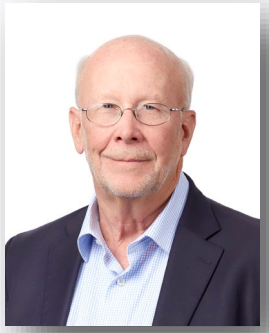
Multiple Challenges in Accessing Orphan Products for:

Patients, Families, and Clinicians



Presented by:

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Co-founder of Emerging Therapy Solutions® (ETS)

RARE DISEASE DAY®

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

THERAPY & MANUFACTURER	CONDITION	ACTUAL/ANTICIPATED APPROVAL DATE
Kymriah® (tisagenlecleucel; tisa-cel) | Novartis Pharmaceuticals	Acute lymphoblastic leukemia	Approved 8/30/2017
Yescarta® (axicabtagene ciloleucel; axi-cel) | Kite Pharma	Diffuse large B-cell lymphoma Non-Hodgkin lymphoma Follicular lymphoma	Approved 10/18/2017
Kymriah (tisagenlecleucel; tisa-cel) | Novartis Pharmaceuticals	Diffuse large B-cell lymphoma Non-Hodgkin lymphoma	Approved 5/1/2018
Tecartus® (brexucabtagene autoleucel; brexu-cel) | Kite Pharma	Mantle cell lymphoma Non-Hodgkin lymphoma	Approved 7/24/2020
Breyanzi® (lisocabtagene maraleucel; liso-cel) | Bristol Myers Squibb	Diffuse large B-cell lymphoma Follicular lymphoma Non-Hodgkin lymphoma	Approved 2/5/2021
Abecma® (idecabtagene vicleucel; ide-cel) | Bristol Myers Squibb/BBB	Multiple myeloma	Approved 3/26/2021
Tecartus (brexucabtagene autoleucel; brexu-cel) | Kite Pharma	Acute lymphoblastic leukemia	Approved 10/1/2021
Rethymic® (Allogeneic Processed Thymus Tissue) | Enzyvant Therapeutics	Congenital athymia	Approved 10/8/2021
Carvykti™ (ciltacabtagene autoleucel; cilta-cel) | Janssen/Legend Biotech	Multiple myeloma	Approved 2/28/2022
Yescarta (axicabtagene ciloleucel; axi-cel) | Kite Pharma	Large B-cell lymphoma in the second-line setting	Approved 4/1/2022
Kymriah (tisagenlecleucel; tisa-cel) | Novartis Pharmaceuticals	Follicular lymphoma	Approved 5/27/2022
Breyanzi (lisocabtagene maraleucel; liso-cel) | Bristol Myers Squibb	Large B-cell lymphoma in the second-line setting	Approved 6/24/2022
Omisirge® (omidubicel-onlv) | Gamida Cell	Hematologic malignancies (Blood cancers)	Approved 4/17/2023
Lantidra® (donislecel-jujn) | CellTrans, Inc.	Diabetes Type 1	Approved 6/28/2023
Amtagvi™ (Lifileucel) | Iovance Biotherapeutics	Metastatic melanoma	Approved 2/16/2024
Abecma – Moving up in line; **Carvykti** – Second line	Multiple myeloma	PDUFA Delayed PDUFA 4/5/24
Breyanzi (lisocabtagene maraleucel) | Bristol Myers Squibb	Chronic lymphocytic leukemia Small lymphocytic lymphoma Follicular lymphoma Mantle cell lymphoma	PDUFA 3/14/2024 PDUFA 5/23/2024 PDUFA 5/31/2024
Afami-cel (afamitresgene autoleucel; ADP-A2M4) | Adaptimmune Therapeutics	Synovial sarcoma	PDUFA 8/4/2024
Obe-cel (Obecabtagene autoleucel) | Autolus Therapeutics	Acute lymphoblastic leukemia	PDUFA 11/16/2024
Tab-cel® (tabelecleucel; ATA129/EBV-CTL) | Atara Biotherapeutics	Epstein-Barr virus-associated post-transplant lymphoproliferative disease	H2 2024
Afami-cel (afamitresgene autoleucel; ADP-A2M4) | Adaptimmune Therapeutics	Myxoid/round cell liposarcoma	H2 2024
Lete-cel (letetresgene autoleucel) | Adaptimmune Therapeutics	Synovial sarcoma	H2 2024
Lete-cel (letetresgene autoleucel) | Adaptimmune Therapeutics	Myxoid/round cell liposarcoma	H2 2024
Lifileucel (LN-144) | Iovance Biotherapeutics	Cervical cancer	2024 - 2025
Zevor-cel (zevorcabtagene autoleucel, CT053) | CARsgen Therapeutics	Multiple myeloma	2024 - 2025
Yescarta (axicabtagene ciloleucel; axi-cel) | Kite Pharma	Marginal zone lymphoma	2025

