AMCP MANAGED CARE & SPECIALTY PHARMACY ANNUAL MEETING 2019

specialty CONNECT 2019

focus on gene therapy

Welcome

Mitzi Wasik

AMCP President

2018-2019

AMCP Academy of Managed Care Pharmacy®

Meet Today's Moderator

Clifford Goodman, PhD

Senior Vice President & Director

Lewin Center for Comparative Effectiveness Research

Falls Church, Virginia

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- At your seats, final program and instructions on process CPE credit
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Today's Agenda

Timing	Agenda
1:00 pm – 1:15 pm	Welcome and Introductions
1:15 pm – 2:15 pm	Didactic Presentation: Introduction to Gene Therapy: Key Terms, Concepts, and International Perspectives
2:15 pm – 3:00 pm	Didactic Presentation: Developments, Research, Pipeline, and Applications of Gene Therapy
3:00 pm – 3:20 pm	Networking Break
3:20 pm – 4:20 pm	Didactic Presentation: Financial Models to Manage Drug Spend of Gene Therapy
4:20 pm – 5:20 pm	Panel Discussion: Perspectives in Gene Therapy Management
5:20 pm – 5:30 pm	Closing Remarks
5:30 pm – 6:30 pm	Networking Reception (Marina Foyer)

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Introduction to Gene Therapy: Key Terms, Concepts, and International Perspectives

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  - Session-specific attendance code
- Complete and submit session evaluation **no later than Monday, April 29, 2019 (5:00 PM ET)**
- Information shows in CPE Monitor approximately 72 hours after submission completion

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Learning Objectives

- Explain the key terms and concepts of gene therapy.
- Describe investigational gene therapy strategies and how they may influence manifestations of various disorders.
- Compare and contrast various types of vectors used in the delivery of gene therapy.
- Describe the experience of gene therapies internationally.

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Faculty

Sophie Schmitz, BA, MA
Managing Partner
Partners4Access
Hilverum, Noord-Holland
Netherlands

Learning Objectives

1. **Explain the key terms and concepts of gene therapy**
2. Describe investigational gene therapy strategies and how they may influence manifestations of various disorders
3. Compare and contrast various types of vectors used in the delivery of gene therapy
4. Describe the experience of gene therapies internationally

Gene Therapy Defined

The American Society of Gene and Cell Therapy: Gene Therapy definition[1]:

*"The **introduction, removal, or change in the content of a person's genetic code** with the goal of treating or curing a disease. Moreover, it is a set of strategies that modify the expression of an individual's genes or repair abnormal genes. **Each strategy involves the administration of a specific nucleic acid (DNA or RNA). Nucleic acids are normally not taken up by cells, thus special carriers, so-called 'vectors' are required. Vectors can be of either viral or non-viral nature".***

Education | ASGCT - American Society of Gene & Cell Therapy. https://www.asgct.org/education. Accessed February 18, 2019.

The Genome and Gene Manipulation Technology

- **Every cell has a copy of the genome** in the **nucleus** of the cell
- The **genome is made of DNA**
- It can be viewed as a '**recipe book**' with different sections 'coding' for different 'recipes' needed in the cell and the body
- Not all of this book codes for recipes, some codes for **instructions when to use a certain recipes**
- If a gene is expressed, the **genetic code** instructs for this gene to be used in this cell type, which makes up part of a certain tissue, e.g. skin cell
- **Expressed genes can be silenced, defective genes can be replaced or edited**
- Silencing genes can be done using **antisense technology**. These changes gene expression but is **not considered gene therapy in the traditional sense**, as genetic code itself is not being changed

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How Does Gene Therapy Work?

Normal Cells	*Disease State*	*Gene Therapy*
DNA →	Defective DNA →	Functional DNA →
RNA →	Defective RNA	Functional RNA →
Protein	↙ ↘	Functional Protein
	Defective Protein / No Protein	

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So What is Cell Therapy?

The American Society of Gene and Cell Therapy: Cell Therapy definition:

*"**Administration of living whole cells** for the patient for the treatment of a disease. The origin of the **cells can be from the same individual** (autologous source) or **from another individual** (allogeneic source). Cells can be **derived from stem cells**, such as **bone marrow** or **induced pluripotent stem cells (iPSCs)**, reprogrammed from skin fibroblasts or adipocytes. Stem cells are applied in the context of bone marrow transplantation directly. Other strategies involve the application of more or less mature cells, differentiated in vitro (in a dish) from stem cells."*

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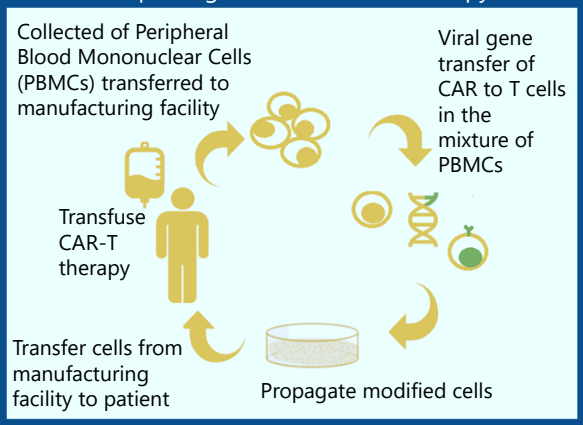
Education | ASGCT - American Society of Gene & Cell Therapy. https://www.asgct.org/education. Accessed February 18, 2019.

...and Gene-modified Cell Therapy?

Chimeric Antigen Receptor T cell (CAR-T) therapies are an example of gene-modified cell therapy



- Genetic modification of cells outside the patient before reintroducing them back. Cell therapy does not necessarily require the gene-modification of the cells
- T-Cells play a central role in cell-mediated immunity. The National Cancer Institute definition of CAR-T therapy
- *"A type of treatment in which a **patient's T cells are changed in the laboratory so they will attack cancer cells**..."*

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1. Sharpe M et al Disease Models & Mechanisms. 2015. http://dmm.biologists.org/content/8/4/337. Accessed February 18, 2019.
2. How CAR T-Cell Therapy Works - Dana-Farber Cancer Institute | Boston, MA. https://www.dana-farber.org/cellular-therapies-program/car-t-cell-therapy/how-car-t-cell-therapy-works/. Accessed February 18, 2019.

Genetic "Defects"

Monogenic Diseases

- Modifications in a **single gene** occurring in all cells of the body
- >10,000 monogenic diseases worldwide
- Often rare diseases
- Sickle cell anaemia, cystic fibrosis (CF)

Polygenic/Multigenic Diseases

- Caused by **multiple genes**
- More complex
- May have disease associated mutations
- Large environmental component

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American Society of Gene & Cell Therapy. https://www.asgct.org/education. Accessed February 18, 2019.

Inherited or Acquired Diseases

Inherited Diseases

- **Recessive disorders** have mutations in both of copies of the gene
- **Dominant disorders** have mutations in one copy
- Difficult to treat dominant disorders by adding genes

Acquired Diseases

- Develop during a patient's life due to **random mutations**
- Many **cancers** have a multitude of acquired mutations

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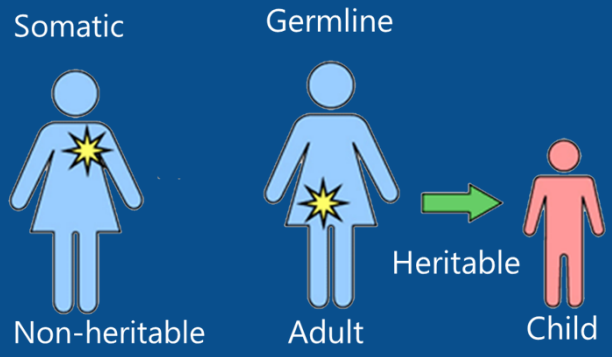
Germline–Raising Ethical Questions



Major concern late 2018 CRISPR technology used to modify human embryos

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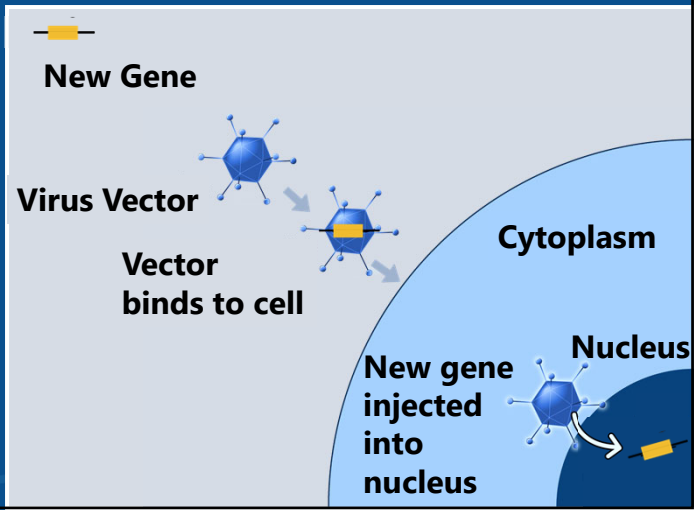
https://edition.cnn.com/2018/11/28/health/genetic-editing-he-speaks-int/index.html. Accessed February 18, 2019.
https://www.theguardian.com/science/2018/nov/26/worlds-first-gene-edited-babies-created-in-china-claims-scientist. Accessed February 18, 2019.

Vectors Can Be Divided into Two Types

A. Viral Vectors
- Viruses have evolved to **insert their genetic material into cells** in order for it to be expressed
- Viral vectors are **engineered** versions of viruses occulting in nature
- These types of vectors are used in the vast majority of late-stage developed gene therapies

B. Non-viral Vectors
- Use other technologies to deliver DNA into the cell
- E.g. **Electroporation** which makes the cytoplasm more permeable

Viral vectors infect cells and inject a "new gene" into the nucleus



Source: Partners4Access

Gene Therapy: *Ex Vivo* and *In Vivo*

Both need vectors to introduce the gene into the cells

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Ex Vivo

- Practicalities of this over *in vivo* include:
  - Collecting the cells
  - Culturing the cells
  - Manipulating the cells with the gene therapy
  - Transplantation of these cells as a gene-modified cell therapy back into the patient
- Such techniques are useful in **hematopoietic stem / progenitor cells (HSPCs)**
- Ideal vectors for *ex vivo:* **retrovirus and lentivirus**

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In Vivo

- Potentially easier than *ex vivo* with respect to practicalities, and regulatory hurdles, but this is dependant on disease area
- Things to consider are inadvertent germline modification, and immune responses to vector components
- Such techniques are useful in solid tissues like the CNS, liver, muscle and retina
- Adeno-associated vector (AAV)
  - The different subtypes have different tropisms which make them suitable for targeting different cells

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1. Addgene: Adeno-associated virus (AAV) Guide. https://www.addgene.org/viral-vectors/aav/aav-guide/. Accessed February 18, 2019.
2. Manufacturing of AAV Vectors for Gene Therapy. GEN - Genetic Engineering and Biotechnology News. June 2017. https://www.genengnews.com/magazine/297/manufacturing-of-aav-vectors-for-gene-therapy/. Accessed March 13, 2019.

Learning Objectives

1. Explain the key terms and concepts of gene therapy
2. **Describe investigational gene therapy strategies and how they may influence manifestations of various disorders**
3. Compare and contrast various types of vectors used in the delivery of gene therapy
4. Describe the experience of gene therapies internationally

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Recent Progress in Disease Areas Targeted *In Vivo*

Cell type	Disease	Latest vector
CNS	Parkinson's	AAV2
	AADC	AAV2
	Spinal muscular atrophy	AAV9
Liver	Haemophilia A and B	multiple AAV serotypes
	Hunter's syndrome	AAV2/6
Muscle	Lipoprotein lipase deficiency	AAV1
Retina	arCSRD	AAV2

- *In vivo* gene therapies advances have mainly used the **AAV vector** in the latest advances
- **Different serotypes of this vector** exist which have **tropisms to different tissues**

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Naso MF, et al. *BioDrugs*. 2017;31:317-334.
Dunbar CE, et al. *Science*. 2018;359(6372).

Recent Progress in Disease Areas Targeted *Ex Vivo*

Cell type	Disease	Vector
T-cells	ALL (Adult and Paediatric)	Retrovirus/Lentivirus
	Diffuse large B-cell lymphoma	Retrovirus/Lentivirus
	CLL	Retrovirus/Lentivirus
	Multiple Myeloma	Retrovirus/Lentivirus
	Synovial sarcoma	Retrovirus
Hematopoietic stem and progenitor cells	β-Thalassemia	Lentivirus
	Sickle cell anemia	Lentivirus
	Wiskott-Aldrich syndrome	Retrovirus/Lentivirus
	Adenosine deaminase deficiency	Retrovirus/Lentivirus
	SCID	Lentivirus
	Adrenoleukodystrophy	Lentivirus
	Metachromatic leukodystrophy	Lentivirus

- *Ex vivo* gene therapy advances have used both **retroviral and lentiviral** vectors
- The merits of each type are discussed later. Retroviral vectors generally refers to **γ-retroviral vectors**

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Dunbar CE, et al. *Science*. 2018;359(6372).

There are 5 Main Considerations for Investigational Gene Therapy Strategies

1. **The disease** characteristics
2. **The science** chosen to suit this
3. **The logistics** of administering and manufacturing
4. **The safety and efficacy**, particularly long-term
5. **The sustainability**

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1. Investigational Gene Therapy Considerations – The Disease

- **Monogenic vs polygenic diseases**
  - Are there any genes with a stronger association e.g. Parkinson's?
  - What is the genetic variation within the disease?
  - What is the epidemiology of the disease?
- **Disease type**
  - What is the cell type which needs to be transfected?
  - Is it a rare disorder?
  - Is it a paediatric immune disorder?
  - Is this amenable to *in vivo* or *ex vivo*?
- **Existing treatment and diagnosis**
  - What is the standard of care?

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Source: Partners4Access

2. Investigational Gene Therapy Considerations – The Science

- **The gene manipulation technology**
  - Is the disease dominant or recessive?
  - Does it need to be gene replacement or editing?
- **Vector type**
  - Will the gene fit in the vector, e.g., Haemophilia?
  - What levels of expression will be therapeutic?
- **Vector targeting**
  - Which tissue?
  - Delivery method?

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Source: Partners4Access

3. Investigational Gene Therapy Considerations – The Logistics

- **The manufacturing is a complex process**
  - How will the vectors be made?
  - If *in vivo*, how will these vectors be made into something which be delivered?
  - If *ex vivo*, how will the patients cells be removed and modified?
- **Administration**
  - If *in vivo*, how will the vectors be delivered?
  - If *ex vivo,* can the modified cells be transported to the patient, and how will the cell therapy be administered?

A service model is more appropriate for gene therapy, with manufacturing and operations at the front line, and the supply chain being much more involved

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Source: Partners4Access

4. Investigational Gene Therapy Considerations – The Safety and Efficacy

- **Short-term and long-term safety**
  - Is there a risk of short term immune response to the viral vector?
  - Other immune response?
  - Long term, what is the risk of insertional mutagenesis and oncogenesis?
- **Long-term efficacy**
  - Is the therapy curative?
  - How can efficacy be tracked long term?

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Source: Partners4Access

5. Investigational Gene Therapy Considerations – The Sustainability

- **Gene therapies are extremely expensive, and many are in development**
  - How sustainable is this for healthcare systems?
  - What happens when therapies for the less rare indications are developed?
- **Their efficacy is uncertain**
  - How can this be worked into pricing and reimbursement, with limited data?
- **Curative therapies are a paradigm shift**
  - Will payments be made up front or over the course of the rest of the patients life?

