The Gene Therapy Transformation:
A Guide for Managed Care Decision Makers

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Postgraduate Institute for Medicine
Professional Excellence in Medical Education

Impact Education LLC

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Live Webcast
July 16, 2020
12:30pm – 2:00pm ET

Welcome

Mari-Pat Pusey, MBA
Senior Product Director
OptumRx

Agenda

12:30pm – 12:35pm ET	Opening Comments/Overview **Mari-Pat Pusey, MBA**
12:35pm – 1:05pm	*Principles of Gene Therapy and Measurement of Clinical Outcomes* **John Petrich, RPh, MS**
1:05pm – 1:25pm	*Assessing the Curative Benefits of Gene Therapy in a Cost Conscious Environment* **Edmund Pezalla, MD, MPH**
1:25pm – 1:45pm	*Medical and Pharmacy Management Strategies for Optimal Gene Therapy Outcomes* **Mari-Pat Pusey, MBA**
1:45pm – 2:00pm	Audience Q&A Session
2:00pm	Key Takeaways and Closing Comments

Learning Objectives

- Explain the molecular and physiologic principles of gene therapy in the treatment of rare diseases
- Review outcomes measures for clinical trials in gene therapy and the pertinent clinical trial data for investigational treatments
- Evaluate the financial implications of gene therapy in terms of acquisition costs reconciled with the potential for improved outcomes and reduced health care service utilization
- Assess current and proposed payment models aligned with appropriate use for high-cost therapies

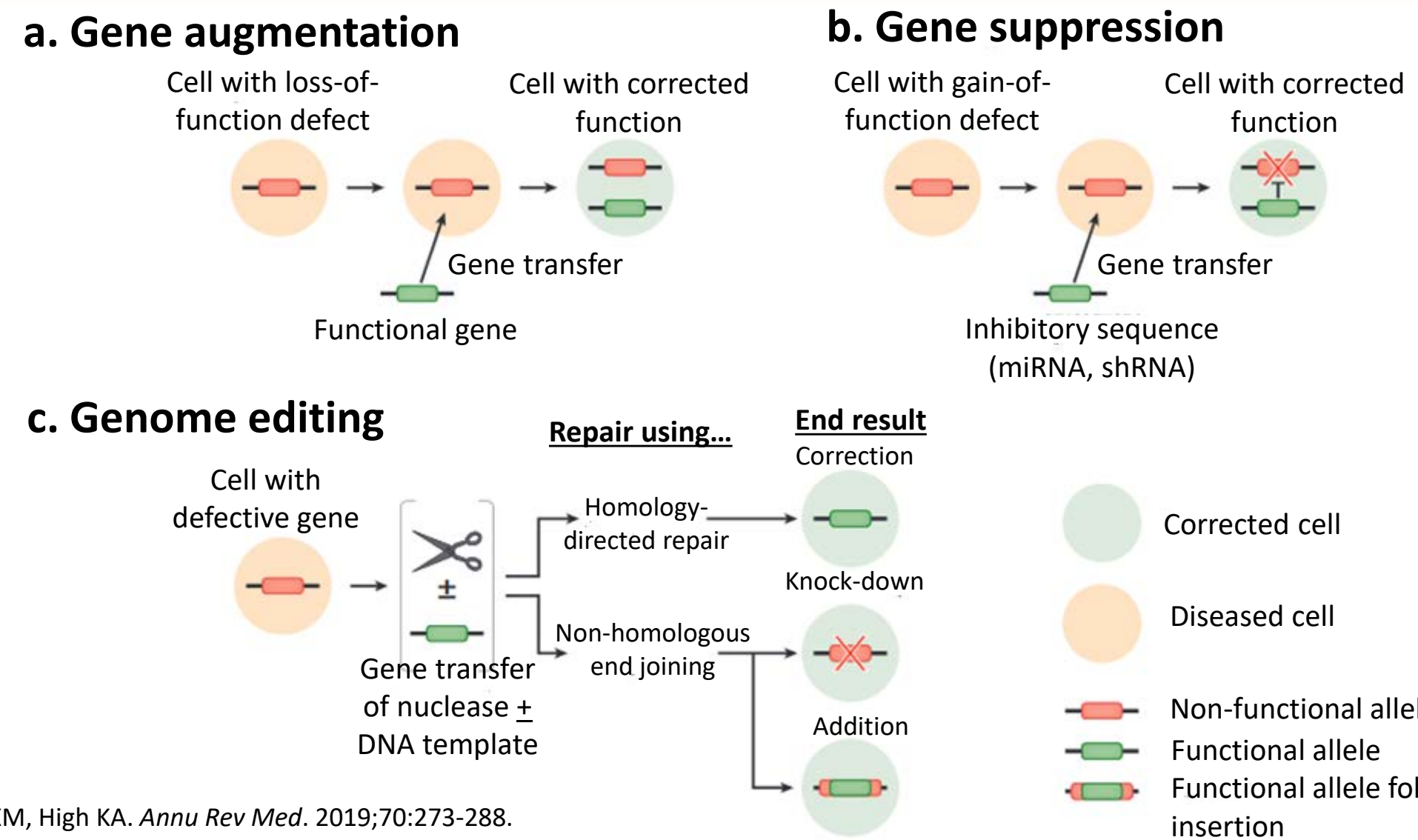
Which of the following best describes your area of greatest educational need with regards to this program?

1) The molecular and physiologic principles of gene therapy in the treatment of rare diseases
2) Outcomes measures for clinical trials in gene therapy and the pertinent clinical trial data for investigational treatments
3) The financial implications of gene therapy in terms of acquisition costs reconciled with the potential for improved outcomes and reduced health care service utilization
4) Current and proposed payment models aligned with appropriate use for high-cost therapies

Principles of Gene Therapy and Measurement of Clinical Outcomes

John Petrich, BS Pharmacy, MS
Manager, Investigational Drug Service
Cleveland Clinic

Gene Therapy Aims to Restore Healthy Physiologic Function or Suppress Aberrant Activity



Anguela XM, High KA. *Annu Rev Med*. 2019;70:273-288.

Somatic Cell Gene Therapy

- Therapeutic genes transferred into the somatic cells
- Will not be inherited by later generations
- All current research is directed at correcting genetic defects in somatic cells

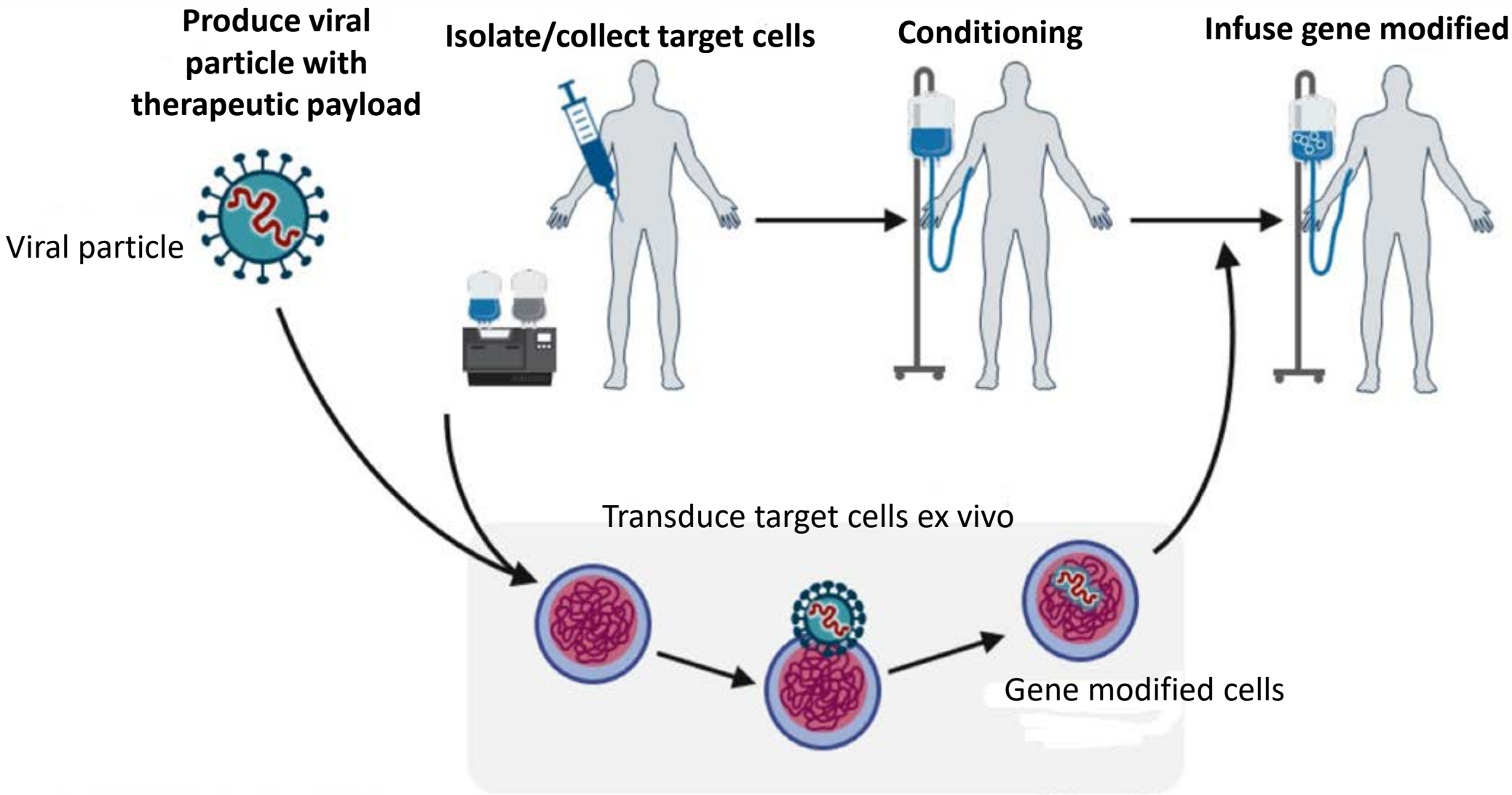
Germ-Line Gene Therapy

- Normal version of gene is inserted into germ cells
  - Those germ cells will divide normal versions of the gene
  - Any zygote produced as a result of this germ cell will have a correct version of the defective gene and will continue passing it on to *their* offspring
- Not being attempted in present research due to safety, ethical, and technical issues

