TCR, NK

Gene Therapy

Transfer of genetic material, usually in a carrier or vector, with uptake of the gene into target cells of the body.

Gene replacement, addition, disruption, silencing

Examples: Adenovirus, Lentivirus

Types of Gene and Cell Therapy

Chimeric Antigen Receptor (CAR) T-cell Therapy	• CAR genes are transfected into autologous T-cells using an inactivated virus to redirect lymphocytes in a specific antigen
Tumor-Infiltrating Lymphocyte (TIL) Therapy	• Autologous tumor infiltrated T-cells are harvested, activated and expanded to amplify their effect against a tumor
Engineered T-Cell Receptor (TCR) Therapy	• Arms autologous T-Cells with a new engineered T-cell receptor to allow the T-cells to target a tumor specific antigen of choice
Natural Kill (NK) Cell Therapy	• Equips autologous NK cells with a CAR directed toward a tumor-associative target
Gene Therapy	• Modification or manipulation of the expression of a gene or alter the biological proport of living cells for therapeutic use

In Vivo vs. Ex Vivo Drug Delivery

In vivo: genetic materials are delivered directly into the patient's cells or tissues

- Administered IV infusion, directly into a target organ, or topically for skin conditions.

Ex vivo: Cells are isolated (e.g. collected), treated with a therapeutic gene in a lab, then transplanted back into the patient.

- Lentiviral viruses (best for rapidly dividing cells like stem cells)
- Casgevy is administered ex vivo, however CRISPER Cas9 technology can be given in vivo.

Updates in Gene and CAR-T Therapies. *IPD Analytics Podcast*. August 1, 2024.

