Multiple Challenges in Accessing Orphan Products for:

Patients, Families, and Clinicians

Presented by:

David McLean, PhD
Co-founder of Emerging Therapy Solutions® (ETS)
Agenda

Objective for today:

1. Review Industry Background
2. Today’s Challenges in Providing Access
3. Considerations for the Future in Meeting Patient Needs
Review Industry Background
Access Challenges

• Scientific Advancements & Technologies

• New Hope Solutions

• Patient / Family Challenges
  - Treatment alternatives
  - Insurance coverages
  - Total financial burdens
  - Value
    - Life-saving capabilities
    - Societal implications
Background Information: Orphan and Rare Diseases

• Orphan diseases: Effect less than 200,000 people in US
• Ultra orphan: Less than 5,000 - 10,000 people
• 39 percent of orphan drugs cost more than $100,000
• Orphan Drug Act of 1983:
  ➢ To stimulate development of drugs for rare diseases
  ➢ US Food and Drug Administration (FDA) grants designation
  ➢ Pharmaceutical manufacturer financial & tax incentives
• 1 in 10 Americans have a rare disease
• There are 7,000 known rare diseases:
  ➢ Less than 10 percent have a treatment and fewer have cures
• NORD: National Organization for Rare Disorders
Access Challenges

Challenges for Stakeholders in Creating Access
- Patients
- Scientists and clinicians
- Provider systems
- Payers
- Pharma

Opportunities to Facilitate Access
- Partnerships / Collaboration
- Providers / Clinicians
- Manufacturers (Pharma)
- Payers
- Patients
## Approved & Investigational Cell Therapies Pipeline

<table>
<thead>
<tr>
<th>THERAPY &amp; MANUFACTURER</th>
<th>CONDITION</th>
<th>ACTUAL/ANTICIPATED APPROVAL DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kymriah</strong> *(tisagenlecleucel; tisa-cell)</td>
<td>Acute lymphoblastic leukemia</td>
<td>Approved 8/30/2017</td>
</tr>
<tr>
<td><strong>Yescarta</strong> *(axicabtagene ciloceleucel; axi-cell)</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Approved 10/18/2017</td>
</tr>
<tr>
<td><strong>Kymriah</strong> *(tisagenlecleucel; tisa-cell)</td>
<td>Non-Hodgkin lymphoma</td>
<td>Approved 5/1/2018</td>
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<tr>
<td><strong>Tecartus</strong> *(brexucabtagene autoleucel; brexu-cell)</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Approved 7/24/2020</td>
</tr>
<tr>
<td><strong>Breyanzi</strong> *(lisocabtagene maraleucel; liso-cell)</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Approved 2/5/2021</td>
</tr>
<tr>
<td><strong>Abecma</strong> *(idecabtagene vicleucel; ide-cell)</td>
<td>Multiple myeloma</td>
<td>Approved 3/26/2021</td>
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<td><strong>Tecartus</strong> *(brexucabtagene autoleucel; brexu-cell)</td>
<td>Acute lymphoblastic leukemia</td>
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<tr>
<td><strong>Rethymic</strong> *(Allogeneic Processed Thymus Tissue)</td>
<td>Congenital athymia</td>
<td>Approved 10/8/2021</td>
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<tr>
<td><strong>Carvykti</strong> *(cilta-cabtagene autoleucel; ciltacel)</td>
<td>Multiple myeloma</td>
<td>Approved 2/28/2022</td>
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<td><strong>Yescarta</strong> *(axicabtagene ciloceleucel; axi-cell)</td>
<td>Large B-cell lymphoma in the second-line setting</td>
<td>Approved 4/1/2022</td>
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<tr>
<td><strong>Kymriah</strong> *(tisagenlecleucel; tisa-cell)</td>
<td>Follicular lymphoma</td>
<td>Approved 5/27/2022</td>
</tr>
<tr>
<td><strong>Breyanzi</strong> *(lisocabtagene maraleucel; liso-cell)</td>
<td>Large B-cell lymphoma in the second-line setting</td>
<td>Approved 6/24/2022</td>
</tr>
<tr>
<td><strong>Omisirge</strong> *(omidubicel-onlv)</td>
<td>Hematologic malignancies (Blood cancers)</td>
<td>Approved 4/1/2024</td>
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<tr>
<td><strong>Lantidra</strong> *(donislecel-jujn)</td>
<td>Diabetes Type 1</td>
<td>Approved 6/28/2023</td>
</tr>
<tr>
<td><strong>Amtagvi</strong> *(Lifileucel)</td>
<td>Metastatic melanoma</td>
<td>Approved 2/16/2024</td>
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<tr>
<td><strong>Abecma – Moving up in line; Carvykti – Second line</strong></td>
<td>Multiple myeloma</td>
<td>PDUFA Delayed</td>
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<tr>
<td><strong>Breyanzi</strong> *(lisocabtagene maraleucel)</td>
<td>Chronic lymphocytic leukemia Small lymphocytic lymphoma</td>
<td>PDUFA 3/14/2024</td>
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<td><strong>Afami-cell</strong> *(afamitresgene autoleucel; ADP-A2M4)</td>
<td>Follicular lymphoma</td>
<td>PDUFA 5/24/2024</td>
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<tr>
<td><strong>Obe-cell</strong> *(Obecabtagene autoleucel)</td>
<td>Mantle cell lymphoma</td>
<td>PDUFA 5/31/2024</td>
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<tr>
<td><strong>Tab-cell</strong> *(tablecleucel; ATA129/EBV-CTL)</td>
<td>Synovial sarcoma</td>
<td>PDUFA 8/4/2024</td>
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<tr>
<td><strong>Afami-cell</strong> *(afamitresgene autoleucel; ADP-A2M4)</td>
<td>Acute lymphoblastic leukemia</td>
<td>PDUMA 11/16/2024</td>
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<tr>
<td><strong>Lete-cell</strong> *(letetresgene autoleucel)</td>
<td>Epstein-Barr virus-associated post-transplant lymphoproliferative disease</td>
<td>H2 2024</td>
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<td><strong>Afami-cell</strong> *(afamitresgene autoleucel; ADP-A2M4)</td>
<td>Myxoid/round cell liposarcoma</td>
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<td><strong>Lete-cell</strong> *(letetresgene autoleucel)</td>
<td>Synovial sarcoma</td>
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<td><strong>Lifileucel</strong> *(LN-144)</td>
<td>Cervical cancer</td>
<td>2024 - 2025</td>
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<td><strong>Zevor-cell</strong> *(zevorcabtagene autoleucel, CT053)</td>
<td>Multiple myeloma</td>
<td>2024 - 2025</td>
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<tr>
<td><strong>Yescarta</strong> *(axicabtagene ciloceleucel; axi-cell)</td>
<td>Marginal zone lymphoma</td>
<td>2025</td>
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</tbody>
</table>