3 Means of Introducing Modified Genes to Patients

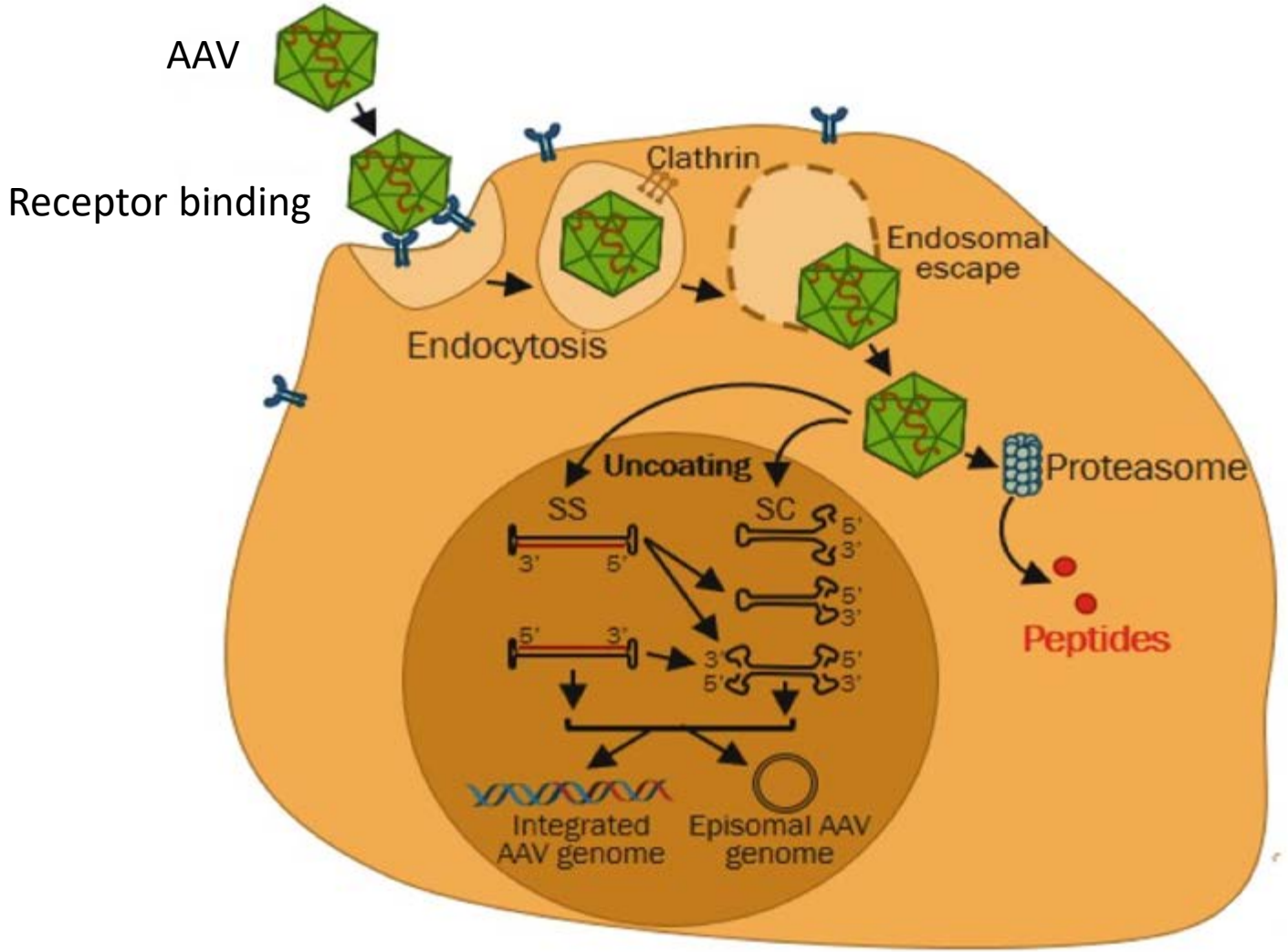
- *Ex vivo* strategy
  - The patients' cells are cultured in the laboratory, the new genes are infused into the cells, and modified genes are administered back to the patient
- *In situ strategy*
  - The carrier of the gene is injected to the patient either intravenously or directly to the tissues
- *In vivo* strategy
  - The vector is administered directly to the cell

Ex Vivo Gene Therapy Process



Walters M, et al. Abstract S814. Oral presentation at 22nd Congress of the European Hematology Association; June 22-25, 2017; Madrid, Spain.

In Vivo Gene Therapy Process



Wang D, Tai PWL, Gao G. *Nat Rev Drug Discov*. 2019;18(5):358-378.

In which of the following conditions does in vivo gene therapy offer a potential advantage?

1) Hemoglobin diseases, hematological cancer, immune deficiencies
2) Conditions that benefit from modification of hematopoietic stem cells
3) Hemophilia A and hemophilia B, metabolic diseases
4) None of the above
5) Unsure

Potential Advantages and Challenges Associated with Ex Vivo and In Vivo Strategies

Ex Vivo Gene Therapy		In Vivo Gene Therapy	
Potential Advantages	**Challenges**	**Potential Advantages**	**Challenges**
Suitable for conditions that benefit from modification of hematopoietic stem cells	Not suitable for important target cells (brain, liver,…)	Suitable for target cells that cannot be isolated and processed ex vivo (liver, brain)	Immune reactions
Hemoglobin diseases, hematological cancer, immune deficiencies	Insertional mutagenesis	Hemophilia A and hemophilia B, metabolic diseases	Efficiency of transfer

What Are Vectors and Why Are They Needed?

Different carrier systems are being studied for gene delivery

1) Viral systems
   - Certain viruses are often used as vectors because they can deliver the new gene by infecting the cell
   - The viruses are modified so they cannot cause disease when used in people, but immunogenicity issues may still arise
   - Examples: retroviruses, adenoviruses, adeno-associated viruses (AAVs), herpes simplex viruses (HSVs)
2) Non-viral systems
   - Advantages include simple large-scale production and low host immunogenicity
   - Limited levels of transfection and expression of the gene
   - Examples: naked DNA, oligonucleotides, lipoplexes and polyplexes

Vectors are needed since the genetic material has to be transferred across the cell membrane and preferably into the cell nucleus

Viral Vectors: Retroviruses

Advantage

The virus is replication deficient, so it is safe and suitable for the treatment of a variety of diseases

Disadvantages

1) Random insertion can disrupt normal gene

2) Retroviruses use rapidly dividing cells as targets; non-dividing cells cannot be used

Viral Vectors: DNA Viruses

Adenovirus

- Ideal since they do not produce serious illness in their natural state

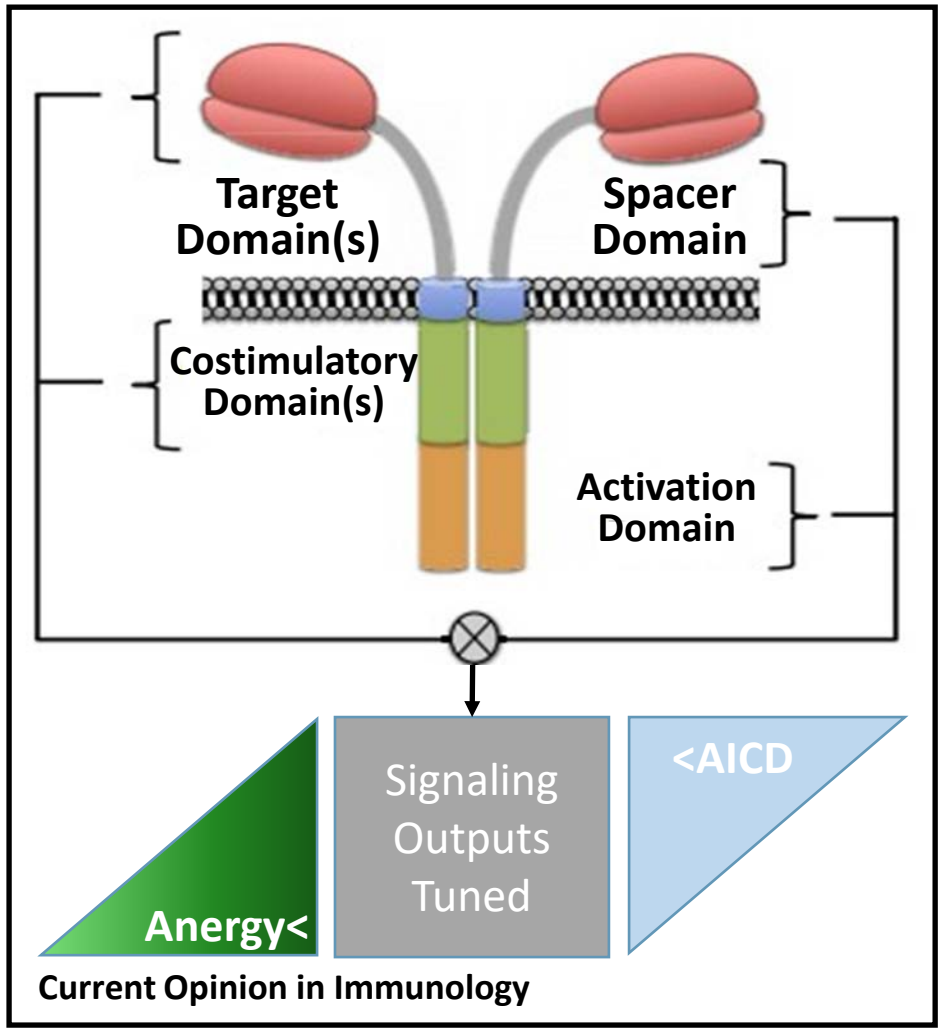
AAV

- No known pathogenic effect and wide tissue affinity
- Integrates at a specific site

Herpes simplex virus

- Disabled single copy virus with defective glycoprotein
- When propagated in the complementary cells, viral particles are generated
- Since they can replicate only once, there is no risk of disease

Gene Therapy for Cancer: Chimeric antigen receptor T-cell therapy (CAR-T)



Jensen MC, Riddell SR. *Curr Opin Immunol*. 2015;33:9-15.

