Gene Therapy: The Future of Medicine in Battling Rare Diseases

Krupa Sivamurthy, Senior Director, Global Medical Affairs, Hematology, CSL Behring

Patrick Plues, Vice President, State Government Affairs, Biotechnology Innovation Organization (BIO)

#WIGDistrict2District
Gene Therapy
An Introduction

Krupa Sivamurthy, M.D.
Therapeutic Area Head Hematology
CSL Behring

Version 1. July 2021
• CSL Behring

• CSL Behring is a leading global biotherapeutics company that develops and delivers innovative specialty plasma-derived and recombinant therapies to patients around the world.
What is gene therapy?

Gene therapy is a transformative treatment that describes the technique of using genetic material to treat or cure a disease, with several agents already approved for use\(^1,2\)

What are the differences between gene therapy and gene editing?

**Gene therapy**¹,²

“involves the transfer of a therapeutic or working gene into specific cells of an individual in order to repair a faulty gene”

- Inserting a new gene to help fight a disease
- Replacing a mutated gene (that causes disease) with a normal copy of the gene
- Inactivating or deleting a mutated gene that is functioning incorrectly

**Gene editing**²⁻⁴

“Genetic engineering in which DNA is inserted, deleted, modified or replaced in the genome of a living organism”

- Protein-based (engineered nucleases, finger nucleases, transcription activator-like effector nucleases)
- RNA-based (CRISPR-CAS9)

CRISPR, clustered regularly interspaced short palindromic repeat.
History of gene therapy

The first gene therapies were approved by the FDA and EMA in the 2010s; rapid advancements are ongoing across a range of diseases.

AAV, adeno-associated virus; AdS, adenovirus type 5; CF, cystic fibrosis; CRISPR, clustered regularly interspaced short palindromic repeats; FIX, clotting factor IX; GT, gene therapy; hem, hemophilia; LPL, lipoprotein lipase; OTC, ornithine transcarbamylase; RNAi, RNA inhibition; rpe-65, 65 kilo-Dalton retinal pigment epithelial protein; RV, gammaretrovirus; SCID-ADA, severe combined immune deficiency due to adenosine deaminase deficiency; TIL, tumor-infiltrating lymphocytes.

References in slide notes.
Gene therapy approaches for the treatment of inherited monogenic diseases have predominantly focused on the delivery of a functional gene using a viral vector.

**Monogenic Diseases**

- Inherited conditions that arise from mutations on a single gene
- Retinal dystrophy*
- Spinal muscular atrophy*
- Beta thalassemia†
- Adenosine deaminase deficient severe combined immunodeficiency†
- Hemophilia

**Viral vectors**, which are inactivated and lack the ability to reproduce, are commonly used to deliver genetic material into cells – this can be done *in vivo* or *ex vivo*1,2

---

* FDA- and EMA-approved gene therapy treatments are available. 2. FDA- and EMA-approved gene therapy treatments are available.

Gene therapy has demonstrated durable benefit to patients from a single administration.

The goal of gene therapy for inherited diseases is to achieve **durable expression** of the therapeutic gene or “transgene” at a level sufficient to ameliorate or cure disease symptoms with minimal adverse events.

AAV, adeno-associated virus.
Hemophilia B is a rare, hereditary, bleeding disorder

Hemophilia B results from the absence or deficiency of coagulation factor IX (FIX)\(^1\)–\(^3\)

**FIX plays a key role in the initiation and propagation of a blood clot****\(^4,5\)**

Hemophilia B prevalence at birth is estimated at 5 cases per 100,000 males, globally\(^1\)

**Hemophilia B comprises approximately 15–20% of all hemophilia cases\(^1\)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated prevalence of hemophilia B (all severities) per 100,000 male births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data from national patient registries, 1991–2010(^2)</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>5.5</td>
</tr>
<tr>
<td>UK</td>
<td>4.9</td>
</tr>
<tr>
<td>Canada</td>
<td>4.3</td>
</tr>
<tr>
<td>Age-adjusted data from HTCs 2012–2018(^3)</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>3.7</td>
</tr>
</tbody>
</table>

HTC, hemophilia treatment center.
More than two-thirds of PWHB have severe or moderate disease

<table>
<thead>
<tr>
<th>Severity of disease</th>
<th>Proportion of PWHB with each phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>22.8%</td>
</tr>
<tr>
<td>Moderate</td>
<td>37.5%</td>
</tr>
<tr>
<td>Severe</td>
<td>39.1%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

PWHB, people with hemophilia B.
Severe hemophilia B is characterized by spontaneous and/or traumatic bleeding into joints, muscles, and internal organs.\textsuperscript{1–3}

If inadequately treated, hemophilia causes chronic damage to the musculoskeletal system.\textsuperscript{1–3}

The standard of care for hemophilia B is lifelong treatment with coagulation factor replacement

There is no cure for hemophilia B and PWH typically require chronic therapy for prevention of severe bleeding\(^1\)\(^–\)\(^3\)

**Prophylactic (regular) factor replacement** is the standard of care for severe hemophilia B to prevent or reduce bleeds\(^4\)\(^–\)\(^7\)

**Episodic (on-demand) factor replacement** is given to treat bleeding episodes, e.g. at the time of surgery\(^4\)\(^–\)\(^7\)

---

PWH, people with hemophilia.