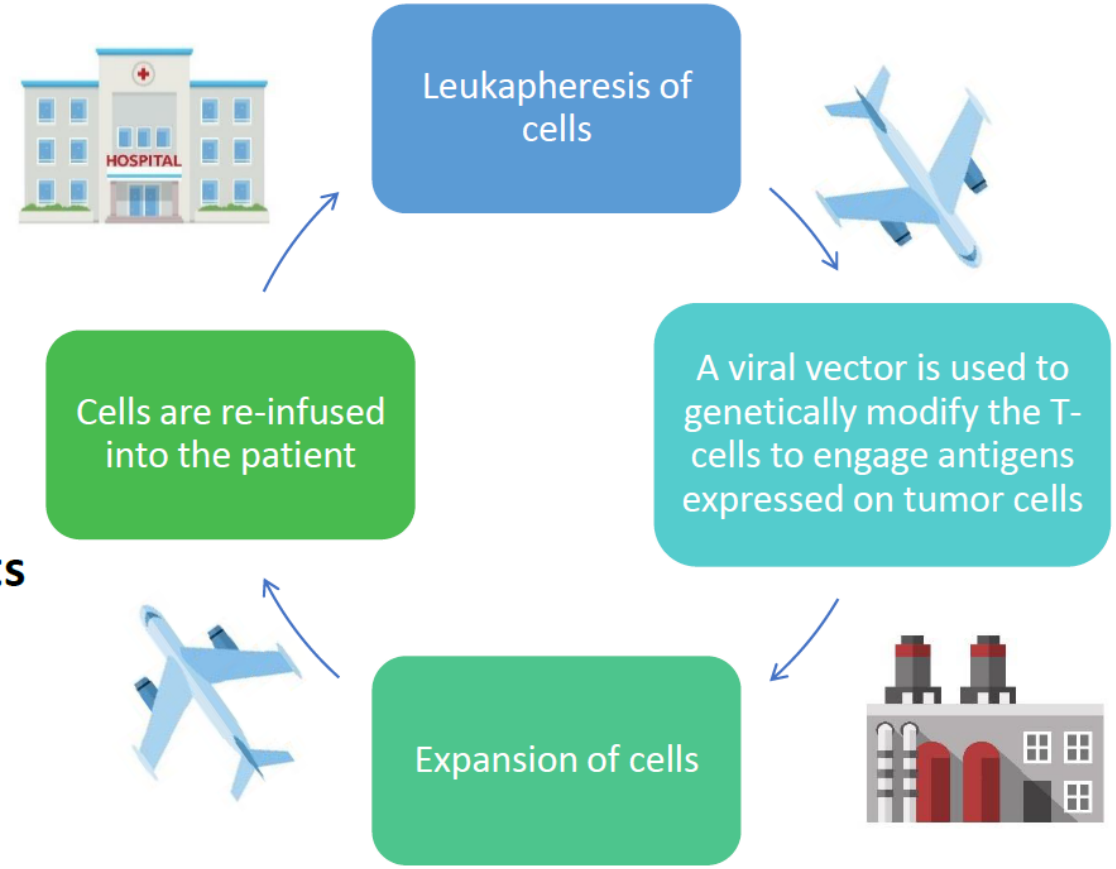
Autologous Cellular Gene Therapy

FDA-Approved Oncology Products

axicabtagene ciloleucel
brexucabtagene autoleucel
ciltacabtagene autoleucel
idecabtagene vicleucel
idecabtagene vicleucel
sipuleucel-T
Tisagenlecleucel