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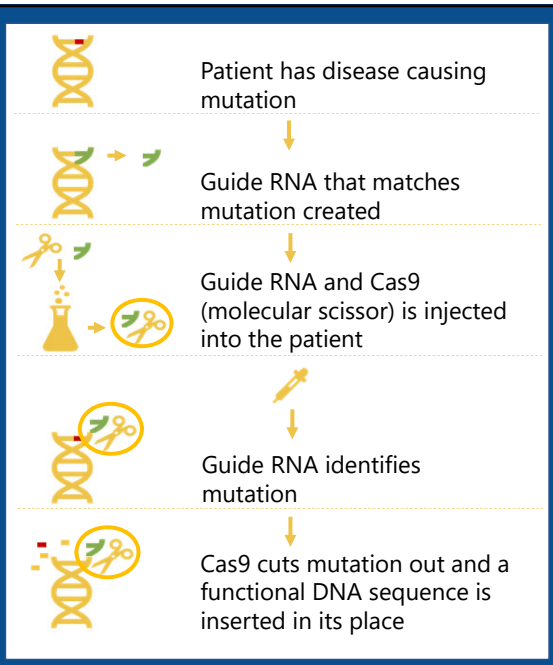
Source: Partners4Access



What is CRISPR

- Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a **gene editing technology which allows the editing, replacement, or deletion of genes**
  - The applications of this are broad
- **Late phase trials are predicted in 5 years**
  - Regulatory issues?
- The **potential impacts of such a bacterial system on humans is unknown,** there are also issues with **unwanted editing**
- These systems can be **delivered via viral and non-viral vectors**

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What Is CRISPR? https://www.cbinsights.com/research/what-is-crispr/. Accessed February 18, 2019
Maeder ML, Gersbach CA. Molecular Therapy. 2016;24:430-446.

Gene Editing Applications and Base Editing Technology

- There a **multiple gene editing applications** which can achieve the same thing, these include **CRISPR/Cas9, CRISPR/Cpf1, ZFNs, Meganucleases** and **TALEN**
- However the CRISPR/Cas9 and CRISPR/Cpf1 systems achieve this **most effectively**, and have as a result come to the forefront
- **Base-editing applications** are the latest development in this area, and use facets of CRISPR-Cas9 based systems
  - These systems have the advantage of not cutting the whole DNA strand, which invokes a more complicated repair and editing process
  - It is also suggested that base editing is easier to deliver and create fewer unwanted changes

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Genome Editing—Principles and Applications for Functional Genomics Research and Crop Improvement. https://www.tandfonline.com/doi/full/10.1080/07352689.2017.1402989. Accessed March 14, 2019.
Maeder ML, Gersbach CA. *Molecular Therapy*. 2016;24:430-446.
Marx V. *Nature Methods*. 2018;15:767.

Timeline of Advancements in CRISPR and Gene Editing Technologies

2018

- *Year of progress for CRISPR*
- *August 2018 - 18 studies listed on clinical trials.gov*

2019

- *January 2019 – 24 studies listed on clinical trials.gov*
- *Set to increase*

2020

- *Other gene editing systems e.g., base editing technology*

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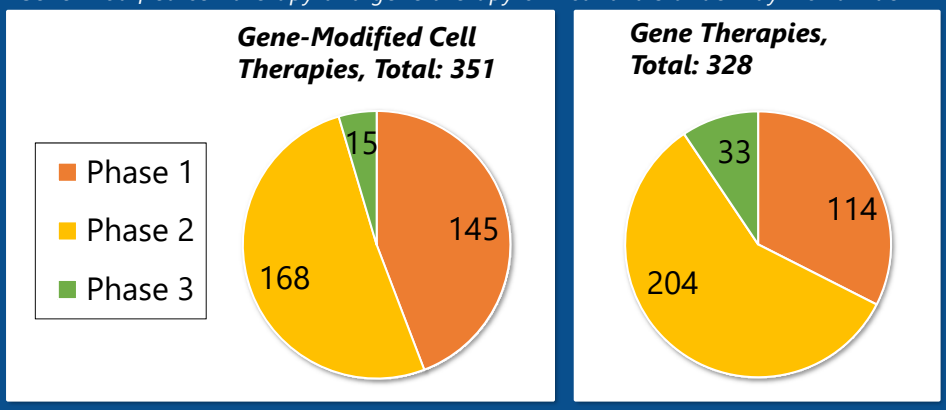
www.clinicaltrials.gov
Marx V. *Nature Methods*. 2018;15:767.

The Pipeline

*Gene-modified cell therapy and gene therapy clinical trials underway worldwide**



*Clinical trials underway worldwide by end of Q3 2018 in the respective categories, from the Alliance of Regenerative Medicine

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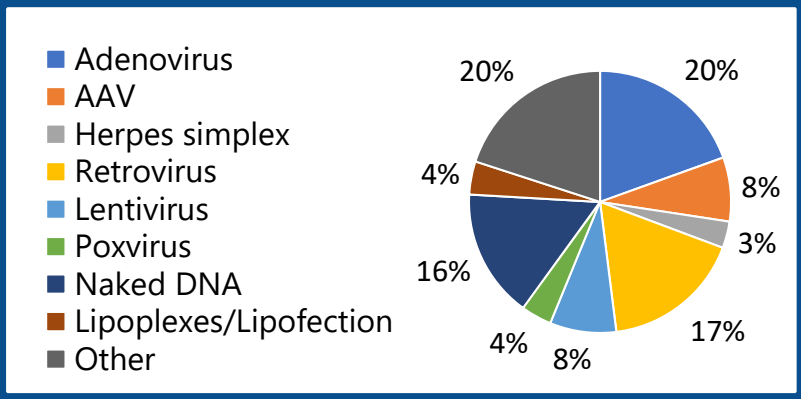
Alliance of Regenerative Medicine. https://alliancerm.org/publication/q3-2018-data-report/. Accessed February 18, 2019.

Many Viral and Non-viral Vectors

*Clinical trials by vector type**



- **Viral vectors** have been used in the majority of clinical trials to date
- **2,805 gene therapy trials** (August 2018)

**All clinical trials in gene therapy conducted to date, provided by the Journal of Gene Medicine. Last updated on August 2018*

1. Gene Therapy Clinical Trials Worldwide. http://abedia.com/wiley/index.html. Accessed February 18, 2019.
2. Ginn SL, et al. *J Gene Med*. 2018;20(5):e3015.

Learning Objectives

1. Explain the key terms and concepts of gene therapy
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Ex Vivo Viral Vectors—An Overview

Type	Vector	Genome integration	Tissues Effective	Insert Capacity (kb)	Features
Virus	Retrovirus	Yes	Broad host range (dividing)	8	Only transfects dividing cells
Virus	Lentivirus	Yes	Broad host range	8	Low cytotoxicity

- Lentiviruses are a subclass of retrovirus, which unlike retroviral vectors can transfect actively dividing cells, which addition to their better safety profile make them useful
- Lentiviral and retroviral vectors are used in the clinic, and are useful for cell therapy because they integrate into the genome and transfected cells can then divide without losing the gene, this makes these types of vectors suitable to transfecting HSPCs and immune cells, as well as in cell therapies

Adenovirus vs. AAV, Which Should You Use? Vector Biolabs. https://www.vectorbiolabs.com/adenovirus-vs-aav/. Accessed March 13, 2019.
Adeno-Associated Virus (AAV) Provides Advantages for Gene Delivery. Cell Biolabs, Inc. https://www.cellbiolabs.com/news/adeno-associated-virus-aav-provides-advantages-gene-delivery. *Accessed March 13, 2019.*
Naso MF, et al. *BioDrugs. 2017;31(4):317-334.*

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In Vivo Viral Vectors—An Overview

Type	Vector	Genome integration	Tissues Effective	Insert Capacity (kb)	Features
Viral	Adenovirus	No	Broad host range	<7.5	Strong immunogenicity
Viral	AAV	No	Relatively broad host range	<4	Slow expression onset

- The principal difference between retroviral and lentiviral vectors and the adenoviral and AAV vectors is genome integration. The latter two do not integrate into the host cells genome
- Non-integration into the host genome means concatomers can exist long term in non-dividing cells but are lost in dividing cells
- AAV is preferred due to high titer, mild immune response and ability to infect a broad range of cells. Adenovirus is effective for research purposes, but AAV viral vectors are the state of the art in the clinic
- Adenoviral vectors exhibit strong immunogenicity which is their main limitation

Adenovirus vs. AAV, Which Should You Use? Vector Biolabs. https://www.vectorbiolabs.com/adenovirus-vs-aav/. Accessed March 13, 2019.
Adeno-Associated Virus (AAV) Provides Advantages for Gene Delivery. Cell Biolabs, Inc. https://www.cellbiolabs.com/news/adeno-associated-virus-aav-provides-advantages-gene-delivery. *Accessed March 13, 2019.*
Naso MF, et al. *BioDrugs. 2017;31(4):317-334.*

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Non-viral Vectors—An Overview

Type	Vector	Genome Integration	Tissues Effective	Insert Capacity (kb)	Features
Non-viral	Naked DNA	Endocytosis	Variety	high	Simple, low transfection efficiency
Non-viral	Lipoplexes	No	Variety	high	Med. transfection efficiency, some immunogenicity

- Viral vectors utilize the virus vector "capsid" to deliver the genes into the cell. This is a sophisticated mechanism which is difficult to replicate
- There are many different types of non-viral vectors
  - Naked DNA (the gene on its own) is broken down by enzymes outside or inside cells
  - DNA is often packed onto "cargo" molecules which prevent this breakdown
  - Lipoplexes have similar molecules to the cell membrane and can 'fuse' with it depositing the gene inside
- Non-viral delivery methods aim to enhance delivery by helping the vector cross the cell membrane. There are a variety of methods including:
  - Electroporation, sonoporation, 'gene guns', magnetofection, hydrodynamic delivery

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Finer M, Glorioso J. *Gene Therapy.* 2017;24(1):1-2.
Lundstrom K. *Diseases.* 2018;6(2).

A Comparison of Non-viral Vectors with Viral Vectors

	Non-viral vectors	Viral Vectors
Delivery	Require a separate delivery method to introduce naked DNA into the cell	Natural or genetically modified mechanism 'built in' to viral vectors
Short-term efficacy	Difficult to achieve transfection into cells in large numbers	Higher transfection rates possible
Immune response	Far less immunogenic	Existing immunity to AAV vectors and risk of immune response
Carcinogenicity	Do not integrate into the genome and as such have low oncogenic potential	Some integrate into the genome which may cause oncogenic mutations
Other safety issues	Bacterial origin of plasmids is problematic for a number of reasons	
Long term efficacy	Transgene expression is diluted by cell division, since the plasmid is not integrated into the genome	Integrating viral vectors are not diluted by cell division

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Hardee CL, et al. *Genes (Basel).* 2017;8(2).

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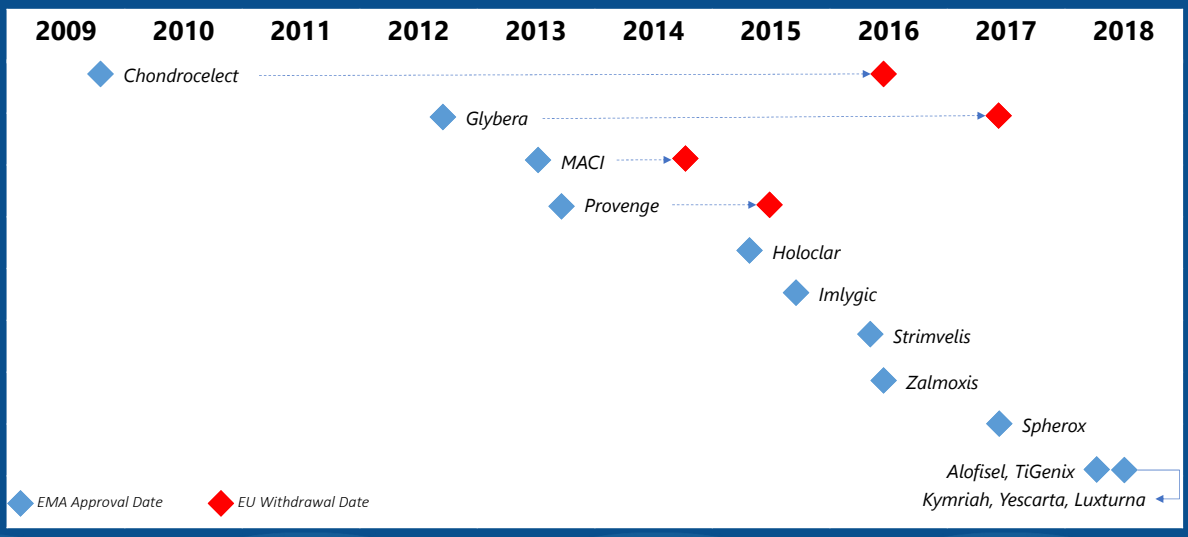
We Are on a Precipice....

Success in Europe is Limited to Date



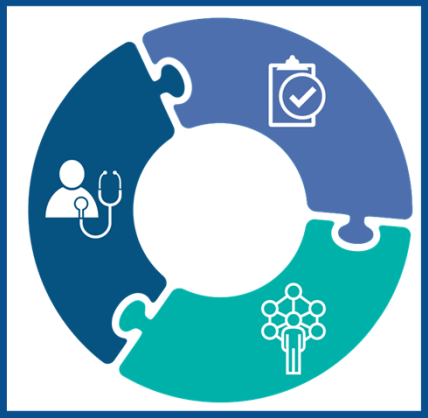
Source: Partners4Access

*Brand names are being used for educational purposes only

Policy, Data, and Market Challenges

1 Data

- Ability to track data
- Ability to communicate and share data across organizations



2 Policy

- Price reporting implications
- Revenue recognition

3 Market Dynamics

- Fragmented market
- Patient movement from one health plan to another

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Payer Challenges

Payer Challenges

One-time treatment with benefit and cost savings accrued

- *Budgets in the short-term*
- *Cost-savings vs increases over the long-term*

Disproportionate cost to some payers

- *Unmanageable cost to individual payers*
- *Patients moving between payers may make this harder to solve*

Uncertainties over long-term benefits

- *Short-term data*
- *Uncertainties caused by differing individual patient responses and long-term side effects*

Overall affordability

- *Opportunity to treat many genetic rare diseases with gene therapy may lead to unsustainable long-term costs*

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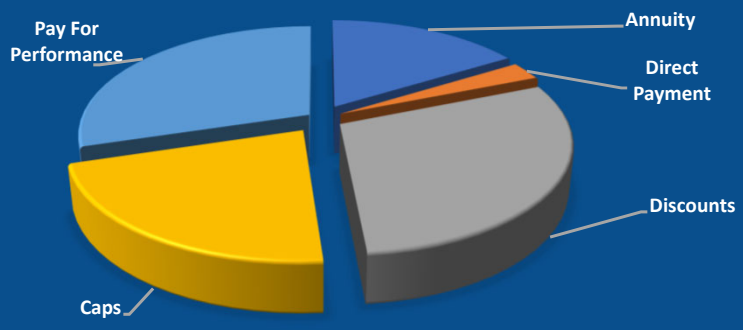
The European Experience

EU Payment Models *(cell and gene therapy)**



Current payment models utilized in Europe are mostly caps, annuity-based schemes, and outcomes-based schemes

***Notes: Proprietary research conducted by P4A in December 2018 across EU13 countries:**
Austria, Belgium, England, France, Germany, Greece, Italy, Netherlands, Poland, Romania, Spain, Switzerland, Turkey
Schemes are not necessarily mutually exclusive

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Source: Partners4Access

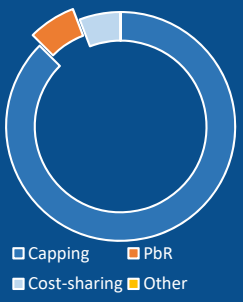
The Italian Experience 2007–2017

History

- Since 2007, AIFA has developed an extensive plan of registries for monitoring pricey drugs
- In Dec 2017, 228 web-based registries were ongoing (50% cancer drugs)
  - 52 outcome-based arrangements, mainly PbR; and 37 financial agreements
- Main critical issues: administrative burden and reliability (selection of endpoints)

Rebates in 2017

- €532 million
- PbR 6.5%



What's next?