Management of hemophilia B imposes a significant economic burden on the healthcare system.

Beyond treatment costs, PWH may also require hospitalization and/or outpatient care\(^1\text{–3}\).

**Total adult lifetime cost** per patient with severe and moderately severe hemophilia B in the US:

>\textbf{$>$20 million}\(^1\)

- FIX treatment accounts for the majority (>90%) of the cost.
- Non-drug costs of hemophilia B management include hospitalizations (due to bleeding, orthopedic surgery, or ICH), and outpatient visits\(^1,2\).

Cost of hemophilia B management increases with the severity of disease\(^4\).

---


\(\text{FIX, factor IX; ICH, intracranial hemorrhage; PWH, people with hemophilia.}\)
Families/caregivers of PWH face employment challenges and the psychological burden of caregiving.

In the B-HERO-S study, evaluating caregivers of PWH:

- 89% reported that caring for children with hemophilia B has negatively affected their work life.
- ~1/3 left employment to care for children with hemophilia B.

PWH, people with hemophilia.
Hemophilia B may have a negative impact on formal education, employment, and career choice\(^1\textsuperscript{–}^3\)
Advances in treatment have improved mortality and reduced major complications; however, new therapeutic options are needed.

Patient-relevant outcomes

- Prevent premature death
- Improved quality of life; participation in activities of daily living
- Ability to engage in low-risk activities
- Participation in work, career and family life without restriction
- Freedom from spontaneous bleeds
- Attain ‘normal’ mobility
- More unrestricted lifestyle
- Not dependent on specialized healthcare

Health equity

- Survival
- Minimal joint impairment

Functional cure

- Undergo surgery or major trauma without additional intervention
- Normal hemostasis

Clinical outcomes

- Optimized health and well-being

Model of milestones towards normal hemostasis:

Treating & Curing Disease: The Promise of Gene & Cell Therapy

WIG Healthcare & Technology Summit
October 2, 2021

Patrick Plues
Vice President, State Government Affairs
• World's largest trade association of biotechnology companies, academic institutions, state biotechnology centers and related organizations
• Based in Washington, D.C. with members across the US and in over 30 countries
• Membership includes large multinational companies, as well as small-to-medium size companies
• Members are involved in three core areas:
  1. Healthcare
  2. Agricultural
  3. Environment
New Therapies Require Novel Approaches to Patients Access

SCIENCE and the REGULATORY APPROVAL POLICY for Genomics Medicine... Have ACCELERATED...

BUT REIMBURSEMENT POLICY LAGS BEHIND!

Short—even single dose—treatment regimens yield lasting health benefits, but large single payments will challenge the current reimbursement system
New Therapies Require Novel Approaches to Patients Access

Challenges:

- Different from traditional drugs
  - Usually very small patient population
  - Often single episode of care instead of chronic therapy
  - Expensive to administer
  - Potentially curative
- Further exacerbated by structural challenges
  - FFS system
  - Medicaid budgeting
  - Limited long-term clinical data on transformative therapies
## Innovative Payment Models

<table>
<thead>
<tr>
<th>Outcomes-Based Arrangements</th>
<th>Payments in Installments</th>
<th>Outcomes-Based with Installments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Payor reimburses manufacturers for treatments based on how successful the patient responds to therapy with pre-determined clinical endpoints</td>
<td>Payor reimburses manufacturers over a predetermined period of time to avoid significant up-front costs</td>
<td>Payor reimburses the manufacturer over time and the payments are portioned out based on how successful the patient responds to therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Warranty Model</th>
<th>Risk Pooling / Reinsurance</th>
<th>Subscription Model “Netflix Model”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer pays for follow-up treatments if they become necessary because treatment fails to deliver on promise</td>
<td>Payors and government set aside a portion of a healthcare budget into a dedicated fund that covers both government and non-government payors</td>
<td>Payor reimburses the manufacturer a set fee for unlimited access to a therapy</td>
</tr>
</tbody>
</table>
Challenges to Innovative Payment Models