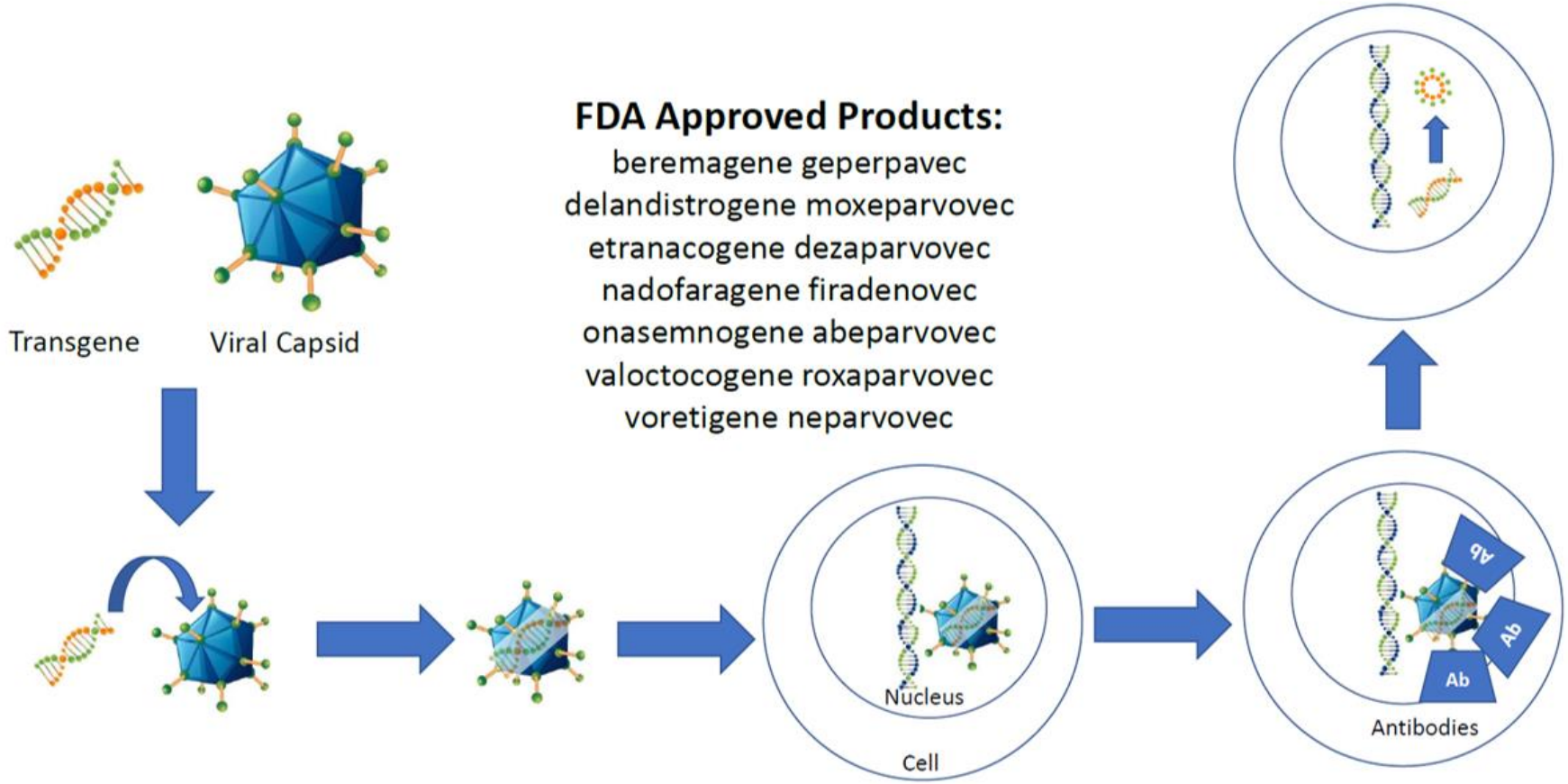
FDA-Approved Non-Oncology Products

betibeglogene autotemcel
elivaldogene autotemcel



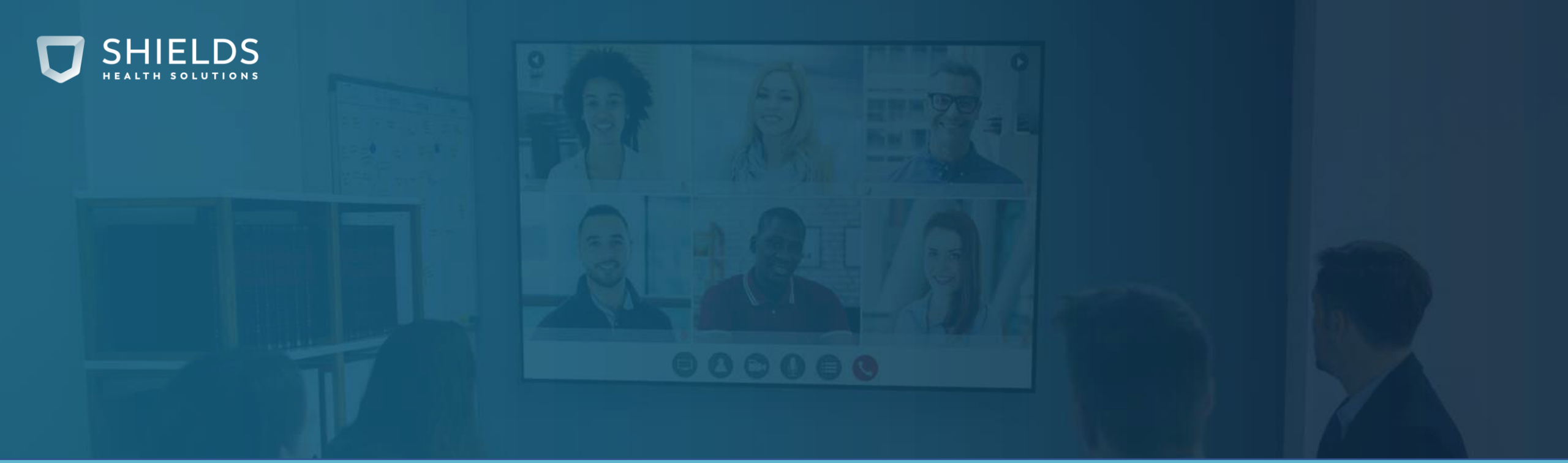
Wolinsky *Managed Care*. 2027;26(10):28-30

Viral Vector Gene Transfer



Available Gene Therapy Products

Drug Name	Indication	Category	WAC
Adstiladrin (nadofaragene firadenovec vcng)	Bladder Cancer	Oncology	$960K
Casgevy (exagamglogene autotemcel exacel)	Sickle Cell, Beta thalassemia	Hematology	$2.2M
Elevidys (delandistrogene moxeparvovec rokl)	Duchenne's	Neurology	$3.2M
Hemgenix (etranacogene dezaparvovec drlb)	Hemophilia B	Hematology	$3.5M
Lenmeldy (atridarsagene autotemcel)	Metachromatic Leukodystrophy	Neurology	$4.25M
Luxturna (voretigene neparvovec rzyl)	Retinal dystrophy	Ophthalmology	$914K
Lyfgenia (lovotibeglogene autotemcel lovocel)	Sickle Cell	Hematology	$3.1M
Roctavian (valoctocogene roxaparvovec rvox)	Hemophilia A	Hematology	$2.9M
Skysona (elivaldogene autotemcel)	Cerebral adrenoleukodystrophy	Neurology	$3M
Vyjuvek (beremagene geperpavec svdt)	Dystrophic epidermolysis bullosa	Dermatology	$900K
Zynteglo (betibeglogene autotemcel)	Beta Thalassemia	Hematology	$2.8M
Zolgensma (onasemnogene abeparvovec xioi)	Spinal muscular atrophy	Neurology	$2.3M