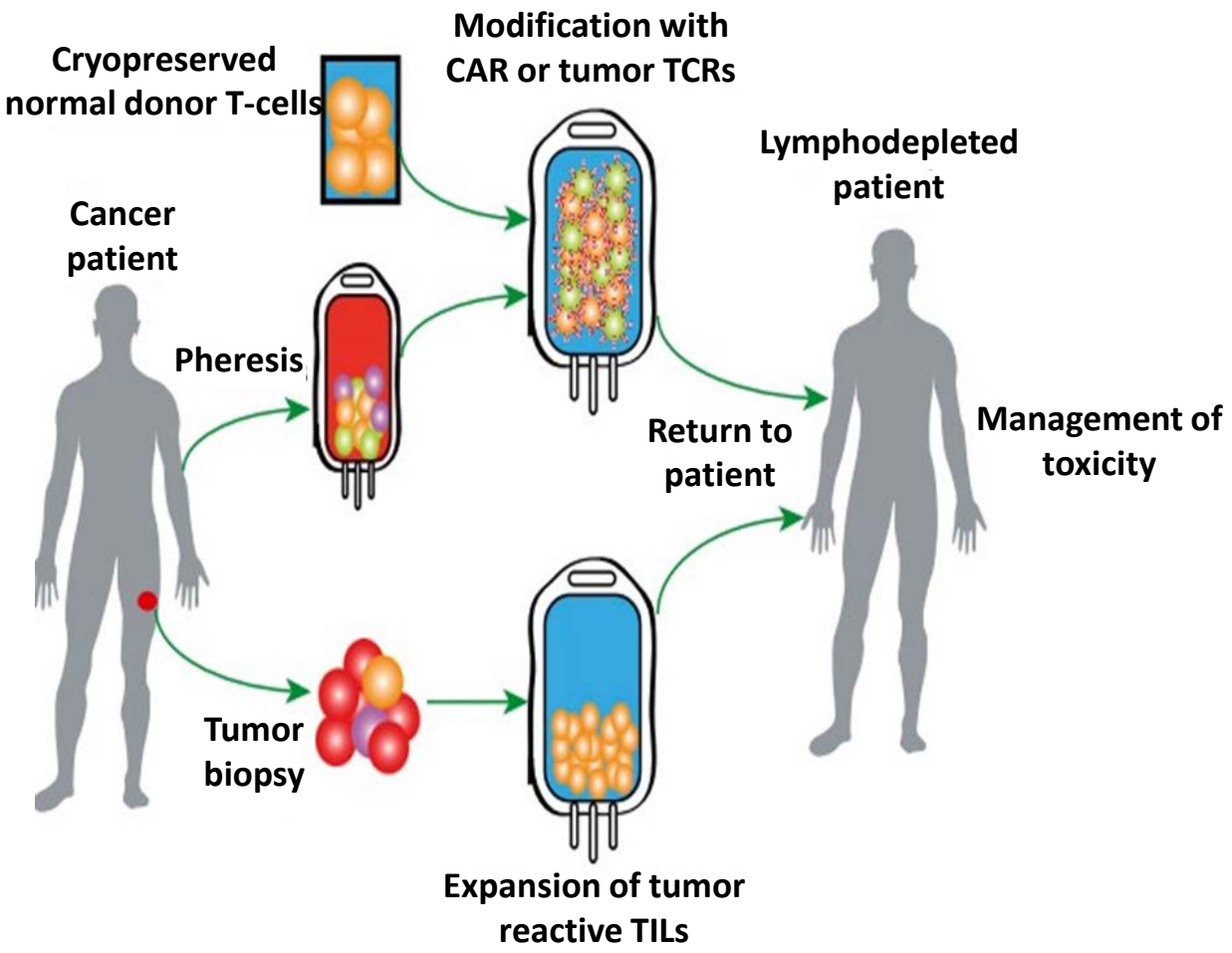
CAR T- cells recognize tumor cells independent of their expression of human leukocyte antigen (HLA) molecules, allowing for the elimination of tumor cells that escape conventional T-cells by downregulating HLA and/or mutating components of the antigen processing machinery

Chimeric antigen receptors (CARs) are fusion molecules typically composed of the following:

- An extracellular single chain variable fragment (scFv) of a monoclonal antibody (mAb) specific for a surface molecule on the tumor cell
- A spacer domain that provides flexibility and optimizes T-cell and target cell engagement
- A transmembrane domain
- Signaling modules that trigger T-cell effector functions

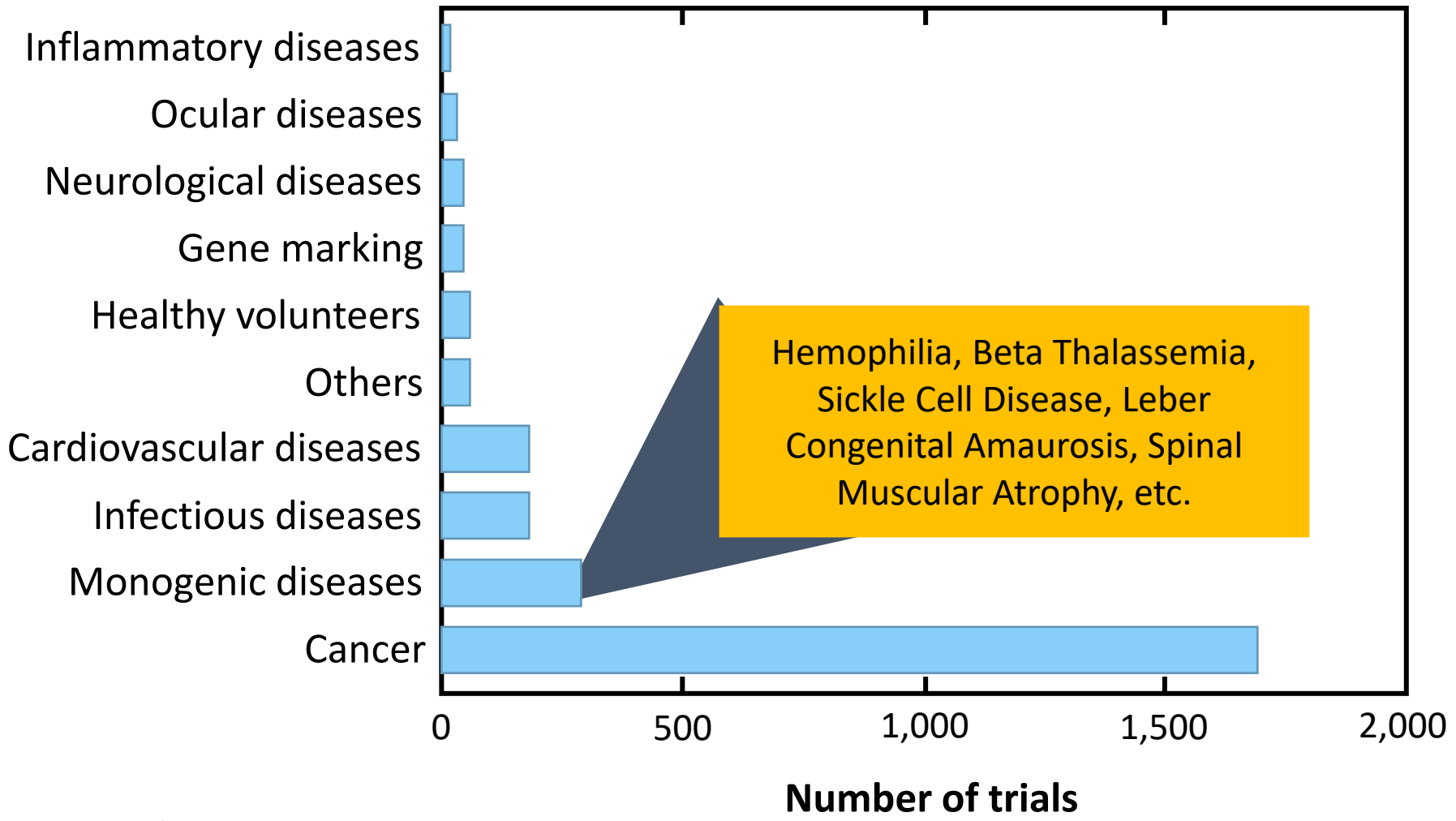
CAR T-cell Therapy: Pathway to the Patient

- Normal donor cells can be modified to inactivate their alloreactivity while being armed with antitumor CARs or T-cell receptors (TCRs)
- Alternatively, a patient's own cells can be modified with antitumor molecules.
- In solid tumors, biopsy specimens can be used to isolate tumor infiltrating lymphocytes (TILs) for expansion
- In most cases, the patient will require some amount of conditioning before receiving antitumor lymphocyte infusions
- Careful management of toxicities emerging from these therapies is also required



Barrett DM, Grupp SA, June CH. *J Immunol*. 2015;195(3):755-761.