According to the guidelines on pharmaceutical governance (Dec 2018):

- Web-based registries should be simplified, and reserved for high-cost medicines or subject to MEAs
- Pay-back arrangements should gradually become residual
- P/V agreements must be made more widely available

PbR = payment by results, MEAs = managed entry agreements, P/V = price volume

The Medicines Utilization Monitoring Centre. National Report on Medicines use in Italy. Year 2017. Rome: Italian Medicines Agency, 2018.

IAAs to Review CGTs are Uncommon in Most Advanced European Markets

ENGLAND

Infrastructure supports IAA, discounts preferred

- Cost effectiveness models allow for long-term extrapolation of benefits and risks of treatment; supportive of CGT pricing
  - Patient registries and large-scale genome mapping initiatives enables gathering of RWE, which can support innovative funding schemes
- Cancer Drugs Fund (CDF)
  - Tisagenlecleucel (Kymriah), voretigene neparvovec (Yescarta)
  - Future uncertain
- Current CGT Favoured Payment Models:
  - Label restrictions
  - Discounts
- BREXIT looms heavy on the horizon

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IAA = innovative access agreements, CGT = cell and gene therapy

IAAs to Review CGTs are Uncommon in Most Advanced European Markets

GERMANY
IAA embryonic with small sick funds

- **Cost effectiveness models allow for long-term extrapolation** of benefits and risks of treatment; supportive of CGT pricing
- **Patient registries and European Reference Networks** enable RWE, which *could support* innovative funding schemes
- **Krankenkassen (KK) is covering CGTs through standard budgets**
  - Smaller innovative KK's e.g., DAK starting to embrace IAAs
- **€50 million threshold under debate in 2019:**
  - MOH proposal to broaden calculations including hospital costs; potential impact for CGTs with higher prevalence

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Barriers to Commercial Adoption

- Single Payer:
  - Favourable environment for setting uniform policy which can facilitate staged-payment models
  - Avoids random fluctuations experienced by small payers in a multi-payer system
- Established cost-effectiveness methodology:
  - Enables consideration of long-term costs, benefits, and risks of a curative vs. chronic therapies
  - Supports cell and gene therapy value proposition

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Source: Partners4Access

Barriers to Commercial Adoption cont.

- Outcomes based reimbursement experience:
  - Countries with more experience have been quicker to adopt Cell and Gene Therapies (CGT)
  - Allows flexibility for payers in managing budget impact and improve value for money
  - Enables manufacturers to set prices that reflect value of therapy and sustain innovation
- Attitude to gene therapy:
  - Favourable review process
  - Expressed intent in leading CGT adoption and diffusion
  - Established designated treatment centres
- CGT challenges:
  - Multiple public and private initiatives around CGT specific clinical and economical evaluations, and payment models
  - Number of public / private focus groups

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Source: Partners4Access

Future International Payer Collaboration

- "Valuing a Cure project
- Institute for Clinical and Economic Review (ICER) US, National Institute for Health and Care Excellence (NICE) England and the Canadian Agency for Drugs, and Technologies in Health (CADTH) are collaborating to determine how best to adapt their cost effectiveness and value for money assessments
- Project goal is to ensure that assessment methods are tailored appropriately to the distinctive nature of the evidence base for potential cures

ICER NICE CADTH

Questions under consideration:

1. *How should value-based prices for potential cures reflect substantial uncertainty regarding clinical safety and effectiveness due to limitations in study design, outcome measures, and the size and duration of clinical trials?*
2. *How should value-based prices for potential cures reflect uncertainty regarding inclusion of additional elements of value that may be important for potential cures, but which are not part of standard cost-effectiveness methods?*
3. *How should value-based prices for potential cures reflect extreme magnitudes of lifetime health gains and cost offsets that are far beyond those generated by traditional therapies?*

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NICE. https://www.nice.org.uk/. Accessed March 13, 2019.
ICER. https://icer-review.org/. Accessed March 13, 2019.
CADTH.ca. https://www.cadth.ca/. Accessed March 13, 2019.
ICER. https://icer-review.org/announcements/icer-launches-international-collaborative-to-develop-new-methods-to-guide-value-based-pricing-of-potential-cures/ Accessed March 14, 2019

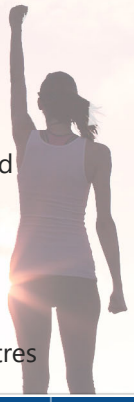
Conclusion: Revolution or Evolution?

From a scientific perspective it's an evolution

- Recombinant DNA technologies
- Virology understanding and viral manipulation techniques
- Upgraded understanding of cell therapies

From a social perspective it's a revolution

- Completely changes treatment paradigms
- Eradicates and fixes the disease, provides definitive cures for untreated & severe medical conditions
- Changes the healthcare system improve the balance in the costs and free up resources
- Removes the specialised disease centres



Questions?
Attendance Code:

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Brand drug names were used for educational purposes only.

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Developments, Research, Pipeline, and Applications of Gene Therapy

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  - NABP e-profile ID
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  - Session-specific attendance code
- Complete and submit session evaluation **no later than Monday, April 29, 2019 (5:00 PM ET)**
- Information shows in CPE Monitor approximately 72 hours after submission completion

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Learning Objectives

- Discuss examples of currently-approved gene therapies.
- Explain potential future applications of gene therapy.
- Describe the current status of the research pipeline for investigational gene therapies.

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Financial Relationship Disclosures

Disclosure Information	Advisory Board	Consultant	Grants / Research	Salary / Contractual	Supported Promotional Education	Stock / Shareholder	Other Financial Support
Judy C. Lofton, MS Planner	None	AMCP	None	None	None	None	None
Iris Tam, PharmD Peer Reviewer	None	None	None	Employee: Achaogen	None	None	None
Susan Trieu, PharmD Speaker	None	None	None	Spouse Employee: AstraZeneca	None	None	None
Brittany N. Vogel, PharmD, MBA Planner	None	None	None	Employee: AMCP	None	None	None

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***The code AMCP1 is not case sensitive**
*Standard text messages apply
*Poll Everywhere cannot see your telephone number

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Faculty

Susan Trieu, PharmD

Director, Enterprise Specialty Clinical Solutions

MedImpact Healthcare System, Inc.

Southlake, Texas

Currently Available Gene Therapies

Food and Drug Administration (FDA) Definition of Gene Therapy

Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use

Gene therapy is a technique that modifies a person's genes to treat or cure disease
Gene therapies can work by several mechanisms:

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease

US. Food and Drug Administration What is gene therapy ? Page last updated: 7/25/2018. https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm573960.htm Accessed February 2019.

Gene Therapy

In Vivo

Vector carrying gene is injected into patient near or in target organ

Example: Adeno-associated viral (AAV) vectors

Ex Vivo

Patients own cells are transduced with genetic material outside of the body and reintroduced into the body

Example: chimeric antigen receptor (CAR) - modified T cells

Molecular Therapy — Methods & Clinical Development (2016) 3, 16034; doi:10.1038/mtm.2016.34

Examples of Approved Gene Therapies

- KYMRIAH — Approved August 30, 2017 Anti-CD19 CAR-T therapy
- YESCARTA — Approved October 18, 2017 Anti-CD19 CAR-T therapy
- LUXTURNA — Approved December 19, 2017 AAV mediated
- GLYBERA — Approved in Europe but withdrawn

FDA U.S. Food & Drug. Drugs@FDA: FDA Approved Drug Products https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Kymriah (tisagenlecleucel)

Indication

≤25yrs old with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Adults with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Clinical Data

	Pediatric ALL	Adult DLBCL
Phase II	Trial with n = **63** patients aged **3-23 r/r B-cell ALL**	Trial with n = **106** adult patients with **r/r DLBCL**
Primary Endpoint	Objective Response Rate (ORR), defined as Complete Remission (CR) or Complete Remission with incomplete blood count recovery (CRi), at 3 months	Objective Response Rate (ORR)
Results	**83%** ORR at **3** months	**50%** ORR median time to first response of **0.9** months
Adverse Events	Cytokine Release Syndrome (CRS) Grade ≥ **3** in **49%** of patients	Cytokine Release Syndrome (CRS) Grade ≥ **3** in **23%** of patients

Kymriah Prescribing Information https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf [Accessed March 2019]

Kymriah (tisagenlecleucel)

~90 Kymriah Treatment Centers

$76M in sales in 2018

Updated analysis from **Eliana trial** in pediatric patients with r/r ALL showed an **82%** remission rate within **3 months** and relapse-free survival of **62%** at **24 months**

Updated analysis from the **JULIET trial** in patients with r/r DLBCL showed a **64%** relapse-free probability and a **43%** probability of overall survival at **18 months**

Hospital buy and bill model

Novartis Annual Results. Annual Results 2018 - Jan 30, 2019 https://www.novartis.com/investors/financial-data/annual-results [Accessed March 2019].
Novartis Press Release. Dec 1,2018. https://www.novartis.com/news/media-releases/novartis-announces-longer-term-analyses-from-pivotal-kymriah-trials-showed-durable-responses-are-maintained-patients-advanced-blood-cancers [Accessed March 2019]

Yescarta (axicabtagene ciloleucel)

Indication

A CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Clinical Data

Phase I/II	Trial in patients **≥18** yrs old refractory NHL
Primary Endpoint	Objective Response Rate (ORR) Complete Remission Rate (CR) Partial Remission Rate (PR)
Results	**72%** - ORR **|** **51%** - CR **|** **21%** - PR
Adverse Events	Grade **≥3 CRS** in **13%** of patients

Yescarta Prescribing Information. https://www.yescartahcp.com [Accessed March 2019].
Crump M, Neelapu S, Farooq U, et al. J Clin Oncol. 2016;34:7516

Yescarta (axicabtagene ciloleucel)

~ 74 authorized treatment centers

$263M in sales in 2018

Center for International Blood and Marrow Transplant Research (CIBMTR) registry for data collection

ZUMA-3 trial median follow-up of **15.1 months** showed **69%** of evaluable patients achieved complete tumor remission.

The rate of undetectable minimal residual disease in patients who achieved complete tumor remission was **100%**

Hospital buy and bill model

Gilead Press Release. Gilead Sciences Announces Fourth Quarter and Full Year 2018 Financial Results February 4, 2019 https://www.gilead.com/news-and-press/press-room/press-releases/2019/2/gilead-sciences-announces-fourth-quarter-and-full-year-2018-financial-results [Accessed March 2019].

Luxturna (voritigene neparvovec)

Indication

Is an
adeno-associated virus vector-based gene therapy
indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.

Patients must have viable retinal cells as determined by the treating physician(s).

Clinical Data

Phase III Study in n = **21** patients ≥ **3**yrs old with biallelic RPE65 gene mutation

Primary Endpoint Change in MLMT performance at **Year 1 from baseline**

Results **52% Luxturna patients** had an MLMT score change ≥2

Adv

Luxturna (voritigene neparvovec)

Patients treated in **10** treatment centers

75 vials have been shipped

In **2018** Luxturna product sales were **$27 million**

~85% of commercial lives have been covered

15 year follow up in progress

Investor Presentation Spark Therapeutics 2019. J P Morgan Conference January 07, 2019.http://ir.sparktx.com/static-files/48eabde5-9d8d-480d-9776-a7d0cadaadec [Accessed February 2019]
Spark Therapeutics Press Release. Spark Therapeutics Reports 2018 Fiancial Results and Recent Business Progress.. February 19, 2019. http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-reports-2018-financial-results-and-recent [Access February 2019].

Glybera—Cautionary Tale

Approved in Europe **October 2012** for hereditary lipoprotein lipase deficiency (LPLD)

In **April 2017** company decided to **no longer market gene therapy** due to lack of market demand

Requirements for additional studies and surveillance of patients were deemed too expensive to continue.

uniQuire Press Release April 20th, 2017. uniQuire Announces It Will Not Seek Marketing Authorization Renewal for Glybera in Europe https://tools.eurolandir.com/tools/Pressreleases/GetPressRelease/?ID=3330232&lang=en-GB&companycode=nl-qure&v [Accessed March 2019].

Future Applications of Gene Therapy

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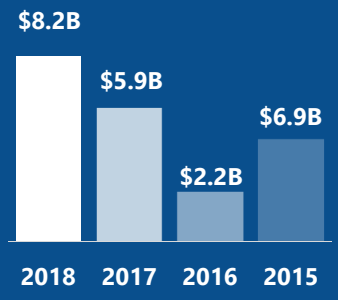
Gene Therapy Research

Gene & Gene-Modified Cell Therapy

$8.2B

↑ **39%** from 2017



Gene therapy Trials: 362

Phase I: 120
Phase II: 210
Phase III: 32

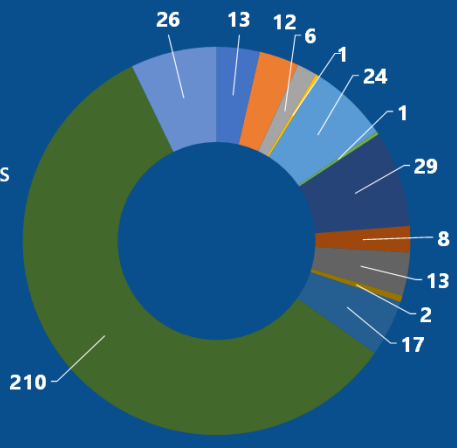
Gene-modified cell therapy trials: 362

Phase I: 158
Phase II: 188
Phase III: 16

Alliance for Regenerative Medicine. State of the Industry presentation JP Morgan Healthcare conference Jan 2019. *Updated data provided by ARM February 2019**

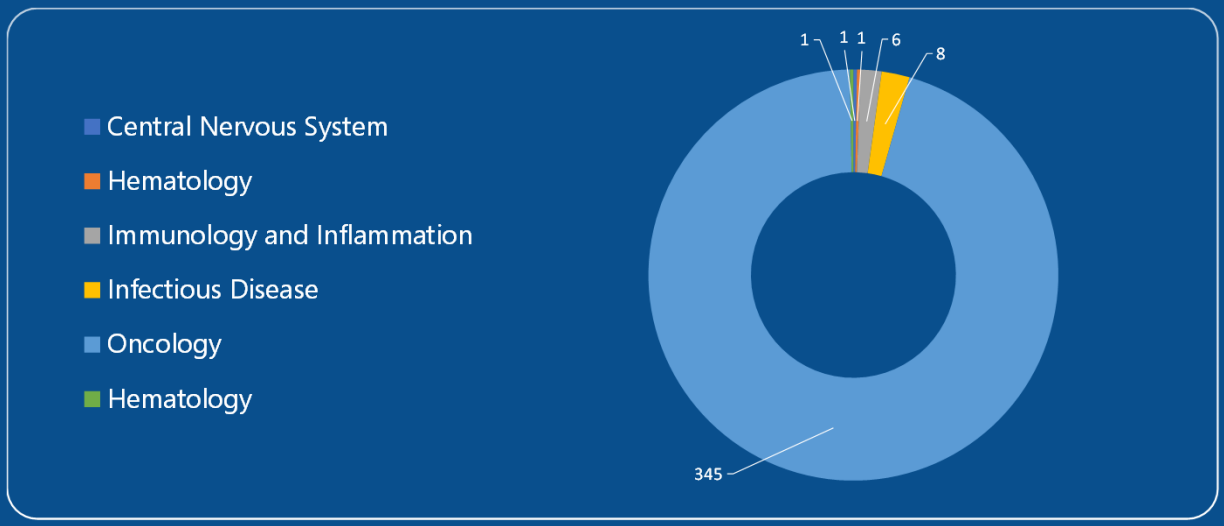
Gene Therapy Research

- Cardiovascular
- Central Nervous System
- Dermatology
- Ear Disease
- Endo, Metabolic and Genetic Disorders
- Genitoruinary Disorder
- Hematology
- Immunology
- Infectious Disease
- Lymphatic Diseases
- Musculoskeletal
- Oncology
- Opthalmology