Understanding the FDA Approval Process – GCT are not typical drugs

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FDA Regulation of Biologics

- **Center for Drug Evaluation and Research (CDER)**
  - Small molecules, chemicals
  - Monoclonal antibodies for therapeutic use
  - Most proteins for therapeutic use (e.g., enzymes, growth factors, cytokines)
- **Center for Biologics Evaluation and Research (CBER)**
  - Cellular products, including products composed of human, bacterial or animal cells or from physical parts of those cells
  - Gene therapy products
  - Vaccines and vaccine-associated products regardless of composition or manufacture
  - Allergenic extracts used for the diagnosis and treatment of allergic diseases
  - Antitoxins, antivenins, and venoms
  - Blood, blood components, plasma derived products (e.g., albumin, immunoglobulins)
  - Human cells, tissues and cellular and tissue-based products

https://www.fda.gov/media/170955/download

FDA Expedited Designations/Programs

- Fast track
- Breakthrough therapy
- Accelerated approval
- Priority review

Conditions for Expedited Programs

- Whether a condition is serious, and whether the drug is intended to treat a serious condition
- If available therapy exists
- If there is an unmet medical need

https://www.fda.gov/media/86377/download

Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Designation	Designation	Approval Pathway	Designation
• A drug that is intended to treat a serious condition ***AND*** • Nonclinical or clinical data demonstrate the potential to address unmet medical need ***OR*** • A drug that has been designated as a qualified infectious disease products	• A drug that is intended to treat a serious condition ***AND*** • Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	• A drug that treats a serious condition ***AND*** • Generally provides a meaningful advantage over available therapies ***AND*** • Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	• An application (original or efficacy supplement) for a drug that treats a serious condition ***AND*** • If approved, would provide a significant improvement in safety or effectiveness ***OR*** • Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505Ab ***OR*** • An application for a drug that has been designated as a qualified infectious disease product ***OR*** • Any application or supplement for a drug submitted with a priority review voucher

Case Example: Elevidys (delandistrogene moxeparvovec-rokl)

- Gene therapy designed to **treat Duchenne muscular dystrophy (DMD)** in patients aged 4 years and older with a confirmed mutation in the DMD gene
- Mechanism: **adeno-associated virus (AAV) vector** delivers a gene encoding a micro-dystrophin protein, which is a shortened version of the dystrophin protein normally found in muscle cells
  - **Treats underlying condition** rather than symptoms
  - Administered as a **single intravenous infusion** over 1 to 2 hours
- **Accelerated approval** for use in both ambulatory and non-ambulatory patients
  - Continued approval may depend on further verification of clinical benefits.
- **Safety Information**:
  - Warnings: Includes risks of infusion-related reactions, serious liver injury, immune-mediated myositis, and myocarditis
  - Side Effects: Common side effects include vomiting, nausea, liver injury, fever, and thrombocytopenia

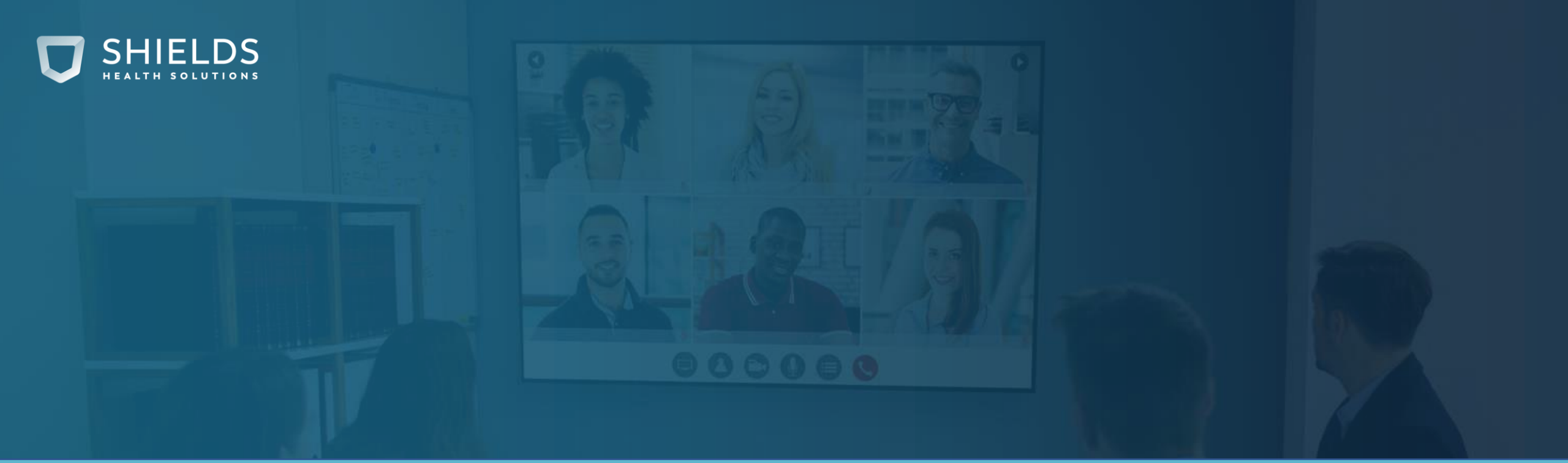
FDA Approves First Gene Therapy for Treatment of Certain Patients with Duchenne Muscular Dystrophy | FDA