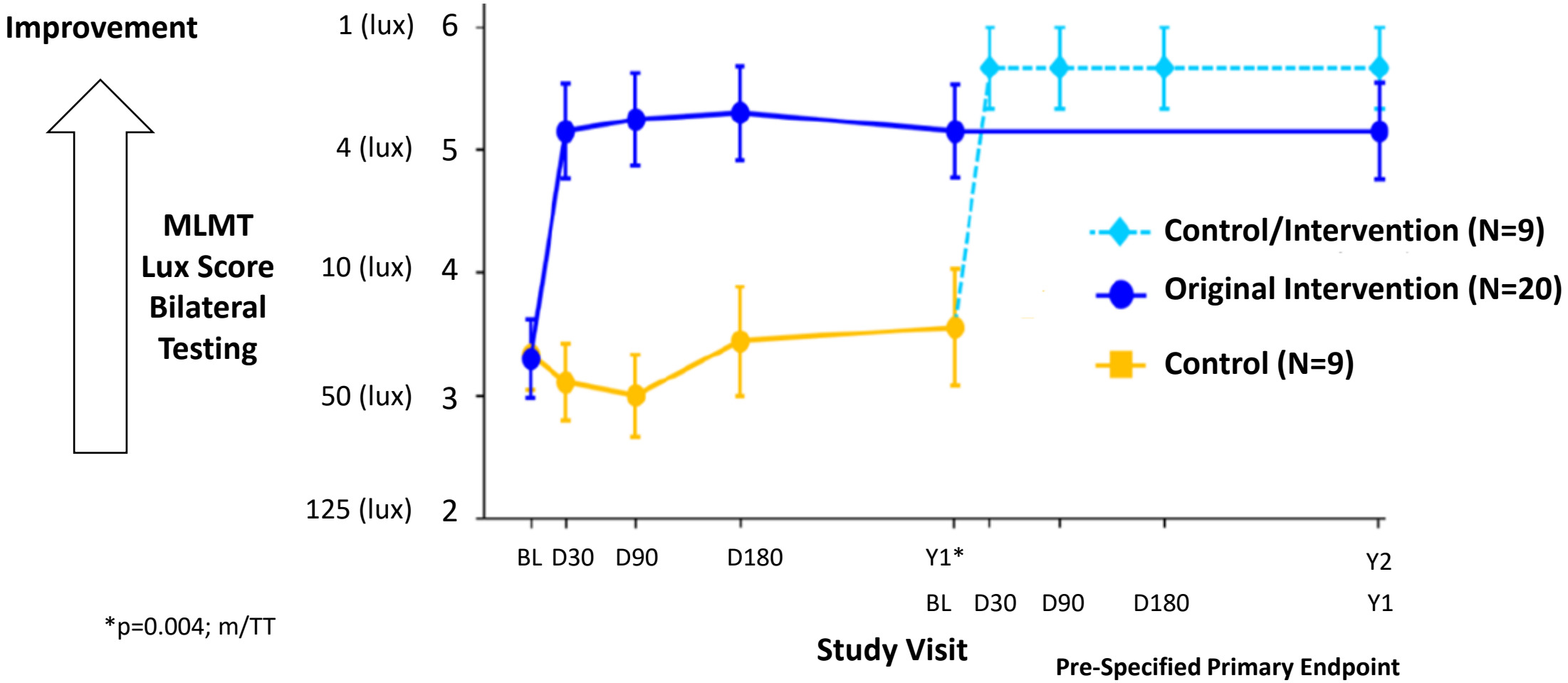
Second to Only Cancer, Monogenic Conditions Represent a Leading Disease Area in Terms of Gene Therapy Research and Development



Anguela XM, High KA. *Annu Rev Med*. 2019;70:273-288.

Voretigene Neparvovec is a Novel Gene Therapy Approved for the Treatment of Leber's Congenital Amaurosis

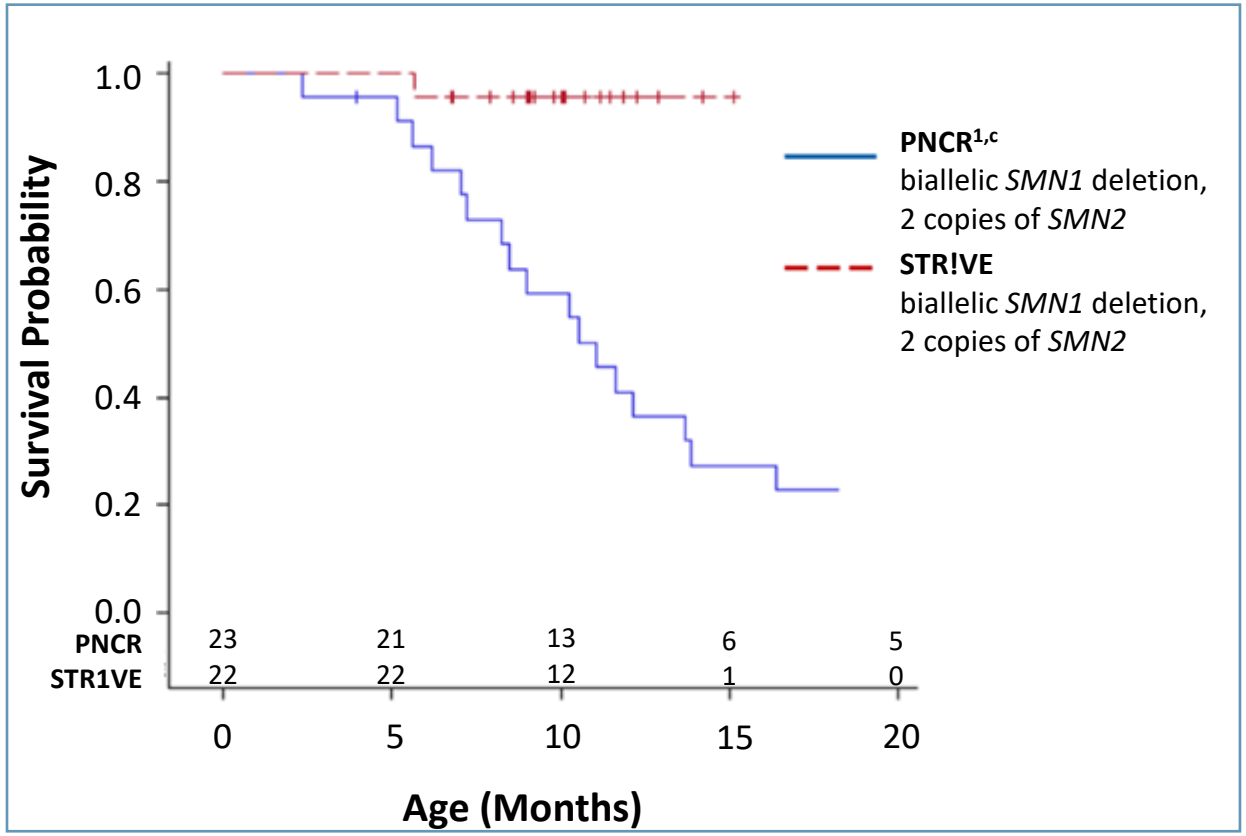
Observed Mean Bilateral MLMT Lux Score in Modified Intent-to-Treat Participants



*p=0.004; m/TT

Russell S, et al. Paper presented at: Annual Meeting of Ophthalmology 2017; November 14, 2017; New Orleans, LA.

Onasemnogene Abeparvovec is a Gene Therapy Approved on the Basis of Significant Therapeutic Benefit in Prolonging Event-free Survival in SMA Type 1 patients



Median age at datacut: 14.4 months

	Survival	
Age (months)	**PNCR[1]**	**CL-303**
10.5	50%	95%[a]
13.6	25%	87%[b]

At datacut (March 8, 2019):

[a]19 of 20 patients (95%) who had reached 10.5 months of age or discontinued the study prior to 10.5 months of age, survived without permanent ventilation[c]

[b]13 of 15 patients (87%) who had reached 13.6 months of age or discontinued the study prior to 13.6 months were surviving without permanent ventilation[c,d]

[a]Survival for PNCR[1] – no death, or no need for ≥16-h/day ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness; n=23 (2 copies of *SMN2*). March 8, 2019 datacut. [c]One patient died at the age of 7.8 months due to causes unrelated to treatment. [d]One patient withdrew at 11.9 months of age. PNCR, Pediatric Neuromuscular Clinical Research; SMA1, spinal muscular atrophy type 1. 1. Finkel RS, et al Neurology. 2014;83:810-7.

Day J, Chiriboga CA, Crawfor TO, Darras BT, Finkel RS, Connolly AM, et al. Poster presented at American Association of Neurology 2019 Annual Meeting; May 5, 2019; Philadelphia

FDA Guidance on Human Gene Therapy For Rare Diseases: Study Population

- If the disease is caused by a genetic defect, the sponsor should perform genetic test(s) for the specific defect(s) of interest in all clinical trial subjects
- Pre-existing antibodies to any component of the GT product may pose a potential risk to patient safety and limit its therapeutic potential
- Sponsors may choose to exclude patients with pre-existing antibodies to the GT product
- Severity of disease should be considered in designing clinical GT trials in the context of the ability to report and detect adverse events as well as considerations related to the anticipated risk and potential benefits to subjects
- It is important that clinical investigations in pediatric patients address ethical considerations for conducting investigations in vulnerable populations
- The risks of most GT products include the possibility of unintended effects that may be permanent, along with adverse effects due to invasive procedures that may be necessary for product administration

Human Gene Therapy for Rare Diseases: Guidance for Industry. U.S. Food and Drug Administration website. https://www.fda.gov/media/113807/download. Published January 2020. Accessed June 2020.