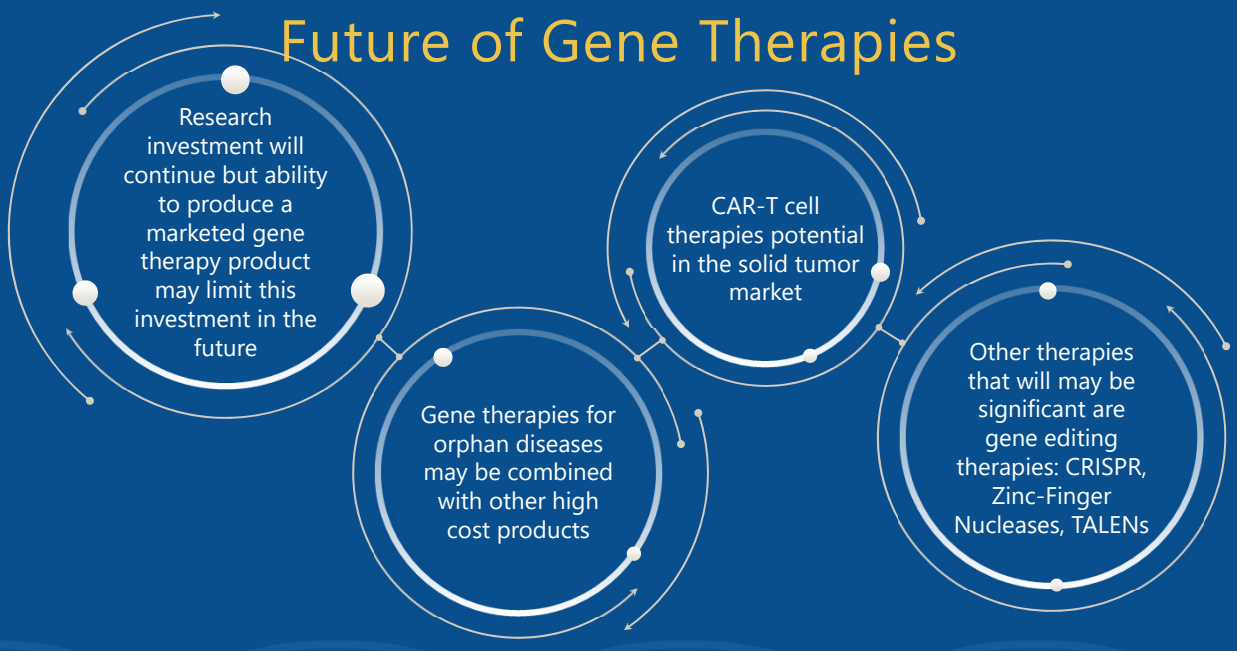
Alliance for Regenerative Medicine. State of the Industry presentation JP Morgan Healthcare conference Jan 2019. Updated data provided by ARM February 2019*

Gene-Modified Cell Therapy



Alliance for Regenerative Medicine. State of the Industry presentation JP Morgan Healthcare conference Jan 2019.
Updated data provided by ARM February 2019*

Future of Gene Therapies



Alliance for Regenerative Medicine. State of the Industry presentation JP Morgan Healthcare conference Jan 2019.

Gene Therapy Pipeline

CAR-T Cell Pipeline-New Cancer Targets

Gene Therapy	Disease State	N	Sponsor	Development
bb2121	Multiple Myeloma	381	Celgene	Phase 3
JNJ-68284528	Multiple myeloma	84	Janssen	Phase 2
JCARH125	Multiple myeloma	118	Juno	Phase 1/2
BPX-601	Pancreatic, gastric and prostate cancer	138	Bellicum Pharmaceuticals	Phase 1/2
KTE-C19	Chronic Lymphocytic Leukemia	108	Kite/Gilead	Phase 1/2

Clincial Trials.gov https://clinicaltrials.gov/ct2/results?term=chimeric+antigen+receptor&recrs=b&recrs=a&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&fund=2&Search=Apply {Access March 2019]

Gene Therapies in Phase III

Gene Therapy	Disease State	N	Sponsor	Primary Completion
AAV2-REP1	Choroideremia	140	Nightstar Therapeutics	March 2020
LYS-SAF302	Mucopolysaccharidosis Type IIIA	20	Lysogene	January 2020
GS010	Leber Hereditary Optic Neuropathy	90	GenSight Biologics	June 2020
Lenti-D Drug Product	Cerebral Adrenoleukodystrophy (CALD)	30/20 (2 studies)	Bluebird bio	July 2020/ February 2023
AAV8-RPGR	X-Linked Retinitis Pigmentosa	63	Nightstar Therapeutics	August 2020
Ad5.hAC6	Heart Failure	536	Renova Therapeutics	June 2020

ClinicalTrials.gov https://www.clinicaltrials.gov/ct2/results?cond=gene+therapy&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Access March 2019]

Gene Therapies in Phase III

Gene Therapy	Disease State	N	Sponsor	Primary Completion
Zolgensma (AVXS-101) (onasemnogene abeparvovec)	Spinal Muscular Atrophy	20	AveXis/Novartis	November 2019
LentiGlobin BB305	Beta-Thalassemia	23/15 (2 studies)	Bluebird bio	January 2020/ April 2021
Valoctocogene Roxaparvovec	Hemophilia A	40/130 (2 studies)	BioMarin	December 2022
PF-06838435/ fidanacogene elaparvovec	Hemophilia B	55	Pfizer	January 2022
AAV5-hFIXco-Padua	Hemophilia B	56	UniQuire Biopharma	March 2020

ClinicalTrials.gov https://www.clinicaltrials.gov/ct2/results?cond=gene+therapy&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed March 2019]

Possible Approvals 2019/2020

Gene Therapy	Disease State	Manufacturer	Regulatory Status
Zolgensma (AVXS-101) (onasemnogene abeparvovec)	Spinal Muscular Atrophy	Avexis/Novartis	FDA Decision: May 2019
Valoctocogene Roxaparvovec	Hemophilia A	BioMarin	FDA filing 2019
Lentiglobin	Beta thalassemia	bluebird bio	FDA filing 2H 2019
GT-AADC	AADC deficiency gene therapy	PTC Therapeutics	FDA filing 2019

*not all inclusive list of gene therapies near approval, examples for the purpose of the presentation

www.clinicaltrials.gov [Access March 2019]

Spinal Muscular Atrophy

Population

Estimated
10,000-30,000 patients in US
Pediatric and adult

Disease

Genetic disease that leads to neurodegenerative decline.
Is comprised of
5 different subtypes
with varying degrees of clinical features

SMA Type 1
is a severe form of disease that often leads to death before the age of 2 years
SMA Type 1 subtype
for **50% of SMA patients**

Some patients (SMA III and IV) have normal life expectancy

Previous Treatment Options

Spinraza,
an antisense oligonucleotide repeated intrathecal injections, which **was approved** for SMA **in 2016**

Patients living longer and reaching development milestones

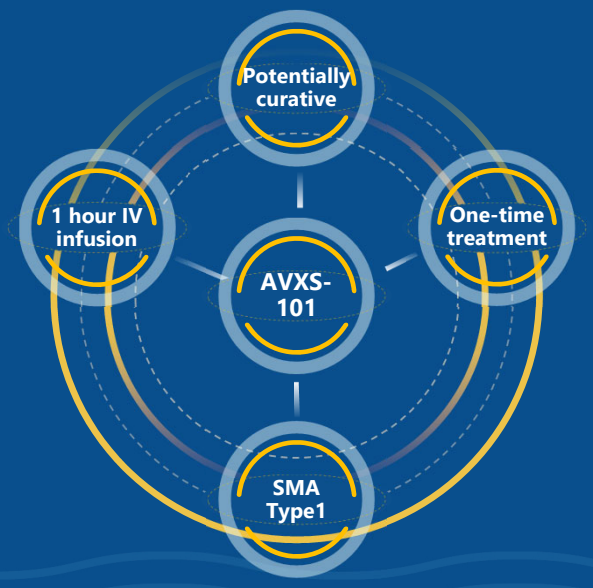
First year cost of $750,000
followed by
annual cost of $375,000

Lunn MR, Wang CH. Spinal muscular atrophy. The Lancet. 2008;371(9630):2120-2133. doi:10.1016/s0140-6736(08)60921-6.
FDA approves first drug for spinal muscular atrophy [Press release]. Updated December 23, 2016. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm534611.htm
Prior TW, Russman BS. Spinal muscular atrophy. GeneReviews. Available at: www.ncbi.nlm.nih.gov/books/NBK1352/
ACOG Committee Opinion: Spinal Muscular Atrophy prevalence of 1/10,000 http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Genetics/Spinal-Muscular-Atrophy

Gene Therapy: AVXS-101

FDA Decision Date: May 2019
Priority Review

Cost potentially
$1- 4million



START Trial

Phase 1 study of 15 patients with SMA type 1

Cohort 1 (n=3)
Minimally-effective dose

Cohort 2 (n=12)
Therapeutic dose

START Trial: 2-year safety data

15-year long-term follow up (LFTU)

Inclusion criteria

< 9 months or < 6 months of age

Proven mutations of SMN1 gene with 2 copies of SMN 2

Hypotonia and muscle weakness at enrollment

LTFU population

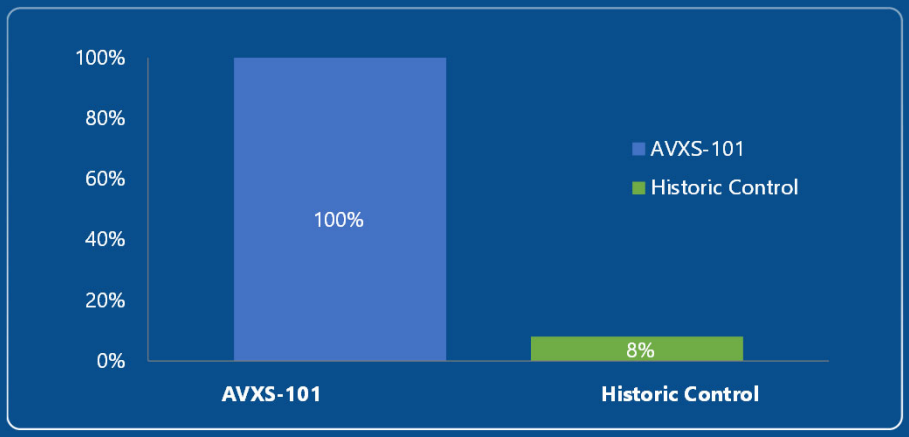
Oldest patient > 4 years

13 patients enrolled

Concomitant Spinraza in 30% of patients enrolled from Cohort 2

N Engl J Med 2017;377:1713-22.

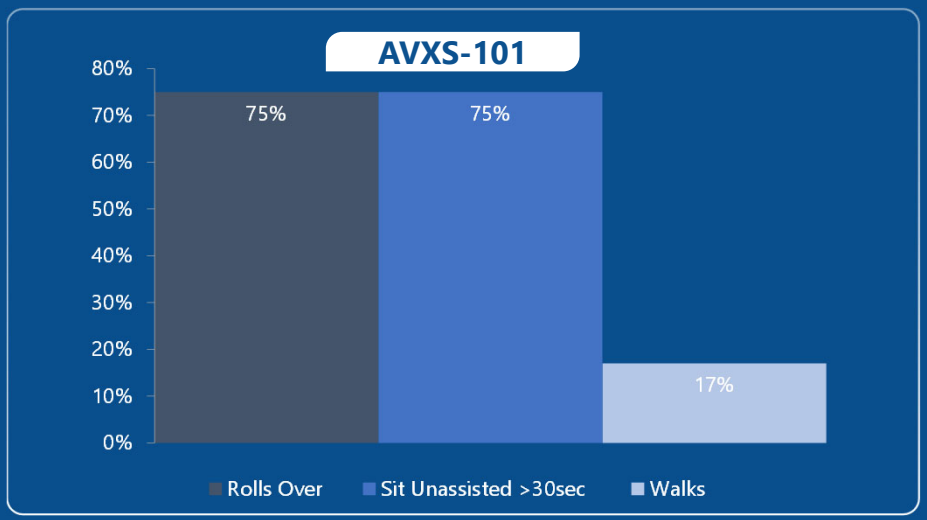
Alive and Free of Mechanical Ventilation



Alive and event-free at 20 months of age

N Engl J Med 2017;377:1713-22.

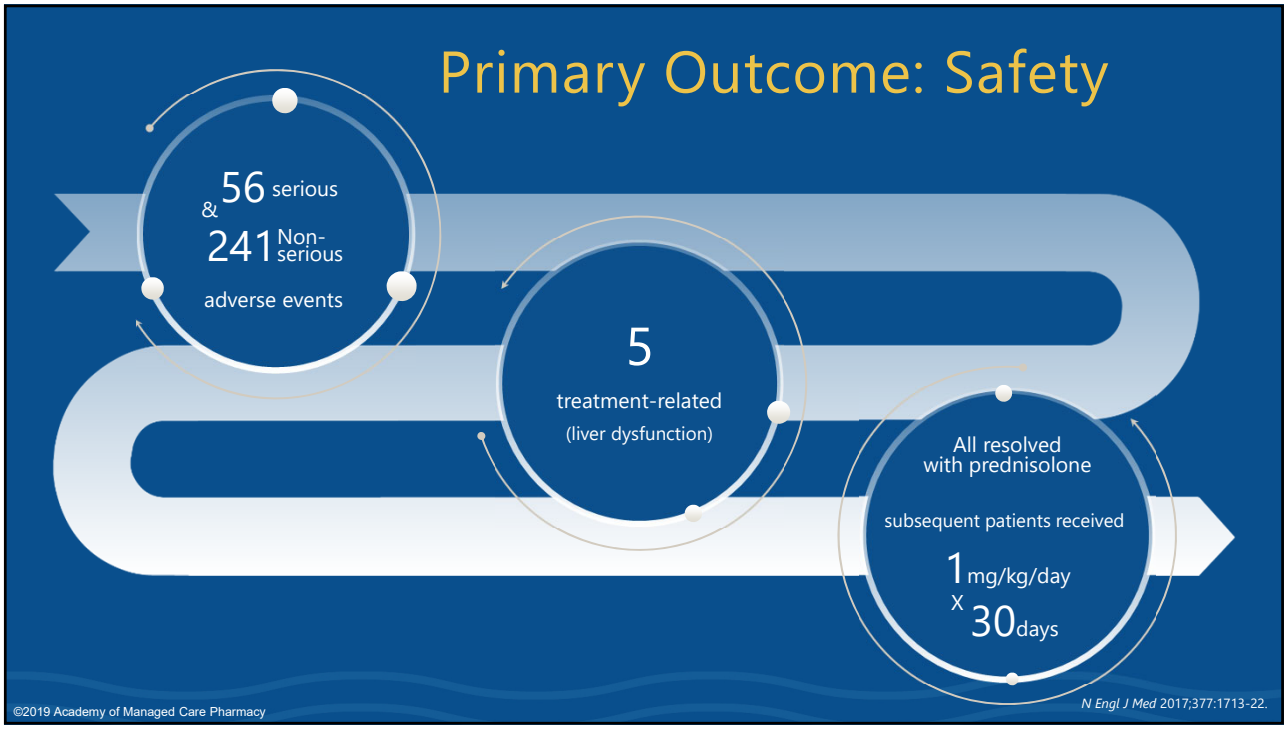
Motor Endpoints

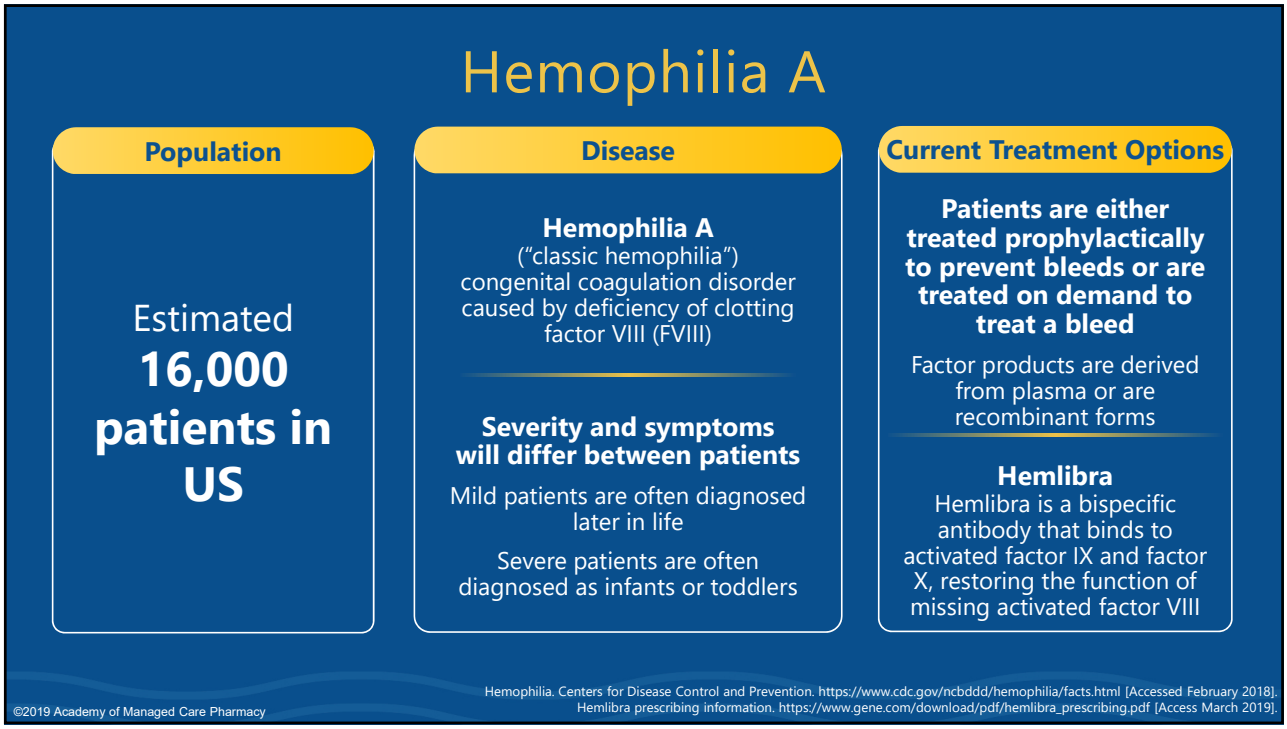


*historic controls did not achieve any of these motor endpoints at 20 months

N Engl J Med 2017;377:1713-22.