Biologic License Approval & Biosimilars

- **Section 351(a) of the PHS Act**
  - Defines Reference Product Exclusivity of Biological Products
- **Section 351(k) of the PHS Act**
  - Added by the Biologics Price Competition and Innovation Act of 2009
  - Biological product must be
    - Highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
    - Have no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product
    - *Same mechanisms, conditions for use, administration details, GMPs, etc.*

Sustainability Challenges with CGT Development & Market

- Small market sizes for rare diseases (“n of few”) limit the potential return on investment in the traditional drug development model, resulting in market failure
  - Example: Adenosine deaminase (ADA)-deficient severe combined immunodeficiency syndrome (ADA-SCID)
- Major contributing factors
  - High manufacturing costs
  - Regulatory challenges
  - Licensing practices
- Without modification, market forces could result in unsustainable costs and/or shifting from rare diseases to common diseases



Operationalizing GCT – It's a program not a treatment

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Implementing Gene & Cell Therapy

Medical

- Provider Champion
- Prescribers
- Infusion manager
- Infusion Nurse
- Patient Coordinator
- Genetic Counselor

Pharmacy

- Pharmacy Champion
- Pharmacists
- Procurement Team
- Sterile Compounding

Operations

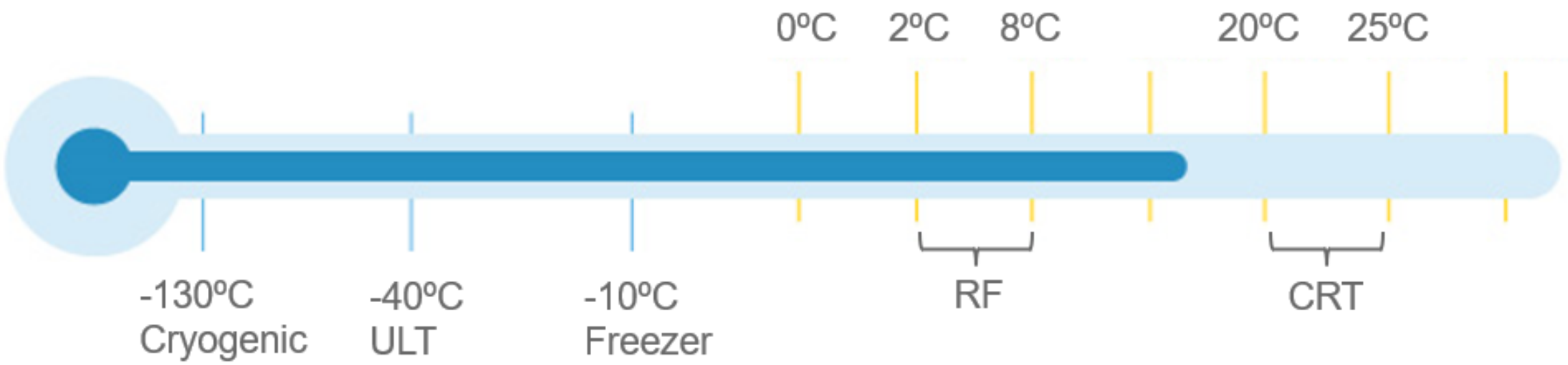
- Site Coordinator
- Patient Coordinator
- Patient Records Manager
- Training Coordinator
- IT Coordinator
- Cell Collection