Approved & Investigational Gene Therapies Pipeline

THERAPY & MANUFACTURER	CONDITION	ACTUAL/ANTICIPATED APPROVAL DATE
Luxturna® *in-vivo* (voretigene neparvovec-rzyl) | Spark Therapeutics	Biallelic *RPE65* mutation	Approved 12/2017
Zolgensma® *in-vivo* (onasemnogene abeparvovec) | Novartis Pharmaceuticals	Spinal muscular atrophy	Approved 05/2019
Zynteglo® *ex-vivo* (betibeglogene autotemcel; beti-cel) | bluebird bio	Transfusion-dependent beta-thalassemia	Approved 8/17/2022
Skysona™ *ex-vivo (*elivaldogene autotemcel; eli-cel) | bluebird bio	Cerebral adrenoleukodystrophy	Approved 9/16/2022
Hemgenix® *in-vivo (*etranacogne dezaparvovec) | uniQure / CSL Behring	Hemophilia B	Approved 11/22/2022
Adstiladrin® *in-vivo* (nadofaragene firadenovec-vncg) | Ferring Pharmaceuticals	Bladder cancer	Approved 12/16/2022
Vyjuvek™ *Topical (*beremagene geperpavec; B-VEC; KB103) | Krystal Biotech	Dominant and recessive dystrophic epidermolysis bullosa	Approved 5/19/2023
Elevidys® *in-vivo* (delandistrogene moxeparvovec-rokl) | Sarepta Therapeutics	Duchenne muscular dystrophy	Approved 6/22/2023
Roctavian™ *in-vivo* (valoctocogene roxaparvovec-rvox) | BioMarin Pharmaceutical Inc.	Hemophilia A	Approved 6/29/2023
Casgevy™ *ex-vivo* (exagamglogene autotemcel; exa-cel) | CRISPR/Vertex	Sickle cell disease	Approved 12/8/2023
Lyfgenia™ *ex-vivo* (lovotibeglogene autotemcel; lovo-cel) | bluebird bio	Sickle cell disease	Approved 12/8/2023
Casgevy™ *ex-vivo* (exagamglogene autotemcel; exa-cel) | CRISPR/Vertex	Transfusion-dependent beta-thalassemia	Approved 1/16/2024
Libmeldy® *ex-vivo* (atidarsagene autotemcel; OTL-200) | Orchard Therapeutics	Metachromatic leukodystrophy	PDUFA 3/18/2024
Pz-cel *keratinocyte sheets* (prademagene zamikeracel; EB-101) | Abeona Therapeutics	Recessive dystrophic epidermolysis bullosa	PDUFA 5/25/2024
Elevidys® *in-vivo* (delandistrogene moxeparvovec-rokl) | Sarepta Therapeutics (expanded indication)	Duchenne muscular dystrophy	PDUFA 6/21/2024
Kresladi™ *ex-vivo* (marnetegragene autotemcel; RP-L201) | Rocket Pharmaceuticals	Leukocyte adhesion deficiency type I	PDUFA 6/30/2024
Fidanacogene elaparvovec *in-vivo* | Pfizer, Inc.	Hemophilia B	PDUFA Q2 2024
RP-L102 *ex-vivo* | Rocket Pharmaceuticals	Fanconi anemia	H1 2024
Elandocagene exuparvovec *in-vivo* (PTC-AADC; Upstaza EU) | PTC Therapeutics	Aromatic l-amino acid decarboxylase	2024
RGX-121 *in-vivo* | REGENEXBIO	Mucopolysaccharidosis type II	2024
botaretigene sparoparvovec *in-vivo* (AAV-RPGR) | MeiraGTx/Janssen Pharmaceuticals, Inc. laruparetigene zosaparvovec *in vivo* (rAAV2tYF-GRK1-RPGR) | Beacon Therapeutics	X-linked retinitis pigmentosa	2024
Lumevoq® *in-vivo* (lenadogene nolparvovec; GS010) | GenSight Biologics	Leber hereditary optic neuropathy	2024 - 2025
Giroctocogene fitelparvovec *in-vivo* | Pfizer and Sangamo Therapeutics	Hemophilia A	2025
fordadistrogene movaparvovec *in-vivo* (PF-06939926) | Pfizer, Inc.	Duchenne muscular dystrophy	2025
DTX-401 *in-vivo* (pariglasgene brecaparvovec) | Ultragenyx Pharmaceuticals	Glycogen storage disease type Ia	2025
DTX301 *in-vivo* | Ultragenyx Pharmaceutical	Ornithine transcarbamylase deficiency	2025
RGX-314 *in-vivo* | REGENEXBIO	Wet age-related macular degeneration	2025 - 2026
Zolgensma® *in-vivo* (onasemnogene abeparvovec-xioi) | Novartis Pharmaceuticals	Spinal muscular atrophy (expanded indications)	2025 - 2026
olenasufligene relduparvovec *in-vivo* (LYS-SAF302) | Lysogene UX111 (fka ABO-102) *in-vivo* | Ultragenyx Pharmaceuticals	Mucopolysaccharidosis type IIIa	2025 - 2026