Novartis Press Release https://ml.globenewswire.com/Resource/Download/6cd49133-c694-4429-a2be-1bd01e5fb9c5.


Primary Outcome: Safety
56 serious
&
241 Non-serious
adverse events
5
treatment-related
(liver dysfunction)
All resolved
with prednisolone
subsequent patients received
1 mg/kg/day
X 30 days
©2019 Academy of Managed Care Pharmacy
N Engl J Med 2017;377:1713-22.


Hemophilia A
Population
Estimated
16,000
patients in
US
Disease
Hemophilia A
("classic hemophilia")
congenital coagulation disorder
caused by deficiency of clotting
factor VIII (FVIII)
Severity and symptoms
will differ between patients
Mild patients are often diagnosed
later in life
Severe patients are often
diagnosed as infants or toddlers
Current Treatment Options
Patients are either
treated prophylactically
to prevent bleeds or are
treated on demand to
treat a bleed
Factor products are derived
from plasma or are
recombinant forms
Hemlibra
Hemlibra is a bispecific
antibody that binds to
activated factor IX and factor
X, restoring the function of
missing activated factor VIII
©2019 Academy of Managed Care Pharmacy
Hemophilia. Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/hemophilia/facts.html [Accessed February 2018].
Hemlibra prescribing information. https://www.gene.com/download/pdf/hemlibra_prescribing.pdf [Access March 2019].

BMN 270 (valoctocogene roxaparvovec) Hemophilia A Gene Therapy

Intervention

Gene therapy was delivered by intravenous infusion one time

Low Dose n=1	Intermediate Dose n=1	High dose n= 7
$6x10^{12}$ vg/kg	$2x10^{13}$vg/kg	$6x10^{13}$vg/kg

vg= vector genomes

Endpoints

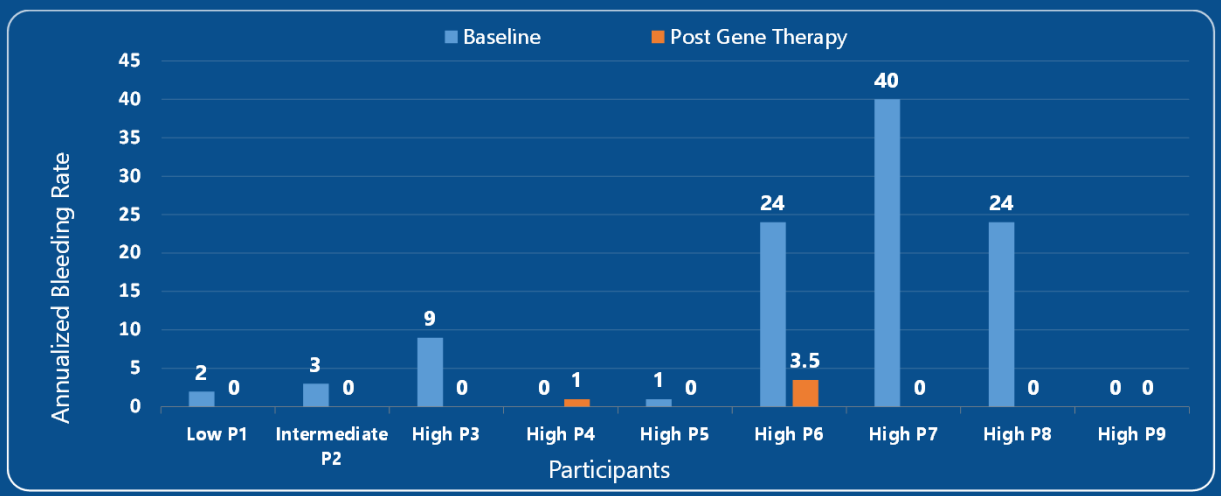
Primary Endpoint:
Safety

Prospective primary efficacy goal was factor VIII activity level of ≥ 5 IU/dl (16 weeks after gene therapy):
Low and intermediate dose participants did not achieve 5 IU/dl
All participants in the high dose achieved 5 IU/dl
Factor VIII activity level at 52 weeks for high dose ranged from 19 to 164 IU/dl

Secondary efficacy endpoints also included:
Frequency of factor VIII use and number of bleeding episodes

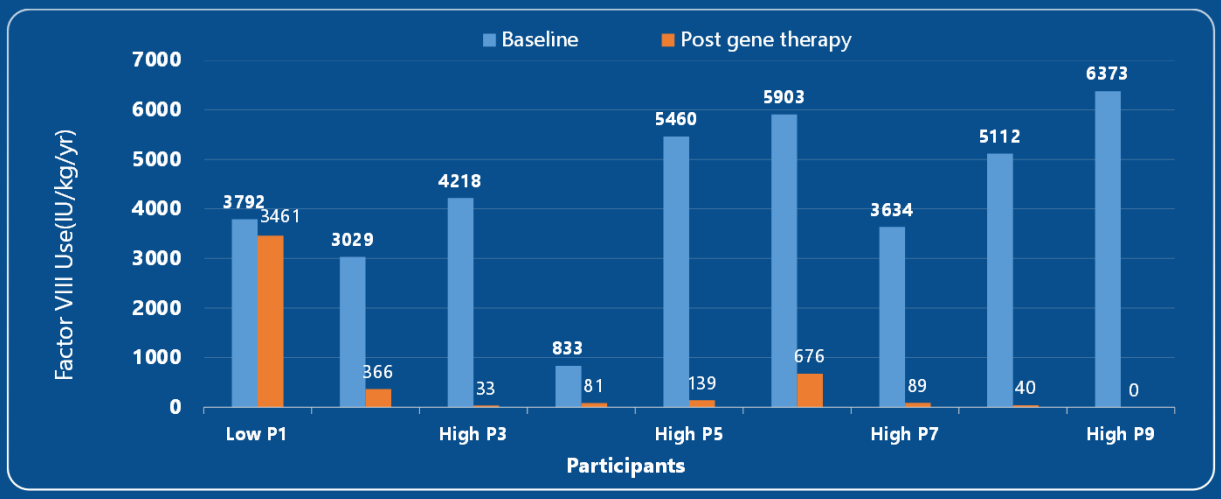
Rangarajan et al., AAV5-Factor VII Gene Transfer in Severe Hemophilia A *NEJM* 2017

Decrease in Annualized Bleeding Rate



Rangarajan et al., AAV5-Factor VII Gene Transfer in Severe Hemophilia A *NEJM* 2017

Decrease in Factor VIII Use



Rangarajan et al., AAV5-Factor VII Gene Transfer in Severe Hemophilia A *NEJM* 2017

Safety

No patients developed **inhibitors to factor VIII or thrombosis**

AAV5 capsid-specific antibodies developed in all participants but no cellular immune response was seen

7 patients experienced increase in alanine aminotransferase levels **Peak values 59 to 128 U/L** (normal range, 6 to 43 U/L) All events resolved All patients in high dose were given glucocorticoids and were tapered off, duration of treatment varied

Vector shedding was seen within **72 hours**, high dose participants still had vector DNA in blood at **week 52**

Rangarajan et al., AAV5-Factor VII Gene Transfer in Severe Hemophilia A *NEJM* 2017

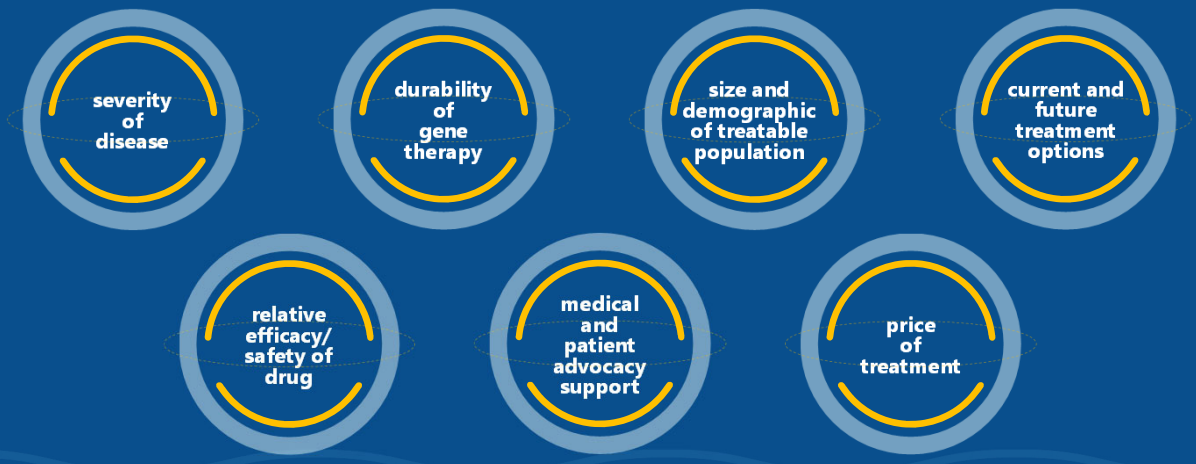
Hemophilia Gene Therapy Pipeline

Gene Therapy	Disease State	Manufacturer	Clinical Trial Phase/ Regulatory Submission
BMN 270 (valoctocogene roxaparvovec)	Hemophilia A	Biomarin	Phase 3
SPK – 8011	Hemophilia A	Spark	Phase 3 (2019)
PF-06838435/ fidanacogene elaparvovec	Hemophilia B	Pfizer	Phase 3
AAV5-hFIXco-Padua	Hemophilia B	Uniqure	Phase 3
SB-525	Hemophilia A	Sangamo/Pfizer	Phase 1/2
SHP654	Hemophilia A	Shire	Phase 1
SB-FIX	Hemophilia B	Sangamo	Phase 1/2
scAAV2/8-LP1-hFIXco	Hemophilia B	St. Jude	Phase 1

Dunbar CE, et al. Gene therapy comes of age. Science. 2018 Jan 12;359(6372). pii: eaan4672. doi: 10.1126/science.aan4672
www.clinicaltrials.gov [Access March 2019]

Adoption of Gene Therapy…Depends

Impact of gene therapy will depend on multiple factors that include



Gene Therapy—New Considerations

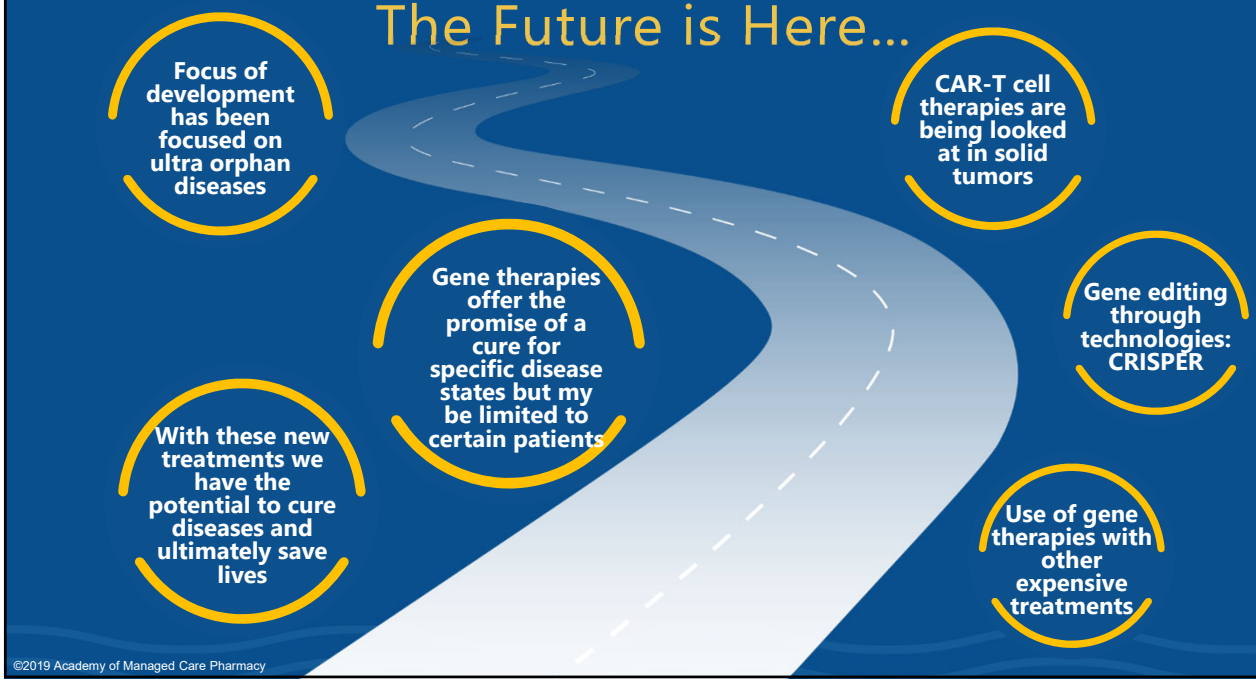
Development of gene therapies
will impact pharmacy benefit by potentially displacing other treatments

Efficacy will be measured but durability will be in question when launched
… is it "worth it?"

Will gene therapy treatments be moved up earlier in the treatment paradigm?

Which cure is more efficacious? Stem Cell Transplant or Gene Therapy? Gene Therapy A or Gene Therapy B?