Access

- Financial Decision Maker
- Manufacturer contracting
- Prior Authorization Coordinator
- Patient Financial Support

Reimbursement

- Payer Contracting Manager
- Revenue Cycle Manager
- Claims, Billing & Coding Staff



Role of Cold Chain

- ULT = ultra low temperature
- RF = refrigerator
- CRT = controlled room temperature

Freezer and below storage GCT

FREEZER	ULTRA LOW TEMPERATURE	CRYOGENIC
Vyjuvek Beremagene geperpavec svdt	Roctavian Valoctocogene roxaparvovec rvox	Tecartus brexucabtagene autoleucel
	Adstiladrin nadofaragene firadenovec	Abecma idecabtagene vicleucel
		Breyanzi lisocabtagene maraleucel
		Carvykti ciltacabtagene autoleucel
		Skysona elivaldogene autotemcel
		Zynteglo betibeglogene autotemcel
		Casgevy exagamglogene autotemcel
		Lyfgenia lovotibeglogene autotemcel

Role of Technology

Augmented Intelligence

- Identify potential patients
- Enhance utilization management

Novel and intense storage requirements

- Capital investments
- Education & specialized staffing
- Risk & monitoring of temperature variance
- Ordering, receiving and distribution

Role of Handling GCT in Pharmacy

Pharmacy advantages

- Medication use process
- Sophisticated electronic medical record build
- Financial management acumen
- Regulatory requirements – TJC medication management standards

Areas that need development

- Management of liquid nitrogen storage
- Thawing/preparing cells
- Accreditation gaps: Foundation for the Accreditation of Cellular Therapy (FACT)

Reimbursement & Financing

- Disproportionate representation of Medicaid as a payer
  - Always the worst payer with coverage below costs
  - Role of 340B discounts
  - Pediatrics facilities highly represented
- No discounts available outside 340B
  - ASP based reimbursement becomes negative when manufacturer increases price
  - Role for CMS outlier payments[1]
- Risk of reimbursement denial if administered outpatient and patient is admitted within 3 days of administration
- Cash flow concerns based on high drug acquisition cost depending on payment and reimbursement terms
- Novel Payment strategies

1. Outlier Payments | CMS

Innovative Payment Models: Value Assurance

Model Type	Description
Value-based Arrangements	Business contract between manufacturer and a payer under which a manufacturer offers some sort of value (e.g. rebated) based on the performance-based outcomes of a product or service.
Warranty	Payer pays full price upfront; manufacturer pays premium to third-party insurer; insurer reimburses payer for costs of treatment failure. The value is related to covered healthcare costs and is not a refund for the cost of the treatment.
Milestone-based contracts	A short-term performance-based agreement in which the payer makes an upfront payment for the entire negotiated price of the therapy. The manufacturer is then contractually obligated to provide a rebate if specific agreed upon performance milestones/outcomes are not met.
Performance-based annuities	A multi-yea payer-manufacturer agreement that includes an up-front payment by the payer of some portion of the medicine cost, as well as a commitment to further payments to the developer from the payer every year for a defined number of years, with outyear payments triggered by outcomes being achieved.

Innovative Payment Models: Expense Management

Model Type	Description
Installment payments	Payer makes fixed payments, dividing total cost of drug over multiple years.
Risk pool	Payer makes contributions to a common fund, Fund reimburses payer for drug costs.
Reinsurance	Payer pays a premium per patient to third-party reinsurer, Reinsurer reimburses payer for drug costs.
Price-volume agreement	Payer pays full price per patient, drug price decreases as more drugs are purchased to treat more patients.
Expenditure cap	Payer pays full price per patient until total spending cap reached, then pays nothing for additional patients.
Orphan reinsurer and benefit manager (ORBM)	Service solution that can provide services to payer organizations not wanting to build their own capabilities to manage durable gene and cell therapies. The proposed intermediary ORBM combines the risk-bearing of reinsurers with the therapy contracting capabilities of pharmacy benefit managers, the provider network building and medical management capabilities of insurers and perhaps a specialty pharmacy distribution capability.
Subscription	Payer pays a set price for unlimited volume of drug; a pharmaceutical company provides treatment for a set fee regardless of the number of patients treated or a set price per patient.