FDA Guidance on Human Gene Therapy For Rare Diseases: Study Design

- For rare diseases, there may be a limited number of patients who may qualify for enrollment into a clinical study
  - As a result, it is often not feasible to enroll unique subjects for all studies conducted under different phases of the clinical development program
- Limitation in the number of prospective subjects warrants the collection of as much pertinent data (e.g., adverse events, efficacy outcomes, biomarkers) as possible from every subject, starting from the first-in-human study
  - All such data may be valuable to inform the design of subsequent studies (e.g., selection of study populations and endpoints)
- The randomized, concurrent-controlled trial is generally considered the ideal standard for establishing effectiveness and providing treatment-related safety data with placebo controls when feasible
- Alternative trial designs and statistical techniques that maximize data from a small and potentially heterogeneous group of subjects (including genetic heterogeneity) should be considered

Human Gene Therapy for Rare Diseases: Guidance for Industry. U.S. Food and Drug Administration website. https://www.fda.gov/media/113807/download.

FDA Guidance on Human Gene Therapy For Rare Diseases: Safety Considerations

- Clinical trials should include a monitoring plan that is adequate to protect the safety of clinical trial subjects
- Development of neutralizing and non-neutralizing immune responses that are directed against the product should be monitored throughout the clinical trial
- Pharmacovigilance systems should actively monitor each recipient of a GT product
- The potential for viral shedding should be addressed early in product development

Human Gene Therapy for Rare Diseases: Guidance for Industry. U.S. Food and Drug Administration website. https://www.fda.gov/media/113807/download. Published January 2020. Accessed June 2020.

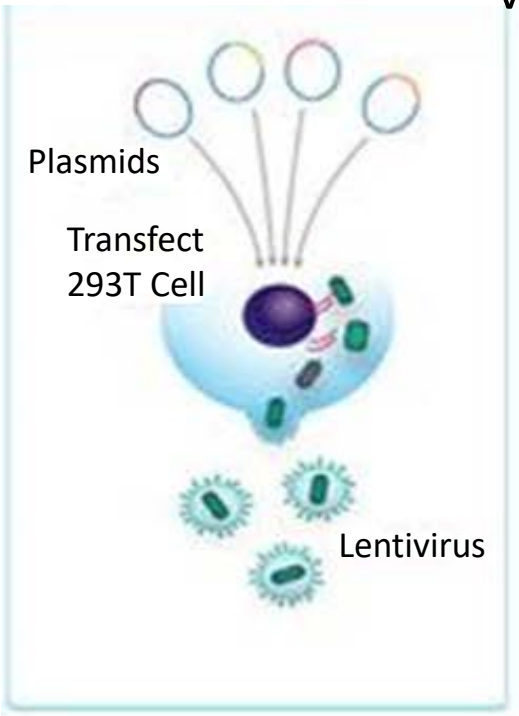
FDA Guidance on Human Gene Therapy For Rare Diseases: Efficacy Endpoints

- For many rare diseases, well-established, disease-specific efficacy endpoints are not available
- Understanding of disease pathophysiology is important in designing clinical trials, including selection of endpoints
  - Disease pathophysiology and natural history can help identify potential surrogate endpoints that are reasonably likely to predict clinical benefit
  - To support accelerated approval, sufficient data is needed to support a conclusion that the proposed endpoint is reasonably likely to predict clinical benefit
  - In general, such data should, at a minimum, demonstrate a correlation between changes in the proposed surrogate endpoint and a beneficial clinical effect

Human Gene Therapy for Rare Diseases: Guidance for Industry. U.S. Food and Drug Administration website. https://www.fda.gov/media/113807/download. Published January 2020. Accessed June 2020.

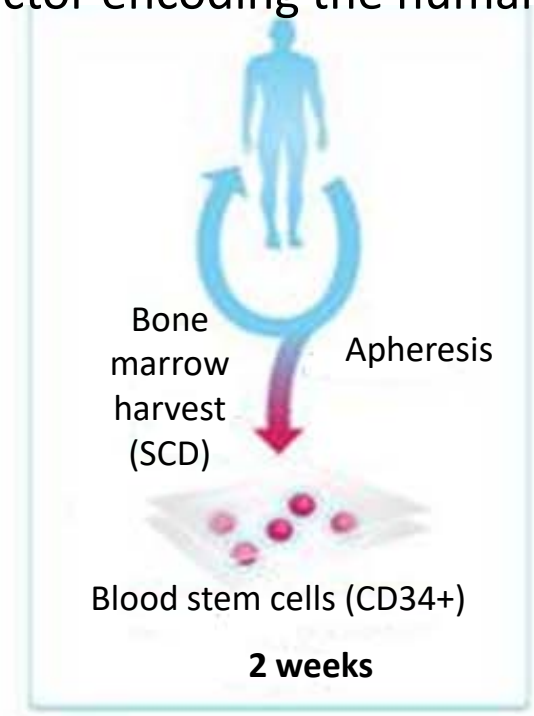
Gene Therapy for Hemoglobinopathies: Thalassemia and Sickle Cell Disease

Autologous CD34+ hematopoietic stem cells transduced with LentiGlobin BB305 lentiviral vector encoding the human beta-A-T87Q globin gene



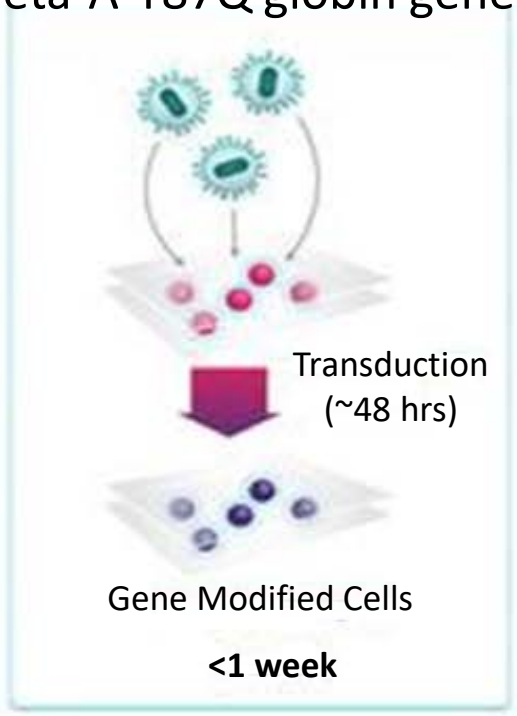
Produce virus with therapeutic payload

Produce Lentiviral vector carrying a functional gene sequence.



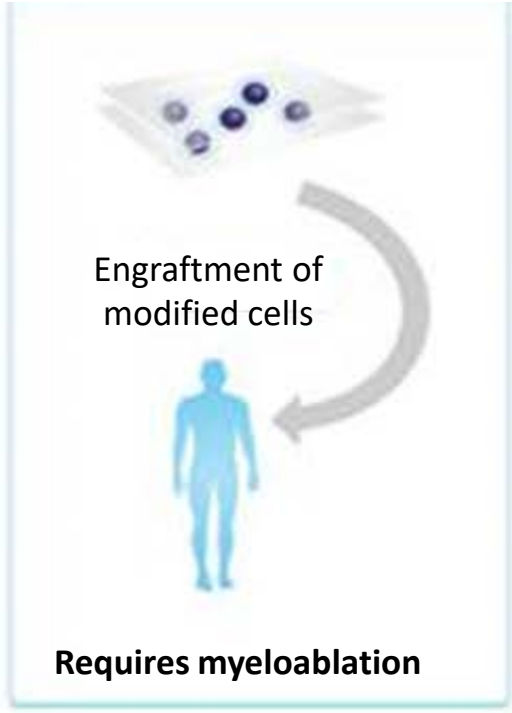
Isolate target cells from patient

Mobilize, extract and isolate patients HSC's or T-cells.