The Future is Here…



Questions?
Attendance Code:

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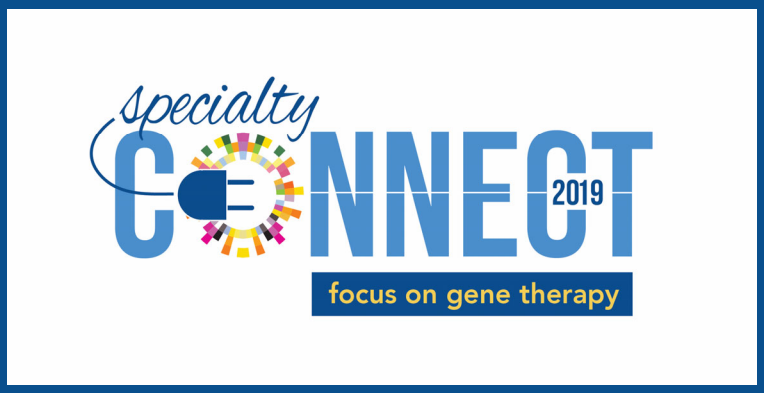
20-Minute Break



Financial Models to Manage Drug Spend of Gene Therapy

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  - Birth month and birthday
  - Session-specific attendance code
- Complete and submit session evaluation **no later than Monday, April 29, 2019 (5:00 PM ET)**
- Information shows in CPE Monitor approximately 72 hours after submission completion

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Learning Objectives

- Explain the short-term and long-term financial impacts associated with gene therapy.
- Discuss managed care strategies for addressing issues posed by gene therapy, including formulary considerations.
- Describe innovative and novel payment strategies that may be used to support access to gene therapy.
- Discuss learnings that have emerged from the development of payment models for the use of gene therapy using real-world examples.

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Financial Relationship Disclosures

Disclosure Information	Advisory Board	Consultant	Grants / Research	Salary / Contractual	Supported Promotional Education	Stock / Shareholder	Other Financial Support
Jane F. Barlow, MD, MPH, MBA Speaker	Pictet	MIT, Real Endpoints	None	None	None	Therapeutics MD	None
Judy C. Lofton, MS Planner	None	AMCP	None	None	None	None	None
Ami Gopalan, PharmD, MBA Peer Reviewer	None	None	None	Employee: Precision for Value	None	None	None
Steven W. Pipe, MD Speaker	Freeline Therapeutics, uniCure	uniCure	None	None	None	None	None
Brittany N. Vogel, PharmD, MBA Planner	None	None	None	Employee: AMCP	None	None	None

This slide deck has been peer reviewed and reviewed by AMCP staff members to mitigate the risk of promotional bias.

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- This program was developed by AMCP and is supported by unrestricted educational grants from Avexis Inc., Genzyme Corporation, Pfizer and Sarepta Therapeutics.

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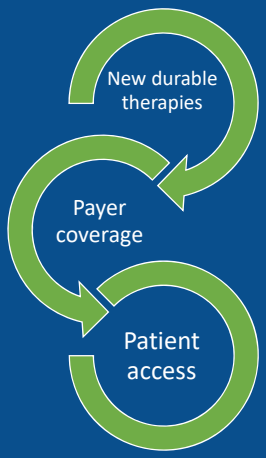
Faculty

Jane F. Barlow, MD, MPH, MBA
Senior Advisor
MIT Center for Biomedical Innovation
Scottsdale, Arizona

Steven W. Pipe, MD
Professor of Pediatrics and Pathology
University of Michigan
Ann Arbor, Michigan

New Treatment Innovations Challenge Current Insurance Paradigms, Threatening Access



- Growing clinical pipeline on innovative durable therapies
- High one-time cost will likely create financial challenges
- Sustainability for all stakeholders is at risk

- **Need to address stakeholder concerns, flesh out hurdles and foster new tools**

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Financial Challenges Grow with Larger Target Populations

- Novel Breakthroughs
  - Therapies for ultra-orphan conditions
  - Small incidence <100, non-oncology
  - Often fatal childhood genetic disorders
- Orphan Disruptors
  - <200,000 patients in the US, non-oncology
  - Nearly 1/3 of expected new therapies
- Oncology
  - Nearly 1/2 expected new therapies (e.g., CAR-T)
  - Small prevalence numbers
  - Alternative, high-cost treatments
- "Quantum Leaps"
  - Approximately 1/8 of new therapies
  - Large incidence & prevalence population conditions (i.e., hepatitis C)

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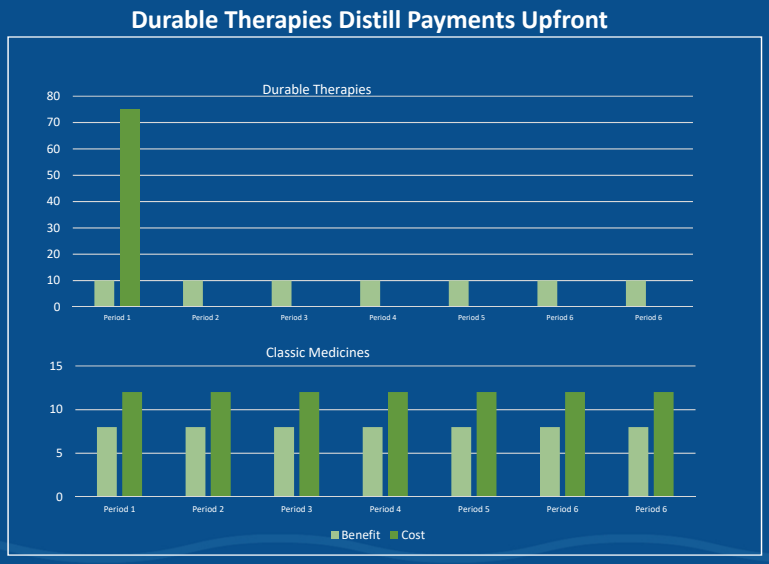
MIT NEWDIGS Research Brief 2018F203v015

One-time Administration Introduces Mismatch with Benefits



- Cost is front-loaded, but benefits accrue over time
- Creates challenges as patients move in and out of plans
- Spike in costs could be present problems

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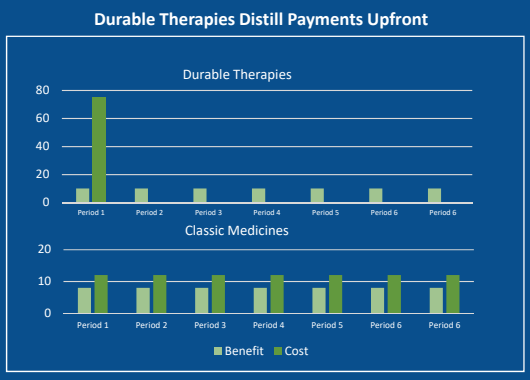
NEWDIGS Initiative • MIT Center for Biomedical Innovation

Emerging Durable Therapies Create Financial Challenges

Pipeline
X
Treatment population



Financial Challenges

1. **Payment Timings**
2. **Product Performance Risk** (Effectiveness & Durability)
3. **Actuarial Risk** (Likelihood of encountering an orphan case)

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Payer Approaches to Management May Vary

	Commercial Fully Insured	Medicare Advantage	Third Party Administrator: Large Employer	Third Party Administrator: Small Employer	Managed Medicaid	All Payers, All Lines of Business
Coverage Exclusion	10%	11%	12%	31%	27%	17%
Benefit Design Only	14%	6%	18%	13%	7%	11%
Reinsurance Only	5%	22%	18%	6%	27%	15%
Payment Agreement Only	5%	28%	6%	13%	27%	15%
Combination Approach:	67%	33%	47%	38%	13%	41%
Payment Agreement and Reinsurance	29%	11%	12%	13%	7%	15%
Benefit Design and Reinsurance	19%	11%	12%	6%	0%	10%
Benefit Design and Payment Agreement	5%	0%	6%	6%	0%	3%
All Three Approaches	14%	11%	18%	13%	7%	13%

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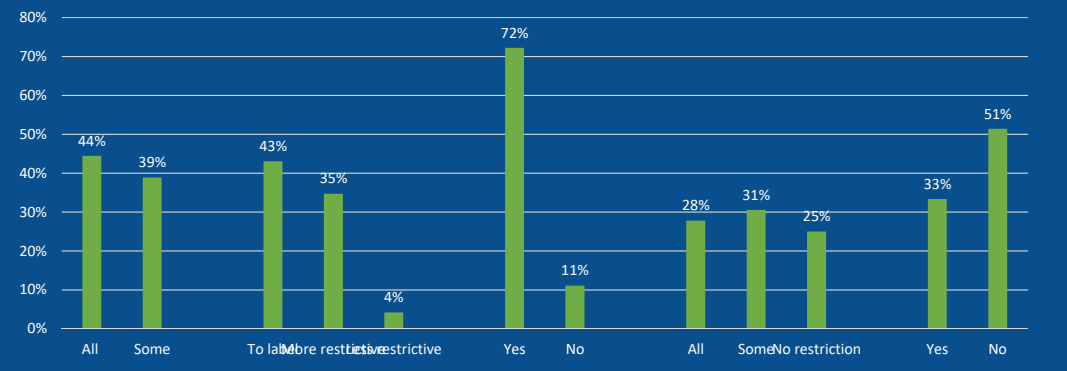
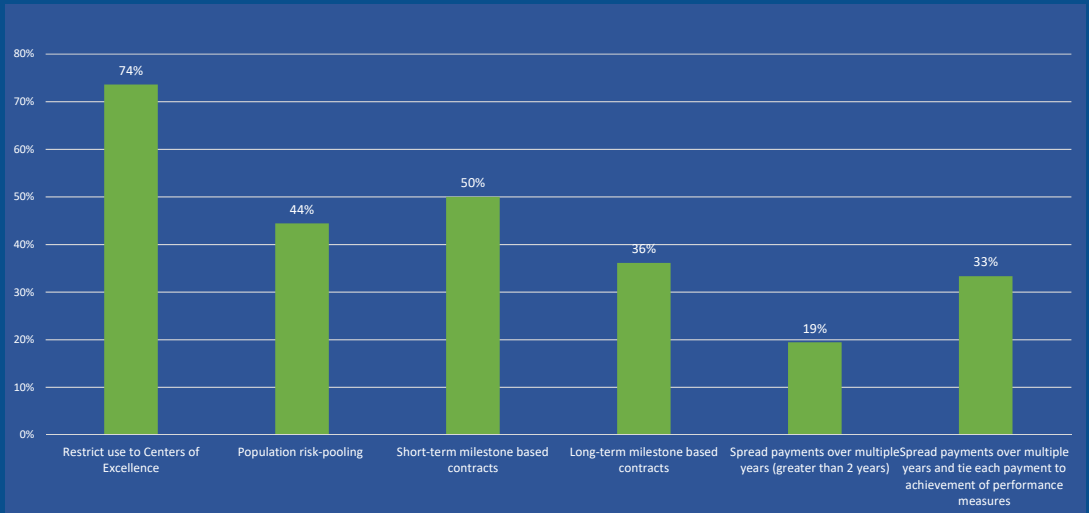
Ciarametaro M, et al. *Health Affairs Blog*, June 28, 2018 DOI: 10.1377/hblog20180626.330036

Payers **Currently** Utilize Multiple Strategies for High Cost Durable Therapies



MIT FoCUS Payer survey Fall 2018 unpublished

In the **Future,** Payers Expect to Manage the Financial Risk and Impact of New High Cost Durable Therapies using Different Mechanisms



MIT FoCUS Payer survey Fall 2018 unpublished

Precision Financing Solutions are Emerging to Address Financial Risks

Milestone-based Contracts

- < 2 year duration
- Specified payment endpoints tied to early outcome

Performance-based Annuities

- > 2 years (likely 3 to 5)
- Payments spread out over contract period
- Tied to performance over time

Risk Pooling

- Underwriting for novel breakthroughs
- Possible state Medicaid budget solution

	Financial Challenge		
Solution	Actuarial Risk	Performance Risk	Payment timing
Milestone-based contract		✓	
Performance-based annuity	✓-	✓	✓
Risk Pooling	✓		

✓ means the risk is addressed

Precision Financing Solutions for Durable/Potentially Curative Therapies MIT NEWDIGS FoCUS White Paper 24 January 2019

Why Multiple Precision Financing Solutions?

Cure characteristics

- Eligible patient population
- Backlog of patients
- Durability
- Data requirements

Financing Challenges

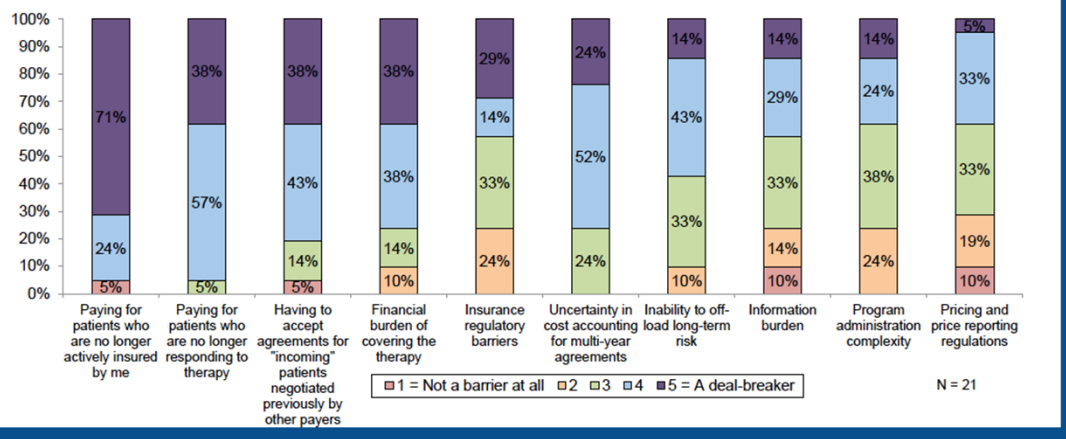
- Cost
- Actuarial risk
- Performance risk
- Payment timing

Payer considerations

- Segment
- Size
- Approval timing
- Focus and purpose

Patient Mobility and Durability are the Greatest Barriers to Alternative Payment Approaches

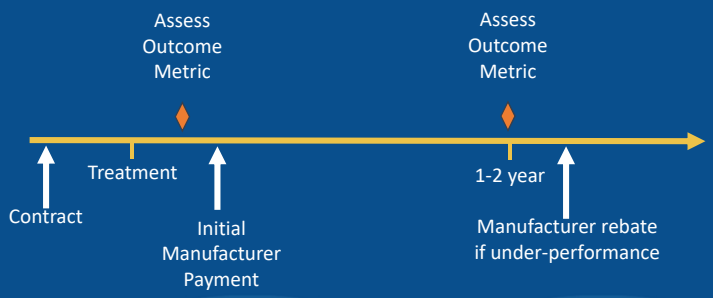
Q. What would you say would be the biggest barriers to your organization accepting alternative payment proposals from drug manufacturers such as milestone-based payments or long-term payment agreements for gene therapies?

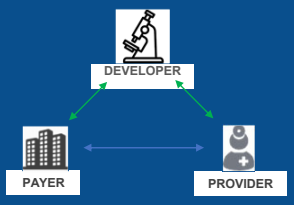


"Are Payers Ready To Address The Financial Challenges Associated With Gene Therapy?, " Health Affairs Blog, June 28, 2018

Milestone-based Contracts Helps Resolve Uncertainties and Adjust Reimbursement Accordingly

- Connect payment milestones to clinical ones
- Performance risk shared among triad
  - Payer to manufacturer via contract
  - Payer to provider center of excellence





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Milestone-based Contracts Public Payer Pilot

Purpose

To model and evaluate a 12-18 month milestone-based contract approach

Scope

1. Medicaid
2. Managed Medicaid

Objectives

1. Model the impact of a milestone-based contract on public payers
2. Identify and evaluate the impact of Medicaid best price
3. Align on impact of anti-kickback legislation (with and without COE delivery)
4. Impact on ASP and 340B
5. Identify methods to track milestones
6. Other barriers

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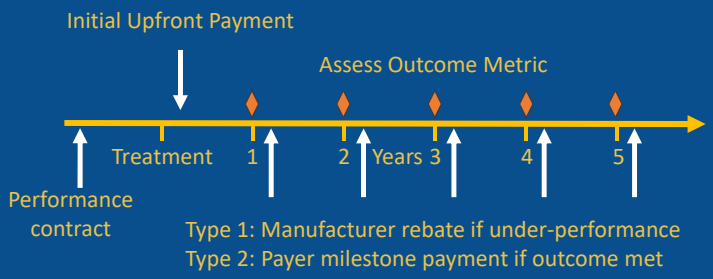
Paying for cures conference 12 February 2019 Washington, DC

Performance-based Annuities Address Multiple Issues

- **Payment timing**: Better matches cost avoidance to lower net impact
- **Performance Uncertainty**:
  Resolves effect size and durability uncertainty naturally over time
- **Actuarial Uncertainty**: Variable patient numbers smoothed over time



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Performance-Based Annuity Pilot

Purpose

To demonstrate and evaluate a performance-based annuity approach for one or more therapies

Stakeholder Scope

1. Multiple commercial payers, fully insured lives, in Massachusetts
2. Developer(s) of durable therapy
3. Providers
4. Patients

Objectives

1. Test a multi-year annuity with performance-based measures
2. Develop a process and contracting to address patient movement between plans
3. Obtain federal freedom-to-operate as needed (Medicaid best price, Medicaid price reporting, Stark law, ASP, etc.)