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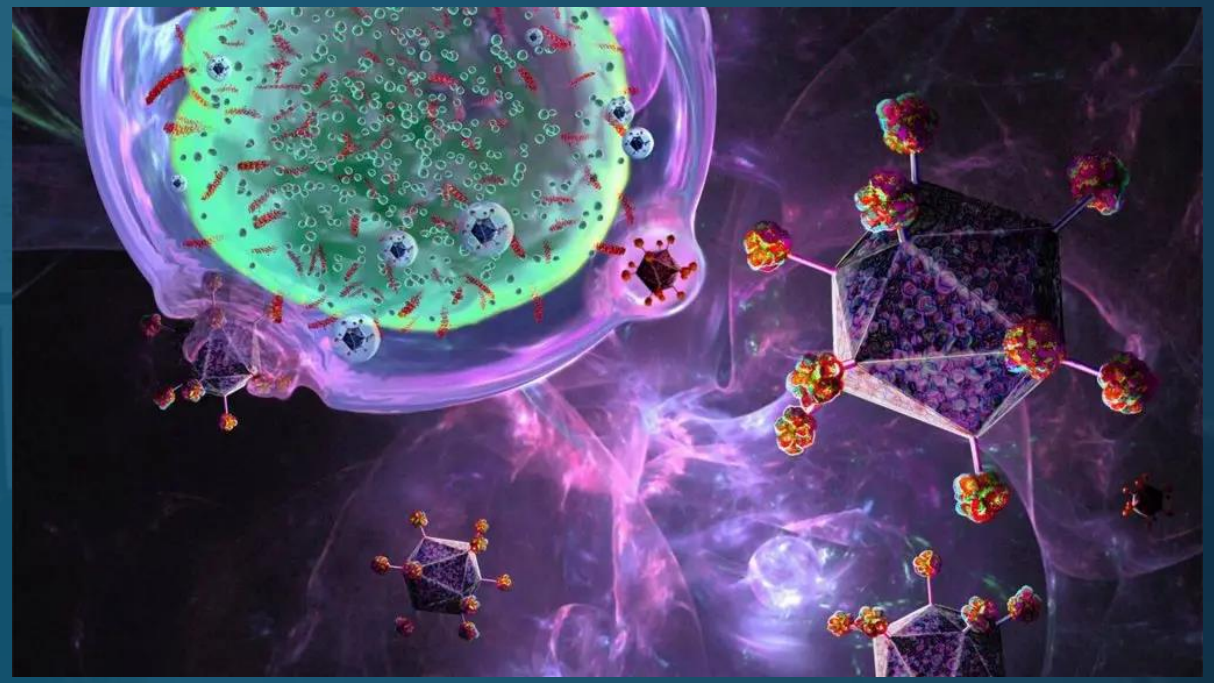

Looking to the Future with GCT

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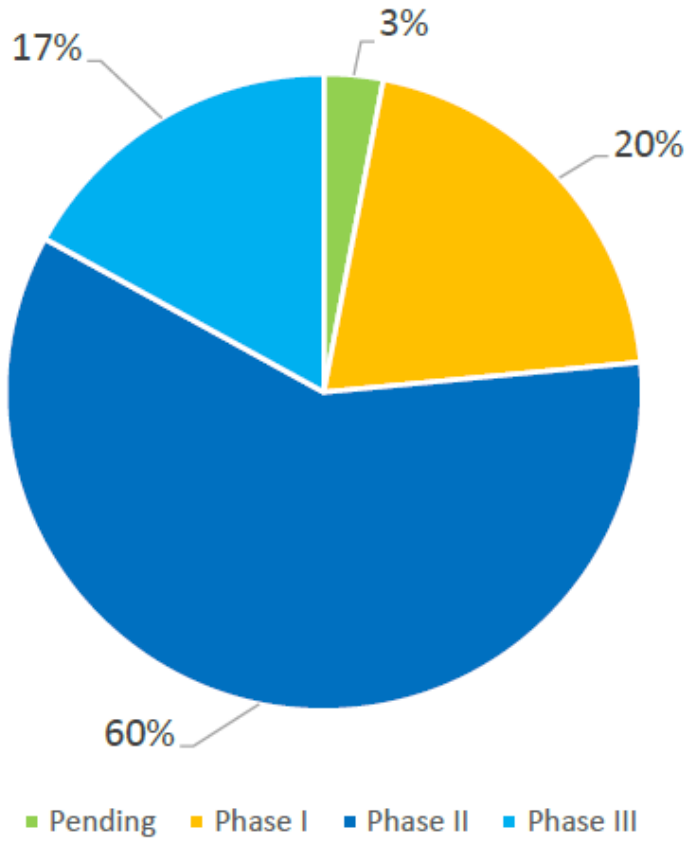
Gene & Cell Therapy Pipeline