Transduce target cells ex vivo

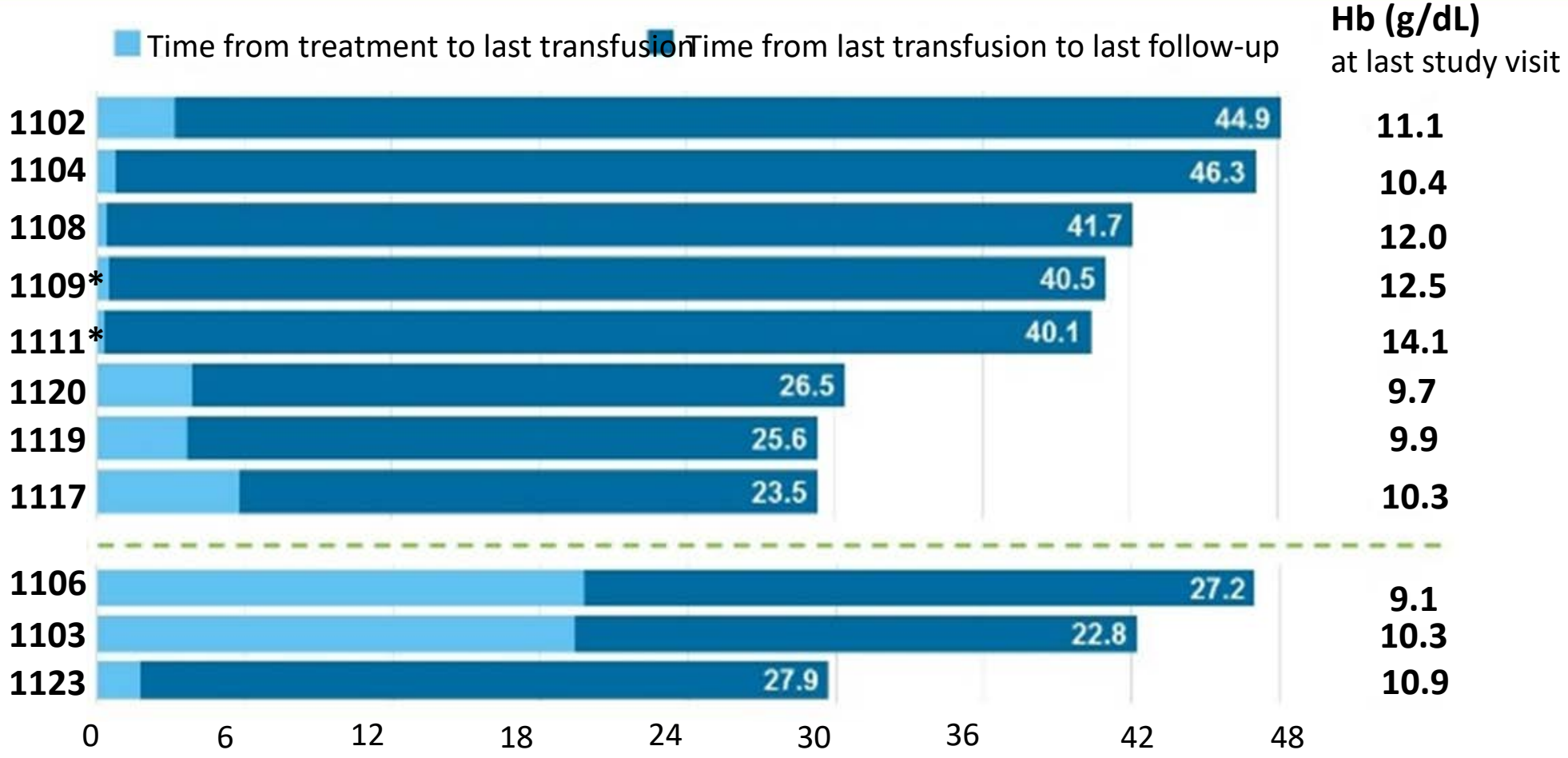
Insert target gene sequence into the patient's HSC's or T-cells



Test & re-infuse gene modified cells

Prepare patient & re-infuse patient's correct HSC's or T-cells.

Northstar Study: 8/10 Patients with Non-β^0/ β^0 Genotypes and 3/8 Patients with β^0/ β^0 Genotypes with Beta Thalassemia are Free from Chronic RBC Transfusions

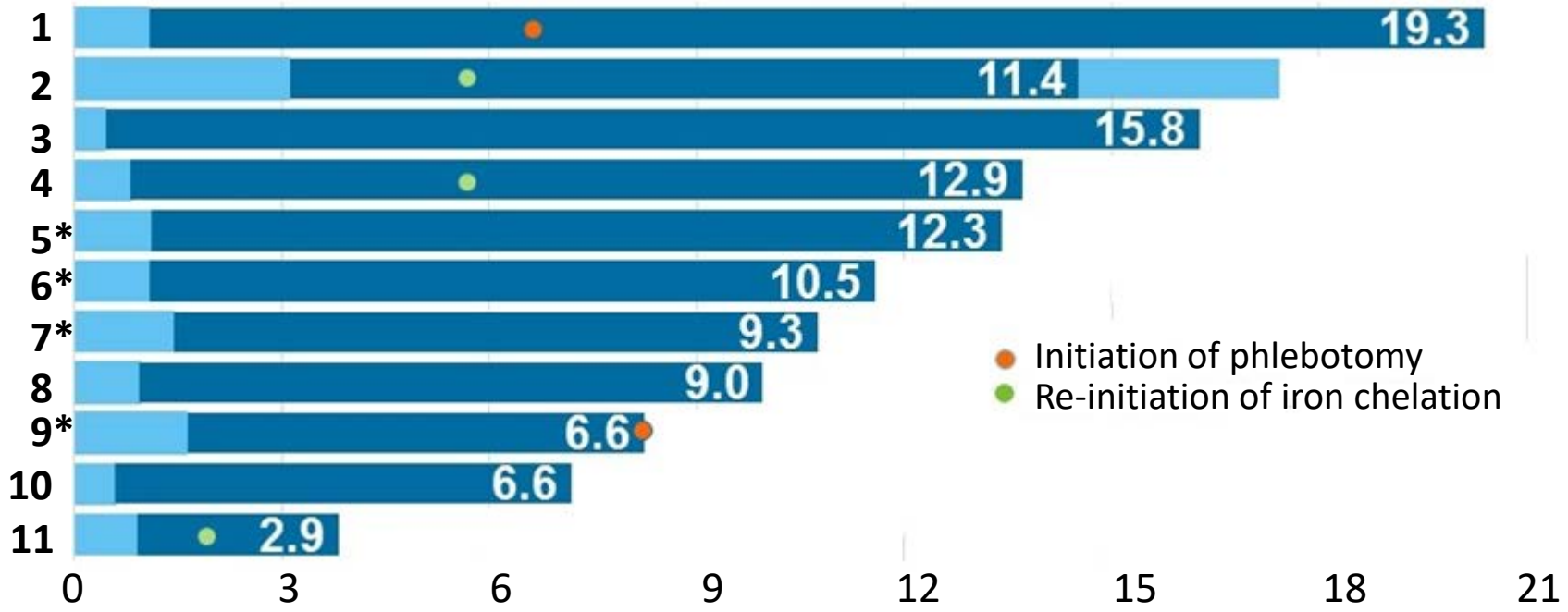


Locatelli F. Abstract 1510. Oral presentation at the 23rd European Hematology Association Congress; June 16, 2018; Stockholm, Sweden.

*Indicates male patients Hb, hemoglobin, TI, transfusion independence (weighted average Hb ~9 g/dL without any red blood cell transfusions for ~12 months)

Northstar-2 Study: 10/11 Patients with Beta Thalassemia Are Transfusion Free with Hemoglobin >11 g/dL

Time free from chronic transfusions in patients with ≥3 months follow-up



Hb (g/dL) at last study visit	Peripheral VCN
13.3	3.2
11.3∓	0.4
11.1	2.2
12.1	1.7
12.3	1.7
12.5	2.9
11.6	5.6
12.4	1.1
11.9	4.9
11.6	5.4
11.2	5.6

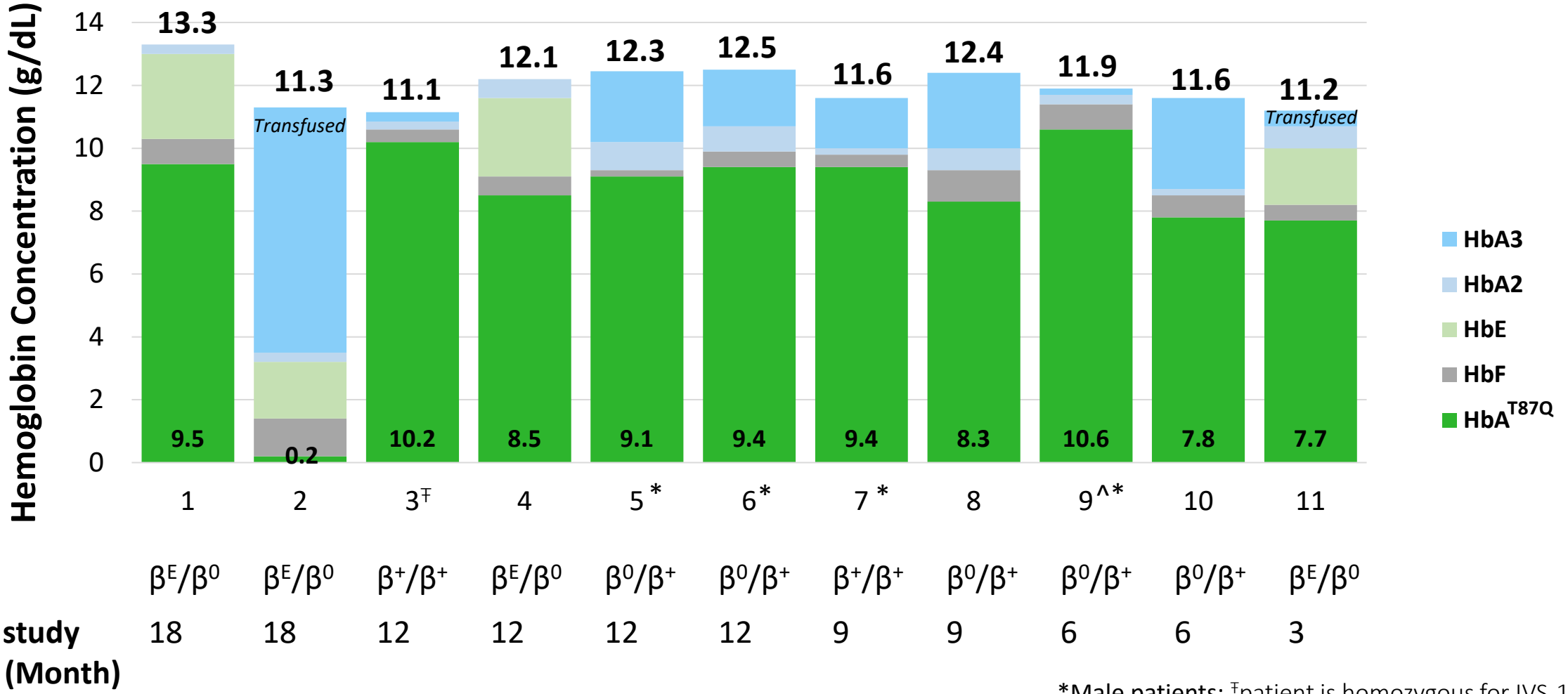
Safety profile post DP infusion remains consistent with myeloablative conditioning

Patients 1 and 3 have achieved the protocol definition of transfusion independence†

*Male patients; ∓Hb supported by transfusions; ǂWeighted average Hb ≥9 g/dL without any RBC transfusions for ≥ 12 months; Hb, hemoglobin; VCN, vector copy number (vendor copies/diploid genome)

Locatelli F. Abstract S1632. Presented at the 24th European Hematology Association Congress. June 16, 2019; Amsterdam, the Netherlands.