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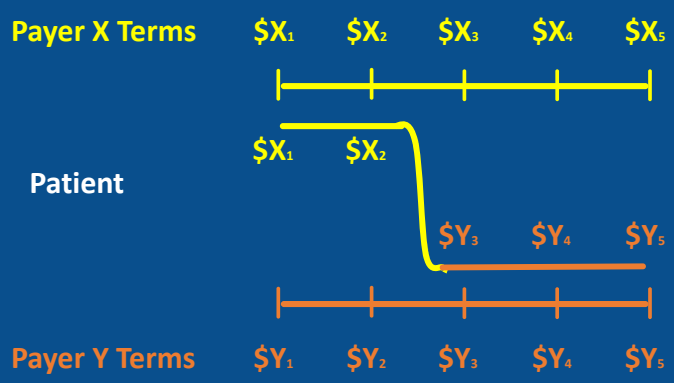
Movement Among Participating Plans: Responsibility Portability not Contract Portability



Requires minimal data transfer

Protects confidential commercial data

Maintains competition

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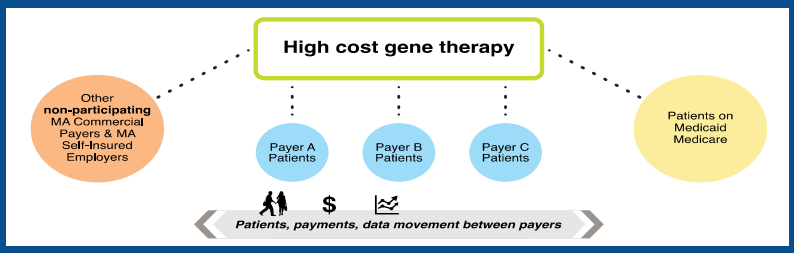
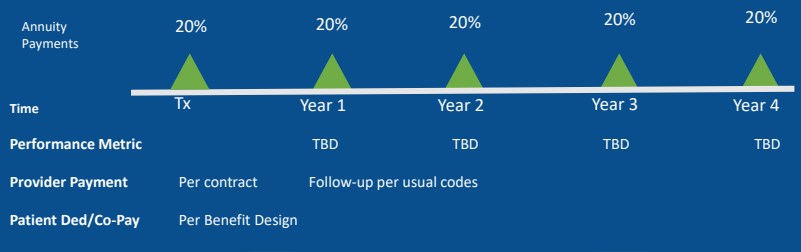
Performance-Based Annuity Pilot Strawman





Pilot Challenges

- Agreement on key common contract terms
- Sufficient # of treated patients to generate meaningful evidence
- Engaging CMS/Feds to facilitate & provide exceptions or waivers
- Designing & implementing the mechanics

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Performance-based Annuity Pilot: Common Structural Elements are Key

Common Structure Elements

- Price of therapeutic
- Provider network and reimbursement
- Member benefit cost-sharing design: deductibles and co-pays
- Patient Mobility payments when movement to non-participating plan
- Internal operational processes, medical policies and program management

Plan-specific Elements

- Patient eligibility criteria
  - Treated to label
  - Commercial fully-insured population
- Payment structure
- Performance metrics
- Patient Mobility payments when movement among participating plans

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Pilot Implementation Challenges

- Legal & Regulatory
  - Medicaid drug price reporting and rebate need adapting to multi-year performance structures
  - Anti-Kickback Statute to define explicit safe harbor for performance rebates
  - FDA communication guidelines to enable appropriate performance metrics: Clinical trial endpoints often not practical for clinicians or present in data systems
  - Others
- Operational
  - Performance data collection
  - Provider reimbursement mechanics under current billing codes and DRG capitation categories
- Risk sharing
  - Interplay with reinsurance and stop-loss insurance
  - Patient mobility mechanisms among payers

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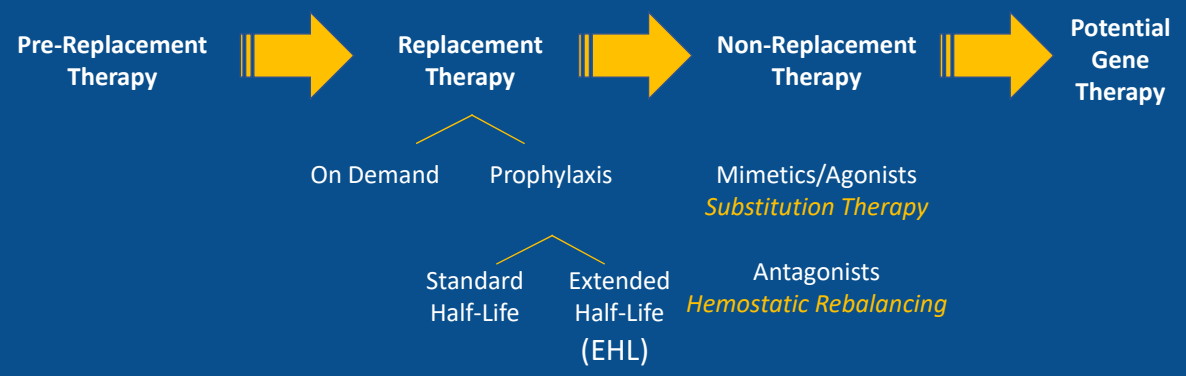
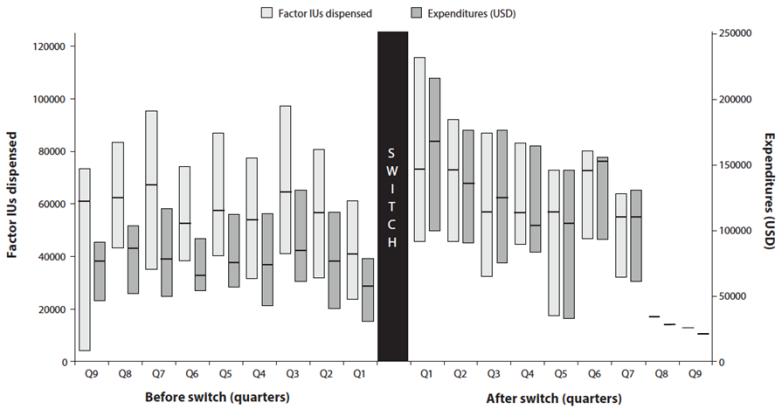
Hemophilia—Current and Future Approaches to Care



Pipe SW. *Hematology Am Soc Hematol Educ Program*. 2016;2016:650-6.

Switches to EHL Factor VIII Associated with Increased Utilization and Expenditures

FIGURE 2
Median IUs dispensed and expenditures associated with switching from a standard half-life to an extended half-life recombinant factor VIII replacement product (Truven Health MarketScan Databases), by quarterly intervals pre- and post-switch

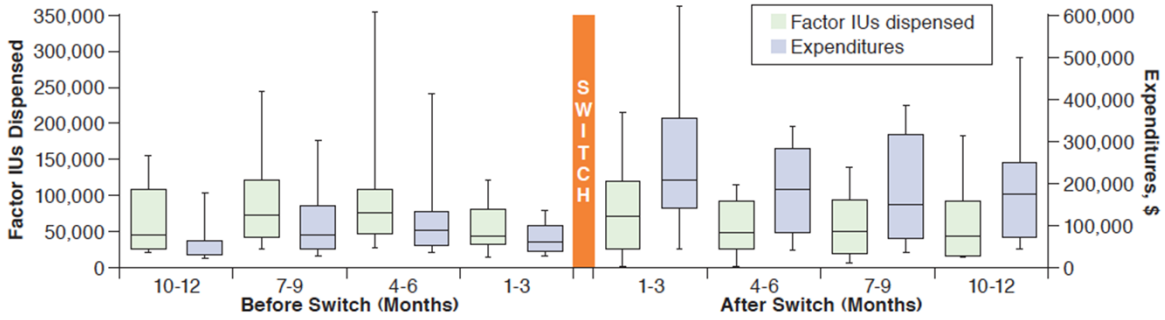


Box=25th and 75th percentiles, crossbar=median.

Chhabra et al., *Managed Care*. 2018;27:39-50. Used with permission.

Switches to EHL Factor IX Associated with Increased Utilization and Expenditures

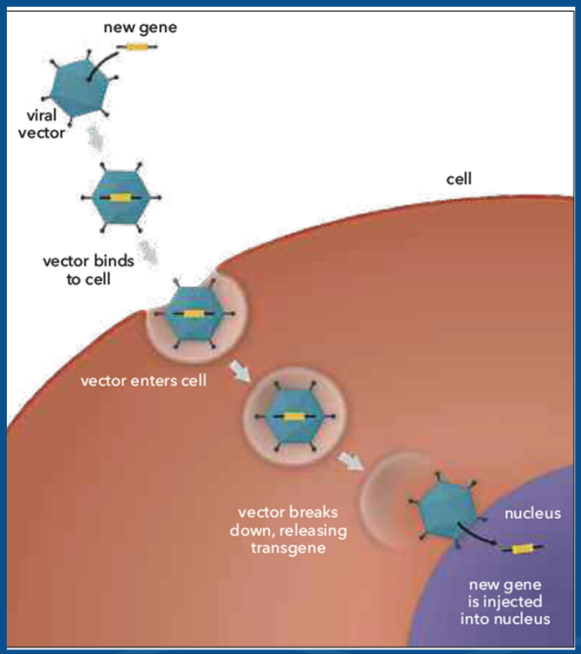
FIGURE 2 Median IUs Dispensed and Expenditures Associated with Switching from a Standard Half-Life (Nonacog Alfa) to an Extended Half-Life (Eftrenonacog Alfa) Recombinant Factor IX Replacement Product, by 3-Month Intervals Before and After Switch[a]



Notes: Expenditures are based on 2015 dollars. Box = 25th and 75th percentiles; crossbar = median; whiskers = minimum and maximum values.
[a]Truven database.
IUs = international units.

Tortella et al., *J Manag Care Spec Pharm.* 2018; 24:643-653. Used with Permission.

Transfer of a New Gene into the Nucleus of a Cell Using a viral Vector



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Gene Therapy for Hemophilia B Clinical Trials – Completed and Ongoing

Table 1. AAV gene therapy trials for hemophilia B.

Sponsor	Serotype	Transgene	Highest dose (vg/kg)	Mean FIX:C (%)	T-cell ELISPOT	↑ ALT	↓ FIX:C with ↑ ALT	Steroid treatment	Status[$]	Ref.
CHOP/UPENN	rAAV2	FIX-WT	2×10^{12}	12*	N/A	1/2	1/2	0/2	Closed	8
UCL/SJCRH	rAAV8	FIX-WT	2×10^{12}	5.1	4/6	4/6	4/6	4/6	Recruiting	13,14
Shire	rAAV8	FIX-Padua	3×10^{12}	0				2/3	Closed	20,22
Spark Therapeutics	Spark100	FIX-Padua	5×10^{11}	33	2/10	2/10	2/10	2/10	Closed	10
uniQure	rAAV5	FIX-WT	2×10^{13}	6.9	0/5	2/5	0/5	2/5	Closed	11
Dimension	rAAV-rh10	FIX-WT	5×10^{12}	6.7	2/3	3/3	3/3	3/3	Closed	23
Sangamo Therapeutics	rAAV6	Zinc finger-FIX	N/A	N/A	N/A	N/A	N/A	N/A	Recruiting	N/A
Freeline Therapeutics	rAAV-engineered	FIX-Padua	N/A	N/A	N/A	N/A	N/A	N/A	Not yet recruiting	N/A

*One subject had peak activity of 12% before immune response and subsequent decline to less than 1%.
[$]Status determined by data available to ClinicalTrials.gov as of March 2018.
AAV, adeno-associated virus; ALT, alanine aminotransferase; CHOP, Children's Hospital of Philadelphia; ELISPOT, enzyme-linked immunospot; FIX, factor IX; N/A, not available; rAAV, recombinant adeno-associated virus; Ref., reference; SJCRH, St Jude Children's Research Hospital; UCL, University College of London; UPENN, University of Pennsylvania; WT, wild type.

Doshi BS et al., *Ther Adv Hematol*. 2018;9:273-293. Used with permission.

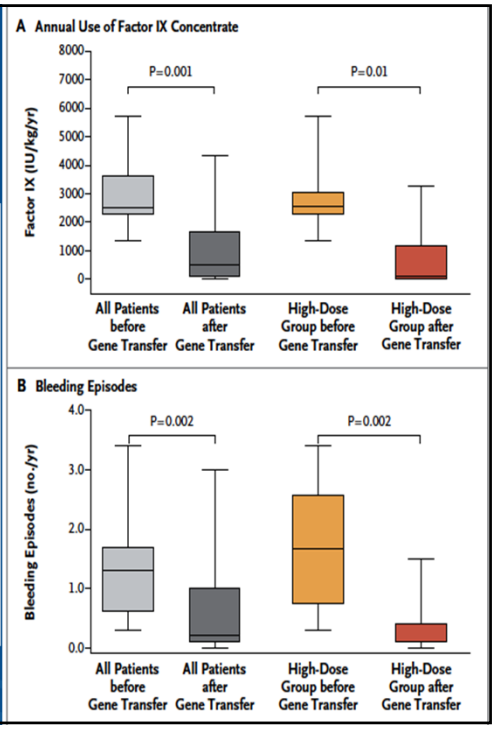
UCL/SJCRH Trial for Hem B

Durable steady state FIX expression (8 yr)
66% decrease in FIX usage
Annual bleed decline of 82%

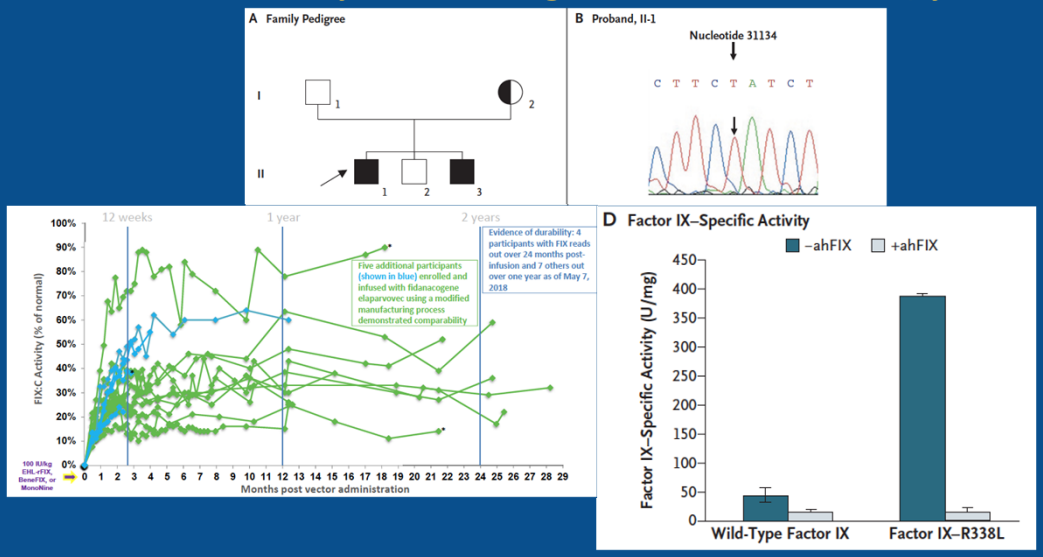
Table 1. *Clinical data*

Patient No.	Duration of observation in months	Factor IX level, vg/kg	Vector dose, vg/kg
1	71	2.1 ± 0.78	2×10^{11}
2	66	3.9 ± 2.1	2×10^{11}
3	64	2.4 ± 1.5	6×10^{11}
4	63	2.8 ± 1.6	6×10^{11}
5	61	4.8 ± 2.4	2×10^{11}
6	60	7.7 ± 2.4	2×10^{12}
7	48	5.7 ± 1.4	2×10^{12}
8	44	5.7 ± 1.4	2×10^{12}
9	42	4.9 ± 1.6	2×10^{12}
10	38	4.8 ± 3.2	2×10^{12}

Davidoff AM et al. *NEJM*. 2014; 371:1994-2004. Used with permission.
Neinhuis AW et al. *Hum Gen Ther*. 2016; 27:305-308. Used with permission.