**NOTE:** This content is informational only and is intended for a US audience. This document has been prepared by Emerging Therapy Solutions (ETS) and provides information about prospective cell and gene therapy treatments as of the date of this presentation. This information has been obtained from third-party sources believed to be reliable, however ETS may not be able to verify accuracy and makes no guarantee, warranty, or representation about this information. Due to the rapidly evolving and changing nature of the information presented, including opinions and estimates, this is subject to change without notice. The information presented is not intended to be a recommendation as to medical care, or any form of legal or medical advice. All trademarks referenced herein are the property of their respective owners.

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Approved & Investigational Gene Therapies Pipeline

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<th>ACTUAL/ANTICIPATED APPROVAL DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luxturna® in-vivo (voretigene neparovec-rzyl)</td>
<td>Biallelic RPE65 mutation</td>
<td>Approved 12/2017</td>
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<td>Zolgensma® in-vivo (onasemnogene abeparvovec)</td>
<td>Spinal muscular atrophy</td>
<td>Approved 05/2019</td>
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<td>Zyneglo® ex-vivo (betibeglogene autotemcel; beti-cel)</td>
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<td>Hemophilia B</td>
<td>Approved 11/2022</td>
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<td>Adstaladrin® in-vivo (nadofaragene xiaeparvovec)</td>
<td>Ferring Pharmaceuticals</td>
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<tr>
<td>Vyuvek™ Topical (beremagene geperpavec; B-VEC; KB103)</td>
<td>Krystal Biotech</td>
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<tr>
<td>Elevidys® in-vivo (delandistrogene moxeparvovec-rokl)</td>
<td>Sarepta Therapeutics</td>
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<td>Roctavian™ in-vivo (valoctocogene roxaparvovec-rvox)</td>
<td>BioMarin Pharmaceutical Inc.</td>
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<td>Casgevy™ ex-vivo (exagamglogene autotemcel; exa-cel)</td>
<td>CRISPR/Vertex</td>
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<td>Adstiladrin® in-vivo (nadofaragene xiaeparvovec)</td>
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<td>Libmeldy™ ex-vivo (atidarsagene autotemcel; OTL-200)</td>
<td>Orchard Therapeutics</td>
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<td>Pe-cell keratinocyte sheets (prademagene zamikeracel; EB-101)</td>
<td>Abeona Therapeutics</td>
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<td>Elevidys® in-vivo (delandistrogene moxeparvovec-rokl)</td>
<td>Sarepta Therapeutics (expanded indication)</td>
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<td>Pfizer, Inc.</td>
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<td>Upstaza EU</td>
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<td>REGENEXBIO</td>
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<td>botaretigene sparoparvovec in vivo (AAV-RPGR)</td>
<td>MeiraGTx/Janssen Pharmaceuticals, Inc.</td>
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<td>Lumeovq® in-vivo (lenadogene nolparvovec; GS010)</td>
<td>GenSight Biologics</td>
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<td>Girotocogene fitelparvovec in vivo</td>
<td>Pfizer and Sangamo Therapeutics</td>
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<td>fordadistrogene movaparvovec in vivo (PF-06939926)</td>
<td>Pfizer, Inc.</td>
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<td>Ultragrenx Pharmaceuticals</td>
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<td>DTX301 in vivo</td>
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<td>RGX-314 in vivo</td>
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<td>Novartis Pharmaceuticals</td>
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<td>olenasufligene relduparvovec in-vivo (LYS-SAF302)</td>
<td>Lysogene</td>
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<tr>
<td>UX111 (fka ABO-102) in-vivo</td>
<td>Ultragrenx Pharmaceuticals</td>
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# Magnitude of Change