- 38 CGTs approved by FDA[1]
- 20% of drugs in investigational pipeline are GCT[2]
- Five GCT approved in 2024[3]
  - Casgevy - Vertex Pharmaceuticals/CRISPR Therapeutics' for beta thalassemia
  - Amtagvi - Iovance Biotherapeutics' for melanoma
  - Lenmeldy - Orchard Therapeutics/Kyowa Kirin's for metachromatic leukodystrophy
  - Beqvez - Pfizer's for hemophilia B
  - Tecelra - Adaptimmune Therapeutics' for synovial sarcoma

1. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
2. https://asgct.careboxhealth.com/en-US
3. https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2024

Pipeline Characteristics

Drug Classes	Number of drugs
Gene therapy	116
CAR-T	37
Cancer treatment vaccines	25
TCR immunotherapy	15
NK cell immunotherapy	5
TIL therapy	2
Cellular therapy not otherwise specified	76



https://clinical–pipeline.ipdanalytics.com/

Key Takeaways

- GCT are an emerging class of new drug approvals and represents a significant portion of future approvals
- GCT are leading to exploration of new payment models
- It takes a multidisciplinary team effort to implement GCT
- The role of pharmacy in GCT is still being defined

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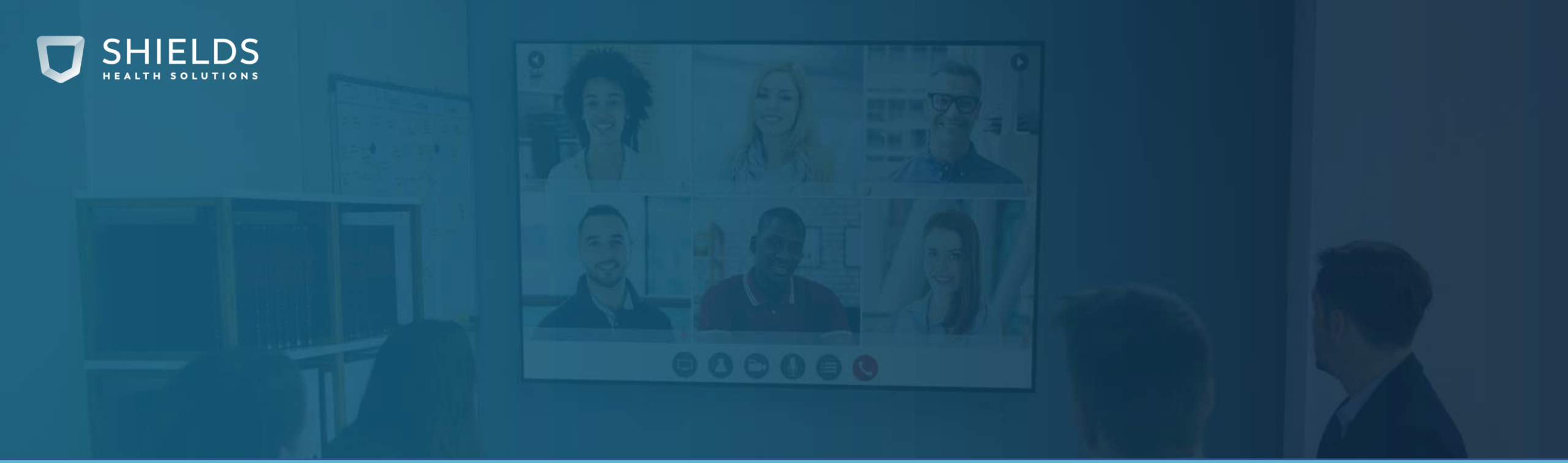

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