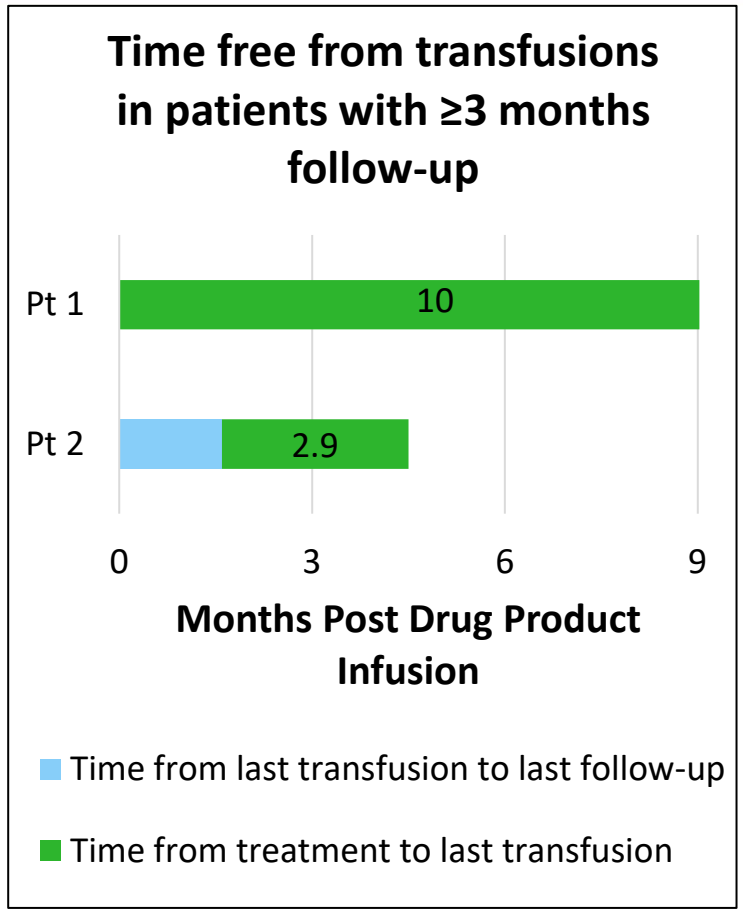
Northstar-2 Study: High Levels of Gene Therapy-Derived HbA^{T87Q} in 10/11 Patients

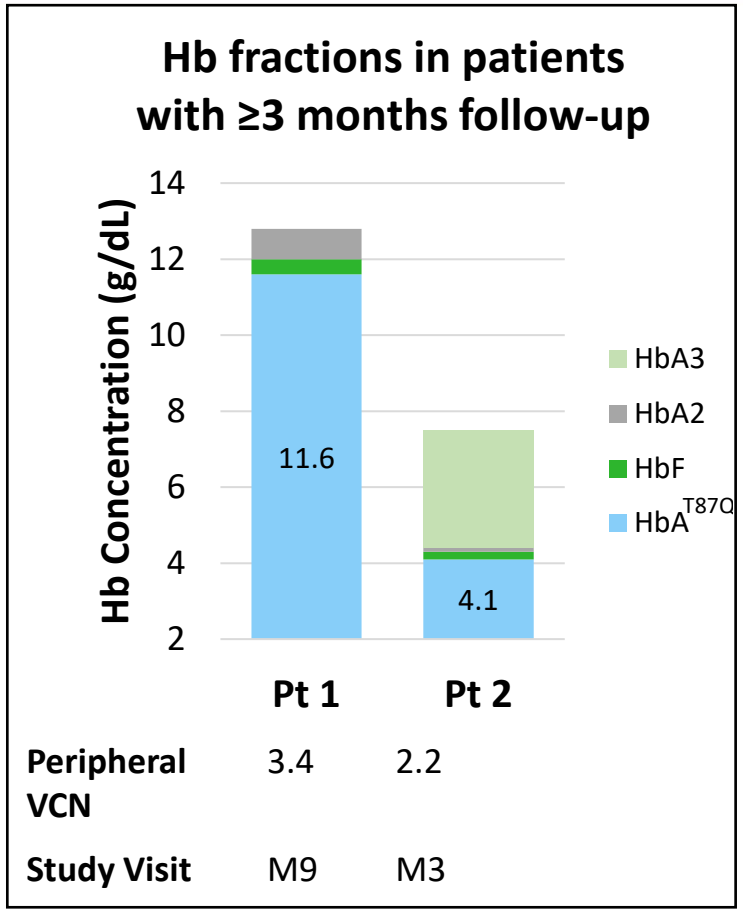


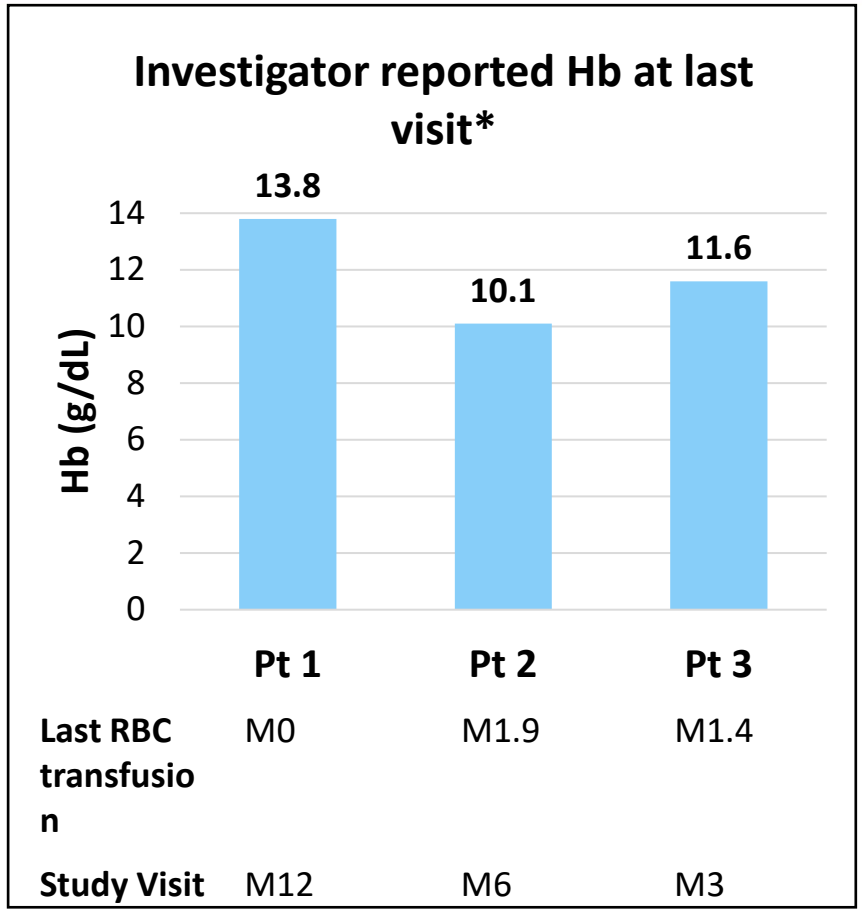
Locatelli F. Abstract S1632. Presented at the 24th European Hematology Association Congress. June 16, 2019; Amsterdam, the Netherlands.