**In Treatments and Costs**

1900 – Today

<table>
<thead>
<tr>
<th>RANGE OF COSTS</th>
<th>TIMEFRAME</th>
<th>SOURCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1 – $10</td>
<td>1900 – 1970</td>
<td>Plant</td>
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<tr>
<td>$11 – $100</td>
<td></td>
<td>Animal</td>
</tr>
<tr>
<td>$101 – $500</td>
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<td>Chemical</td>
</tr>
<tr>
<td>$1 – $1,000</td>
<td>1970 – 2000</td>
<td>Biologics</td>
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<tr>
<td>$1,000 – $100,000</td>
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<tr>
<td>$100,000 – $500,000</td>
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<tr>
<td>$500,000 – $1M</td>
<td>2000 – Today</td>
<td>Early Specialty</td>
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<tr>
<td>$1M – $2M</td>
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<td>$2M – $3M</td>
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<td>New Specialty</td>
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<td>Gene Therapy</td>
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<td>Cell Therapy</td>
</tr>
<tr>
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<td></td>
<td>Immunotherapy</td>
</tr>
</tbody>
</table>

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Emerging Therapeutic Treatments to Treat or Cure Disease

**Cell Therapy**
Transfer of live cells into the body

Uses cells from patient: autologous
Uses cells from donor: allogeneic

**Gene Therapy**
Add new genes (gene addition)
Edit or remove existing genes

Genetically alter outside the body: *ex vivo*
Direct administration of genetic material: *in vivo*
Sourcing of New Specialty Treatments

- Research Institutions (NIH)
- Academic Research Centers
- Biotech Companies
- Pharmaceutical Manufacturers (Pharma)

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Distribution of Treatments from Pharma and Biotech

Distribution Contracts
- Hospitals
- Physicians
- Pharmacies
- Intermediaries (PBMs, Payers)

Selling to Influencers
- Hospitals
- Physicians
- Consumers
- Intermediaries (PBMs, Payers)
Provider Systems for Distribution

- Hospitals
  - In-patient
  - Out-patient
- Physicians
- Pharmacies
- Pharmacy Benefit Managers (PBMs)
- Infusion Providers
- Specialty Providers

Covering costs
Making a margin
Maximizing reimbursement
## Payers: Decisions, Coverages and Influences

<table>
<thead>
<tr>
<th>Insurance Coverage Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Benefit Coverage</strong></td>
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<tr>
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<td><strong>Pharmacy Benefits</strong></td>
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<td><strong>Claim Administration Variances</strong></td>
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<tr>
<td><strong>Data Capture Variances</strong></td>
</tr>
<tr>
<td><strong>Financial Influence Variances</strong></td>
</tr>
</tbody>
</table>
Today’s Challenges in Providing Access
New Era of Specialty Treatments

Patient Challenges and Actions

- Rare and orphan diseases
- Orphan Drug Act of 1983
- Pharma incentives
- New scientific capabilities: gene, cell, immunotherapy

Along with new solutions comes financial challenges and implications for:

1. The FDA approval process
2. Who pays for treatments?
3. Manufacturing
4. Distribution
5. Payer drug formularies
6. Society: ways to pay for high-cost treatments
FDA Approval Process

• New specialty treatments
  - Cell therapy
  - Gene therapy
  - Immunotherapy
  - Other

• Advancement of the FDA approval process
  - Phase I, II and III review steps

• New levels of complexities

• Major focus is still safety
• Smaller number of people in trials
• Larger amounts of data
• Multi-year process per treatment
• Fast Track authority
• Significant increase in staffing approvals
Payer Challenges: Who Pays for these Treatments?

Types of Payers
• Employers
• Health plans
• Government: Medicare, Medicaid, Military
• Individuals: coverage, no coverage

Types of Management of Coverage
• Pricing
• Coverage language and guidelines
• Treatment sources / locations – Centers of Excellence (COE)
• Patient support and care services
• Pharma: price negotiation and outcome measures
• Risk pooling and risk transfer
Many first dollar payers can purchase insurance coverages on dollar amounts that go above certain levels on a per covered individual.