<table>
<thead>
<tr>
<th>FEDERAL PRICE REPORTING*</th>
<th>ANTI-KICKBACK STATUTE</th>
<th>PORTABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solutions</strong></td>
<td><strong>Solutions</strong></td>
<td><strong>Solutions</strong></td>
</tr>
<tr>
<td>• State Plan Amendments</td>
<td>• Demonstration Waivers</td>
<td>• Commercial Contracting Strategies</td>
</tr>
<tr>
<td>• Demonstration Waivers</td>
<td>• OIG Guidance</td>
<td>• Annuity Fund</td>
</tr>
<tr>
<td>• Federal Legislation</td>
<td>• Safe Harbor in Federal Legislation</td>
<td>• Federal Legislation</td>
</tr>
</tbody>
</table>

*Reporting specific to Medicaid best price and average manufacturer price
Biopharmaceutical companies and payers are already coming together in creative ways to address the challenges of a 21st Century innovative health ecosystem.

BIO strongly supports innovative and voluntary alternative payment structures between biopharmaceutical companies and payers (commercial & public).

BIO believes value, outcomes, and/or indication-based arrangements, and alternative payment structures all have merit.

Policymakers and regulators must understand the variety of these arrangements and provide flexibility to ensure new models can be designed as healthcare evolves and new therapies are developed.
Resources To Help You Better Understand Genomics Medicine

General Information on Genomics Medicine

• US Food & Drug Administration
  https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/

• Biotechnology Innovation Organization (BIO)
  https://bio.org/genome-editing-toolkit

• Alliance for Regenerative Medicine (ARM)
  https://alliancerm.org/

Alternative Payment Models

• M.I.T. New Digs
  https://newdigs.mit.edu/papers-publications

• Duke Margolis Center for Health Policy
  https://healthpolicy.duke.edu/
Questions To Consider

• Is your state’s Medicaid department familiar with gene therapies on the market and which ones are in the pipeline?

• Has your state’s Medicaid department begun to consider innovative payment models for new types of therapies?
<table>
<thead>
<tr>
<th>Clinical Trials in Genomics Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncology</strong></td>
</tr>
<tr>
<td><strong>Infectious Disease</strong></td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
</tr>
<tr>
<td><strong>Gastroenterology</strong></td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
</tr>
<tr>
<td><strong>Genitourinary Disorders</strong></td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td><strong>Endocrine / Metabolic Disorders</strong></td>
</tr>
<tr>
<td><strong>Ophthalmology</strong></td>
</tr>
<tr>
<td><strong>Geriatric Diseases</strong></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
</tr>
<tr>
<td><strong>Lymphatic Diseases</strong></td>
</tr>
<tr>
<td><strong>Immunology / Inflammation</strong></td>
</tr>
<tr>
<td><strong>Ear Disorders</strong></td>
</tr>
<tr>
<td><strong>Dermatology</strong></td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
</tr>
</tbody>
</table>
EvaluatePharma Study on Largest Genetic Medicine Pipeline & Companies by 2024

Fig 2. Top 20 indications, based on 2024 forecasted sales.

Sales Forecasts ($ millions)

<table>
<thead>
<tr>
<th>Indication</th>
<th>2017</th>
<th>2024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>155</td>
<td>4,021</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>7</td>
<td>3,872</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>884</td>
<td>2,614</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>1,109</td>
<td>1,730</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>1,217</td>
<td>1,309</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>1,237</td>
<td>1,329</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1,073</td>
<td>1,382</td>
</tr>
<tr>
<td>Melanoma</td>
<td>946</td>
<td>1,046</td>
</tr>
<tr>
<td>Rare eye disorders</td>
<td>856</td>
<td>911</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>827</td>
<td>911</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>755</td>
<td>785</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>735</td>
<td>735</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>686</td>
<td>686</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>582</td>
<td>582</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>573</td>
<td>573</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>504</td>
<td>504</td>
</tr>
<tr>
<td>Gastro-intestinal fistula</td>
<td>499</td>
<td>499</td>
</tr>
<tr>
<td>Dry eye-related macular degeneration</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Sanfilippo syndrome (mucopolysaccharidoses III)</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

Fig 3. Top 20 companies in the field of cell, gene and nucleic acid therapies, based on 2024 sales forecasts.


Source: https://biopharmadealmakers.nature.com/users/9880-biopharma-dealmakers/posts/51056-next-generation-therapeutics-cell-and-gene-therapy-gathers-pace
State Approaches

OUTCOMES-BASED ARRANGEMENTS

Some predetermined clinical endpoints include reduced hospitalization costs and greater patient adherence
States also exploring hybrid approaches such as outcomes-based models and payments over time.
State pays an established fee per month for unlimited amount of a drug

(ideal for curative therapies)