Magnitude of Change

In Treatments and Costs

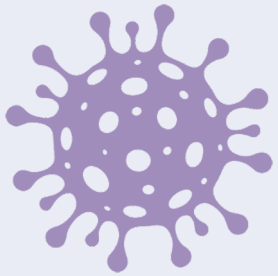
1900 – Today

RANGE OF COSTS	TIMEFRAME	SOURCES
$1 – $10 $11 – $100 $101 – $500	1900 – 1970	Plant Animal Chemical Biologics
$1 – $1,000 $1,000 – $100,000 $100,000 – $500,000	1970 – 2000	Early Specialty
$500,000 – $1M $1M – $2M $2M – $3M	2000 – Today	New Specialty Gene Therapy Cell Therapy Immunotherapy

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)

Distribution of Treatments from Pharma and Biotech

Distribution Contracts

Hospitals

Physicians

Pharmacies

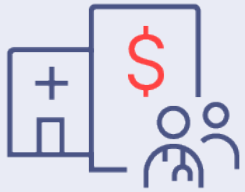
Intermediaries
PBMs, Payers

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

Insurance Coverage Alternatives	
Medical Benefit Coverage	Hospital in-patient Hospital out-patient Home Care Skilled Care Physician Services
Pharmacy Benefits	Out-patient Drugs Self-administered Drugs Some infusion Drugs PBM Influence
Claim Administration Variances	
Data Capture Variances	
Financial Influence Variances	

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

Payer 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

Illustration of potential exposure for commercial claim for SCD

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]

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
PBMs

Selling to Influencers

Hospitals

Physicians

Consumers

Intermediaries
PBMs

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!