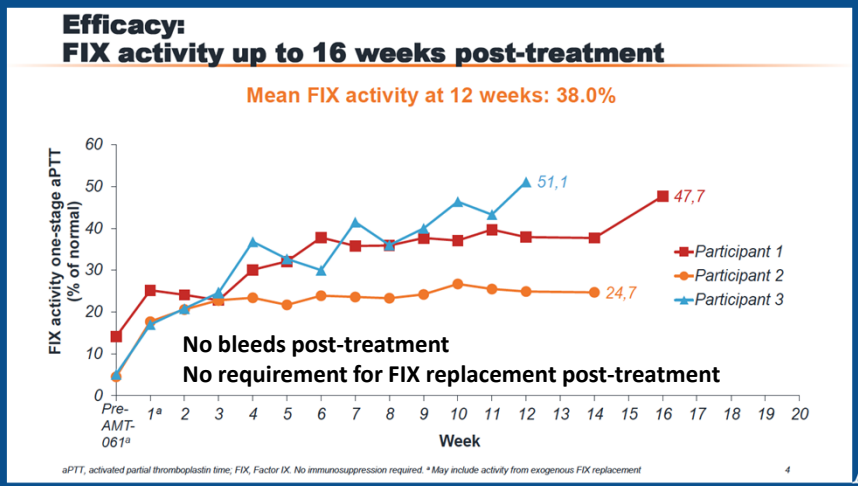


Bioengineered (hyperactive) FIX Leads to Higher FIX Activity Following AAV Gene Therapy



Simoni P, et al. *N Engl J Med*. 2009;361:1671-5. Used with permission.
George LA, et al. *N Engl J Med*. 2017;377:2215-27. Used with permission.

Bioengineered (hyperactive) FIX Leads to Higher FIX Activity following AAV Gene Therapy



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Gene Therapy for Hemophilia A Clinical Trials – Completed and Ongoing

Table 2. AAV gene therapy trials for hemophilia A.

Sponsor	Serotype	Transgene	Highest dose (vg/kg)	Mean FVIII:C (%)	T-cell ELISPOT	↑ ALT	↓ FVII:C with ↑ ALT	Steroid treatment	Status*	Ref.
Biomarin Therapeutics	rAAV5	BDD-FVIII	6×10^{13}	4–270	0/7	7/7	1/7	7/7	Recruiting	12
Spark Therapeutics	Spark200/ LK03	BDD-FVIII	2×10^{12}	N/A	N/A	N/A	N/A	N/A	Recruiting	24
Shire	rAAV8	BDD-FVIII	N/A	N/A	N/A	N/A	N/A	N/A	Recruiting	N/A
Sangamo Therapeutics	rAAV2/6	BDD-FVIII	N/A	N/A	N/A	N/A	N/A	N/A	Recruiting	N/A
UCL/SJCRH	rAAV8	BDD-FVIII	N/A	N/A	N/A	N/A	N/A	N/A	Recruiting	N/A

*Status determined by data available to ClinicalTrials.gov as of March 2018.
AAV, adeno-associated virus; ALT, alanine aminotransferase; BDD-FVIII, B-domain-deleted factor VIII; ELISPOT, enzyme-linked immunospot; FVII, factor VII; FVIII, factor VIII; N/A, not available; rAAV, recombinant adeno-associated virus; Ref., reference; SJCRH, St Jude Children's Research Hospital; UCL, University College of London.

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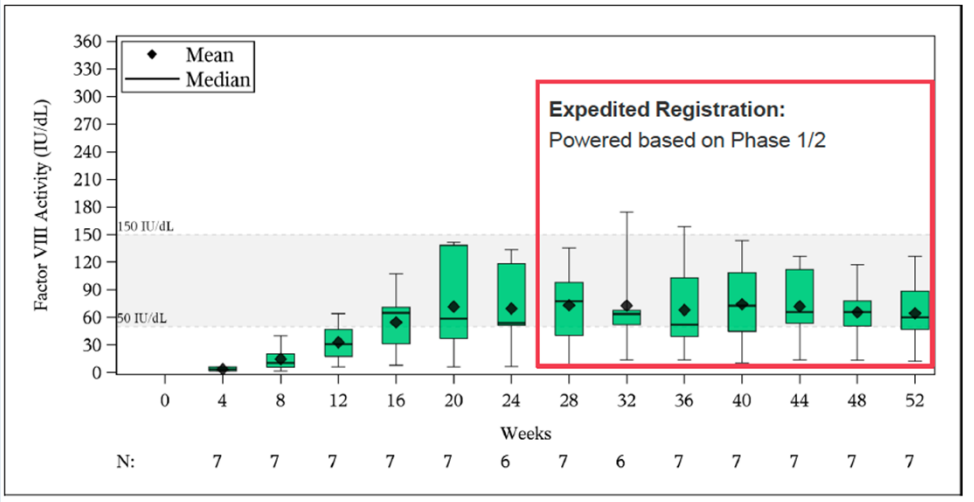
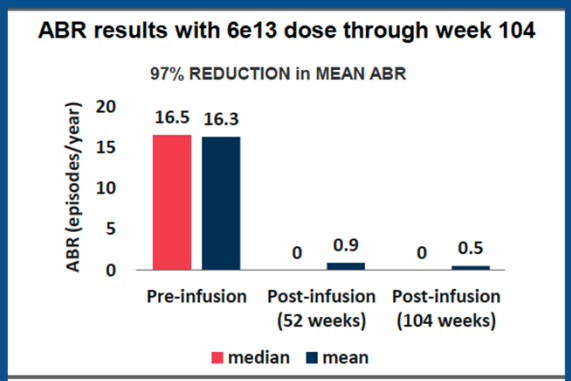
Doshi BS et al. *Ther Adv Hematol*. 2018;9:273-293. Used with permission.

AAV Gene Therapy for Hemophilia A: Durable steady state FVIII levels within the normal range



Biomarin J.P. Morgan 2019 Presentation. https://investors.biomarin.com/events-presentations. Used with permission.

AAV Gene Therapy for Hemophilia A: Results in 97% reduction in annualized bleed rate



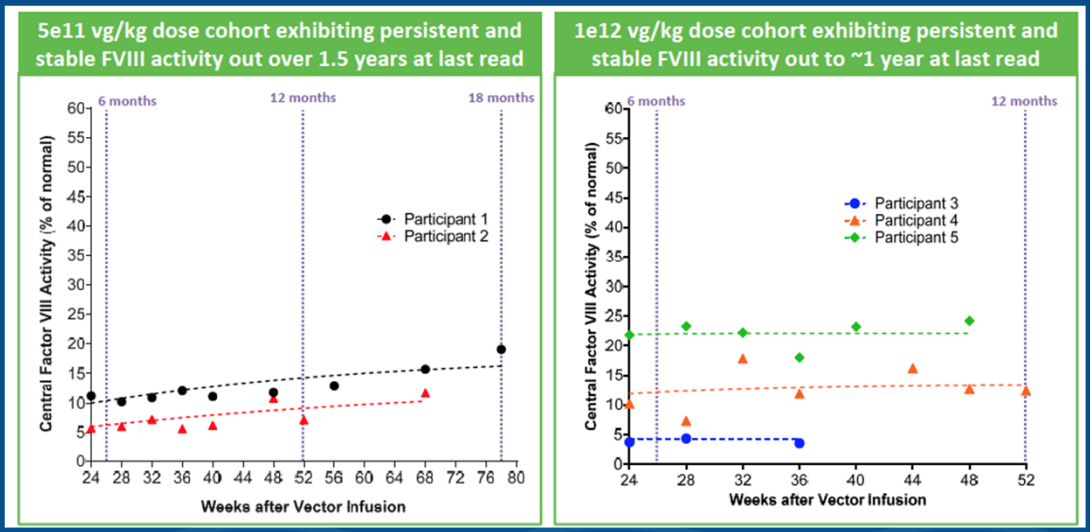
% Patients Bleed Free

Baseline	Year 1	Year 2
14%	71%	86%

All patients off prophylaxis
100% resolution in target joints

Biomarin J.P. Morgan 2019 Presentation. https://investors.biomarin.com/events-presentations. Used with permission.

AAV Gene Therapy for Hemophilia A: Durable steady state FVIII levels above 10%-15%



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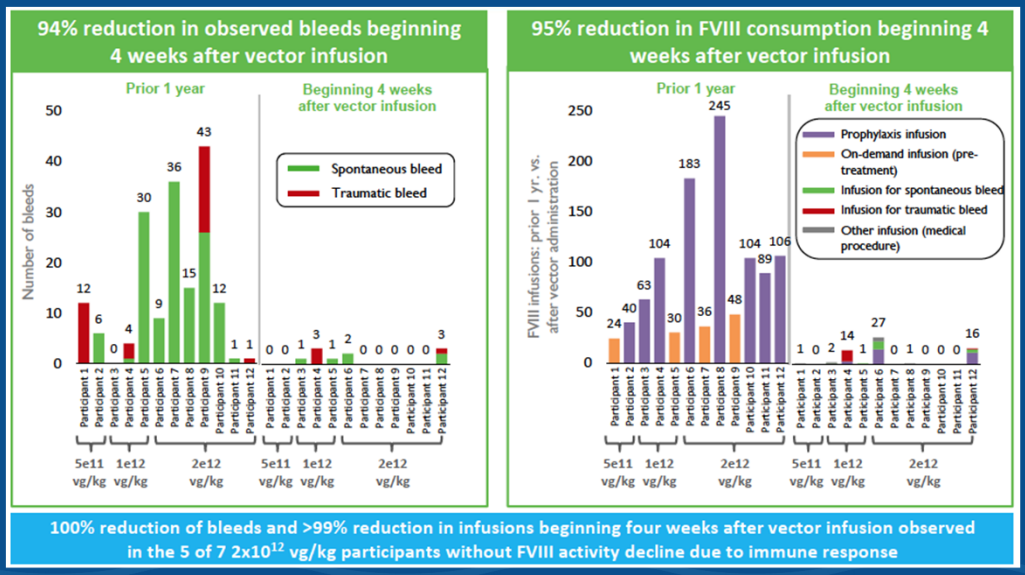
Durable steady state FVIII levels above 10%-15%: 95% reduction in annualized bleeds



100% reduction of bleeds and >99% reduction in infusions beginning four weeks after vector infusion observed in the 5 of 7 $2x10^{12}$ vg/kg participants without FVIII activity decline due to immune response

Spark Therapeutics 2019 JPM Presentation (http://ir.sparktx.com/investor-presentations). Used with permission.

Cost-Effectiveness Evaluation

- Built a Markov state-transition model to evaluate cost-effectiveness of gene therapy vs prophylaxis in a hypothetical cohort of 30- to 40-year old male patients with uncomplicated severe hemophilia
- Third-party payer perspective focusing on direct medical costs
  - >$140,000/yr for prophylaxis
  - Gene therapy assigned cost of $850,000
- Effectiveness measured using:
  - Quality-adjusted life years (QALY)
  - Time spent in health states and quality of life utility values of those states
- 10-year time horizon, assumed 90% success rate

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Machin N, et al. *Blood Adv.* 2018; 2:1792-1798.

Cost-Effectiveness Evaluation

- Over 10-year time horizon
  - Gene therapy cost $1M; resulted in 8.33 QALYs gained
  - Prophylaxis cost $1.7M; resulted in 6.62 QALYs gained

Machin N, et al. *Blood Adv*. 2018; 2:1792-1798.

Potential Financial Solutions: Gene Therapy for Hemophilia

- Milestone-based contracts
  - Based on factor level achieved, liberation from prophylaxis, bleed control
- Performance-based annuities
  - Based on durability of factor levels, reduction in factor concentrate consumption, efficacy in bleed control
- Multi-payer risk pools
  - Limited to no experience
- Business as Usual Creativity
  - Direct partnership with academic centers/HTC/Centers of Excellence
    - CMS Example with CAR-T

HTC = hemophilia treatment center
FoCUS Project Research Compendium, MIT NEWDIGS Initiative

CMS Proposal for CAR-T Cell Therapy

- Proposed new reimbursement policies for chimeric antigen receptor T-cell therapies at cancer centers that meet certain criteria including Registry or Clinical Study to monitor progress
- Policies currently open for public comment

https://www.cms.gov/newsroom/press-releases/cms-proposes-coverage-evidence-development-chimeric-antigen-receptor-car-t-cell-therapy

Federally-funded Hemophilia Treatment Centers as Source for Post-approval Surveillance

- American Thrombosis and Hemostasis Network (ATHN) partners with more than 135 HTCs across the United States to build a safe, secure national database
- used to improve care and support vital research
- National Hemophilia Program Coordinating Center (NHPCC) working with the 8 Health Resources and Service Administration (HRSA)-funded regional hemophilia networks (RHNs)
- Currently developing a registry for gene therapy for hemophilia across the affiliates
  - Could extend well-beyond clinical trial follow up and post-marketing obligations

Questions?
Attendance Code:

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  - Session-specific attendance code
- Complete and submit session evaluation **no later than Monday, April 29, 2019 (5:00 PM ET)**
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Learning Objectives

- Describe how key issues related to the development of gene therapy may impact a variety of stakeholders.
- Discuss the potential place for gene therapy among a number of novel therapeutics recently approved or in the drug development pipeline.
- Discuss the unique requirements for patient follow-up and surveillance for potential adverse events.

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Financial Relationship Disclosures

Disclosure Information	Advisory Board	Consultant	Grants / Research	Salary / Contractual	Supported Promotional Education	Stock / Shareholder	Other Financial Support
Jane F. Barlow, MD, MPH, MBA Panelist	Pictet	MIT, Real Endpoints	None	None	None	Therapeutics MD	None
Steven W. Pipe, MD Panelist	Freeline Therapeutics, uniCure	uniCure	None	None	None	None	None
Sophie Schmitz, BA, MA Panelist	None	None	None	None	None	None	None
Susan Trieu, PharmD Panelist	None	None	None	Spouse Employee: AstraZeneca	None	None	None

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Panelists

Jane F. Barlow, MD, MPH, MBA
Senior Advisor
MIT Center for Biomedical Innovation
Scottsdale, Arizona

Steven W. Pipe, MD
Professor of Pediatrics and Pathology
University of Michigan
Ann Arbor, Michigan

Sophie Schmitz, BA, MA
Managing Partner
Partners4Access
Hilverum, Noord-Holland
Netherlands

Susan Trieu, PharmD
Director, Enterprise Specialty Clinical Solutions
MedImpact Healthcare System, Inc.
Southlake, Texas

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Closing Remarks

Networking Reception

5:30 pm to 6:30 pm

Marina Foyer

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More Learning Available Today!

- Satellite Symposium

"ManagedCareHemo.com Presents Hemophilia Clinical Updates and Cost Management Solutions"

6:00 pm to 8:00 pm

Marriott Marquis San Diego Marina

Marina Ballroom F&G

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