- Employers (self-funded): Stop-loss coverage
- Health Plans: Reinsurance
How Does Stop-loss & Reinsurance work?

**Employer Stop Loss**

Stop-loss insurance (also known as excess insurance) is a product that provides protection against catastrophic or unpredictable losses. It is purchased by employers who have decided to self-fund their employee benefit plans, but do not want to assume 100% of the liability for losses arising from the plans. Under a stop-loss policy, the insurance company becomes liable for losses that exceed certain limits called deductibles.¹

**Reinsurance**

A reimbursement system that protects insurers from very high claims. It usually involves a third-party paying part of an insurance company’s claims once they pass a certain amount. Reinsurance is a way to stabilize an insurance market and make coverage more available and affordable.²

Illustration of potential exposure for commercial claim for SCD

1. www.HCAA.com
2. www.healthcare.gov
Manufacturing: Pharma / Biotech Challenges

• Manufacturing: How are these made?
  ➢ Cell therapy: transfer live cells into the body
  ➢ Gene therapy: add new genes through inert vectors

• Pricing

• Value and Outcomes-based Agreements

• Research & Development

• Marketing
Today's Distribution of Treatments from Pharma & Biotech

**Distribution Contracts**
- Hospitals
- Physicians
- Pharmacies
- Specialty Pharmacies
- Intermediaries
  - PBM

**Selling to Influencers**
- Hospitals
- Physicians
- Consumers
- Intermediaries
  - PBM
Formularies

• Drug Selections by Therapeutic Categories

• Hospitals

• Pharmacy Benefit Managers (PBMs)

• PBM Formulary Evolution
  ➢ Early stage: optimal drug selection (1980 – 1990s)
  ➢ Current issues:
    ▪ Manufacturers purchasing formulary positions in return for rebates to PBMs and payers
    ▪ Industry challenges and rebates

• Growing Interest in Comparative Effectiveness Research
Society: Ways to Pay for High-Cost Treatments

• Life-Saving and Life-Extending Treatments

• Determinations of Value and Efficacy through Outcomes Tracking

• Affordability of:
  ➢ Commercial insurance coverages
  ➢ Medicare coverages
  ➢ Medicaid coverages
  ➢ Co-insured population

• **Industry Stakeholders Common Interests** – actions need to be taken!
Considerations for the Future in Meeting Patient Needs
Considerations for the Industry Stakeholders

1. Patients/Families
2. Provider & Clinicians
3. Payer Systems
4. Pharma/Biotech
Considerations for the Future: Patients & Families

1. Information Sources
   - Medical information sources
   - Patient advocacy groups
   - New pipeline treatments in clinical trials
   - Resources
   - Pharmaceutical company financial support programs

2. Insurance Coverages
   - Provider choices
   - Growing areas of personalized medicine
   - Integrated service models
   - Out-of-pocket financial support

3. Provider Treatment Options
   - Centers of Excellence (COE)
Considerations for the Future: Providers/Clinicians

1. COEs
   - Expanding clinical research to direct patient care
   - Concentrated areas of expertise
   - Marketing areas of clinical expertise
   - Centers of Excellence (COE)

2. Non-Medical Support
   - Reduce barriers to attracting patients
   - Concierge level of patient support
   - Non-medical issues to support taking care of patients

3. Affordability
   - Financial attention to affordability of high-cost treatments
Considerations for the Future: Payers

1. Planning
   - Coverage of Rare, Orphan, and Specialized Treatment
   - Government: Medicare, Medicaid, VA, Military
   - Private Commercial Health Insurance
   - Assessing and Monitoring the Pipeline of Treatments
   - Planning for a Multi-year Approach

2. COEs
   - Centers of Excellence (COE)
   - Marketing knowledge of treatment choices

3. Risk Management
   - Internal Pricing Expertise
   - Insurance Risk Contracting Alternatives:
     - Reinsurance
     - Stop-loss
     - Special risk pools or carveouts
   - Insurance Industry Knows How to Manage Specialized Risk
Considerations for the Future: Pharma/Biotech

1. R&D
   - Continued Scientific Advancements in Research + Development (R&D)
   - R&D: Pharma vs. Biotech
   - Manufacturing challenges
   - Pharma marketing expertise
   - Pricing: competition vs regulation

2. COEs
   - Concentrating patients at COEs for rare diseases
   - Supporting more integrated care service models

3. Results and Patient Outcomes
   - Value-based Agreements
   - Patient Outcome Tracking and Results
   - Financial Recoveries for Treatment Failures
In Conclusion

Opportunities to reduce access challenges

- Partnerships
- Collaborations
- Patient-Focused
- Participation of All Stakeholders
Thank you!