*Male patients; $^{\mp}$patient is homozygous for IVS-1-5; β-globin mutation; ^Patient is heterozygous for IVS-1-5; Hb, hemoglobin

Northstar-3 Study: Normal Total Hemoglobin in First β^0/β^0 Patient







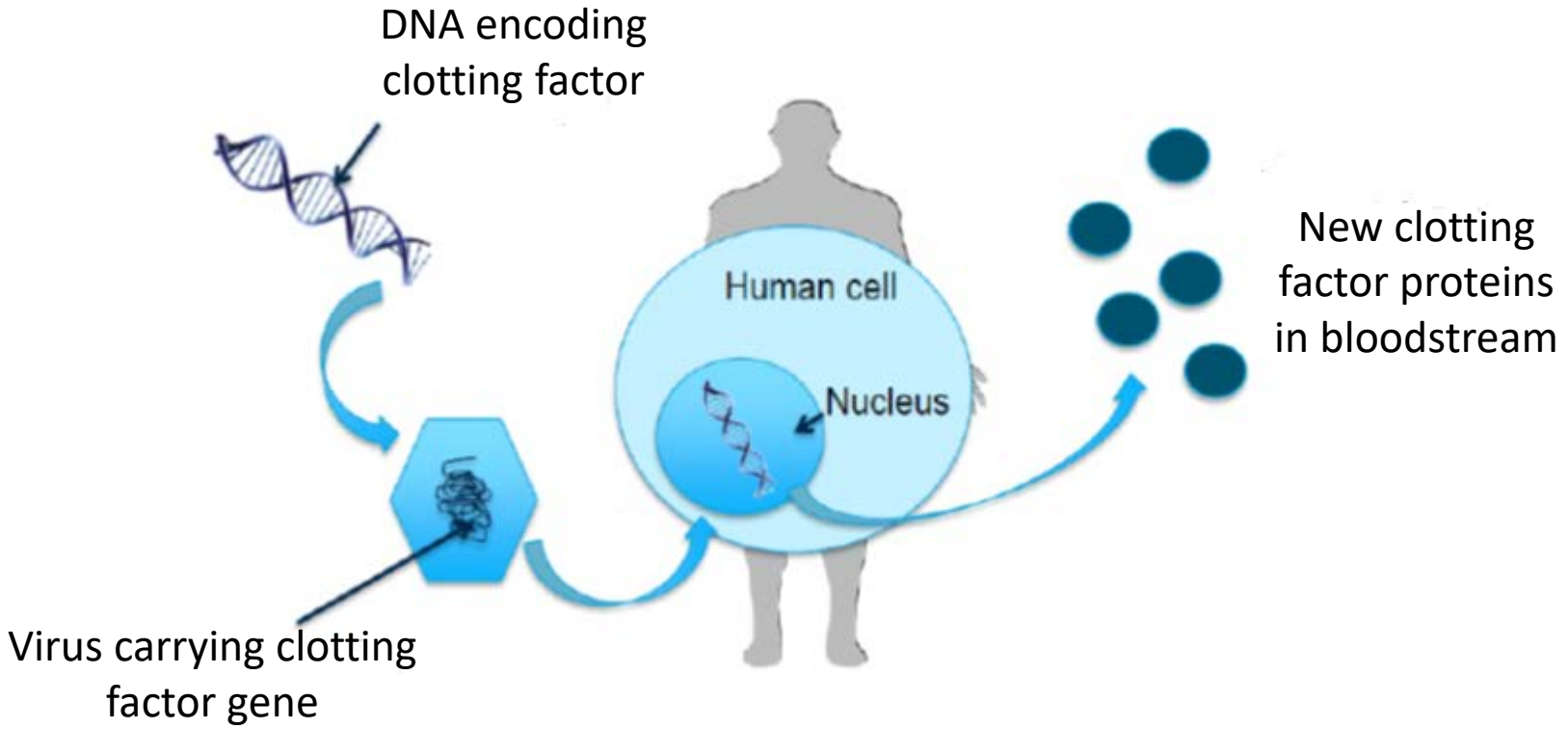
Safety profile post-drug product infusion remains consistent with myeloablative conditioning

AEs, adverse events; DP, drug product; Hb, hemoglobin; VCN, vector copy number (vector copies/diploid genome)

*Includes investigator reported data as of November 19, 2018, not from programmed statistical

Kulozik A. Abstract S140. Presented at the 24th European Hematology Association Congress. June 14, 2019; Amsterdam, the

Gene Therapy for Hemophilia: Restoring Normal Factor Production



Gene therapy has the potential to reduce disease severity by eliciting continuous production of FVIII/FIX with a one-time treatment for gene transfer

- Alleviates the need for repeated, prophylactic treatment
- Numerous trials have now been initiated

Active Gene Therapy Trials for Hemophilia A

Sponsor (Product)	Transgene	Vector
BioMarin (Valoctocogene roxaparvovec)	Codon optimized BDD-FVIII	AAV5
UCL/St. Jude	Codon optimized FVIII; B domain replaced with V3 peptide	AAV8
Spark Therapeutics (SPK-8011)	BDD-FVIII	Hybrid capsid
Dimension Therapeutics/Bayer (DTX-201)	BDD-FVIII	AAVRh10
Takeda (TAK-754)	BDD-FVIII	AAV8
Sangamo Bioscience (SB-525)	BDD-FVIII	AAV6

Koutnik-Fotopoulos E. Innovations in Managing Hemophilia. First Report Managed Care. 2019;16(8): https://www.managedhealthcareconnect.com/articles/innovations-managing-hemophilia. Accessed October 2019.

Investigational Gene Therapy for Hemophilia A: Valoctocogene Roxaparvovec

Gene therapy using an AAV-factor VIII vector:

- Codon optimized BDD-FVIII
- AAV5 vector

Phase 1/2 study

- 15 patients with severe hemophilia A received a single dose valoctocogene roxaparvovec:
  - 7 were treated at a dose of 6e13 vg/kg
  - 6 were treated at a lower dose of 4e13 vg/kg
  - 2 patients in the study were treated at lower doses as part of dose escalation in the study but did not achieve therapeutic efficacy

Valoctocogene Roxaparvovec Demonstrated a Substantial Reduction in Mean Bleed Rate Requiring Factor VIII Infusions Sustained over a 3-year Period (6e13 vg/kg Dose)

6e13 vg/kg Dose*	**Before valoctocogene roxaparvovec Infusion*** **	**After valoctocogene roxaparvovec Infusion**** during Year 1**	**After valoctocogene roxaparvovec Infusion**** during Year 2**	**After valoctocogene roxaparvovec Infusion**** during Year 3**
	Median (mean, SD)	Median (mean, SD)	Median (mean, SD)	Median (mean, SD)
Annualized Bleeding** Rate (bleeding episodes per year per subject)	16.5 (16.3, 15.7)	0.0 (0.9, 2.2)	0.0 (0.2, 0.4)	0.0 (0.7, 1.6)
Annualized FVIII Infusions** (infusions per year per subject)	138.5 (136.7, 22.4)	0.0 (2.1, 5.3)	0.0 (8.8, 21.0)	0.0 (5.5, 9.4)

A 7th patient received Factor VIII on demand prior to treatment with BMN 270 and was not included in analysis. Post infusion data were based on data after Week 4. ***Obtained from medical records.****5 of 6 participants had 0 bleeds requiring Factor VIII infusions and 4 of 6 participants had 0 Factor VIII infusions after Week 4.*

Pasi JK, et al. Oral presentation at ISTH; Monday July 8, 2019; Melbourne, Australia. https://www.professionalabstracts.com/isth2019/programme-isth2019.pdf

Valoctocogene Roxaparvovec Demonstrated a Substantial Reduction in Mean Bleed Rate Requiring Factor VIII Infusions Sustained over a 2-year Period (4e13 vg/kg Dose)

4e13 vg/kg Dose	Before valoctocogene roxaparvovec Infusion	After valoctocogene roxaparvovec Infusion during Year 1	After valoctocogene roxaparvovec Infusion during Year 2
	Median (mean, SD)	Median (mean, SD)	Median (mean, SD)
Annualized Bleeding Rate* (bleeding episodes per year per subject)	8.0 (12.2, 15.4)	0.0 (0.9, 2.2)	0.0 (1.2, 2.4)
Annualized FVIII Use Rate* (infusions per year per subject)	155.5 (146.5, 41.6)	0.0 (2.0, 4.3)	0.5 (6.8, 15.6)

**Post-infusion data were based on data after Week 4.*

Pasi J, et al. Presented at ISHT. Melbourne, Australia; July 6-10, 2019.

Mean Factor VIII Activity Levels Across 2-3 Years with Valoctocogene Roxaparvovec Support Sustained Reductions in Bleed Rates

	Year 1**	Year 2**	Year 3**
Mean (Median) Factor VIII Activity Levels (IU/dL) as Measured using Chromogenic Substrate Assay*	64.3 (60.3)	36.4 (26.2)	32.7 (19.9)
Mean (Median) Factor VIII Activity Levels (IU/dL) as Measured using One-Stage Assay*	103.8 (88.6)	59.0 (45.7)	52.3 (29.8)

	Year 1***	Year 2***
Mean (Median) Factor VIII Activity Levels (IU/dL) as Measured using Chromogenic Substrate Assay*	21.0 (22.9)	14.7 (13.1)
Mean (Median) Factor VIII Activity Levels (IU/dL) as Measured using One-Stage Assay*	31.4 (31.7)	23.2 (23.5)

All patients had severe hemophilia A at baseline, defined as less than or equal to 1 IU/dL of Factor VIII activity levels. **Weeks were windowed by ±2 weeks before 104 weeks, after 104 weeks, weeks were windowed by ±4 weeks, and for week 32, one patient did not have a Factor VIII activity level available. * Weeks were windowed by ±2 weeks before 104 weeks and for week 32, one patient did not have a Factor VIII activity level available.*

Pasi J, et al. Presented at ISHT. Melbourne, Australia; July 6-10, 2019.

Valoctocogene Roxaparvovec Has Been Generally Well Tolerated Over 3 years

- No participants developed inhibitors to Factor VIII, and no participants withdrew from the study
- The most common adverse events (AEs) across all dose cohorts were as follows
  - alanine aminotransferase (ALT) elevation (11 participants, 73%)
  - arthralgia, (10 participants, 67%)
  - aspartate aminotransferase elevation (8 participants, 53%)
  - headache (7 participants, 47%)
  - back pain, fatigue, and upper respiratory tract infection (6 participants, 40%)
  - insomnia (5 participants, 33%)
  - pain in extremity (4 participants, 27%)
- Beyond the two previously reported serious adverse events (SAEs), one new SAE was reported in the past year that involved a participant with advanced arthritis who was hospitalized for surgery

Pasi J, et al. Presented at ISHT. Melbourne, Australia; July 6-10, 2019.

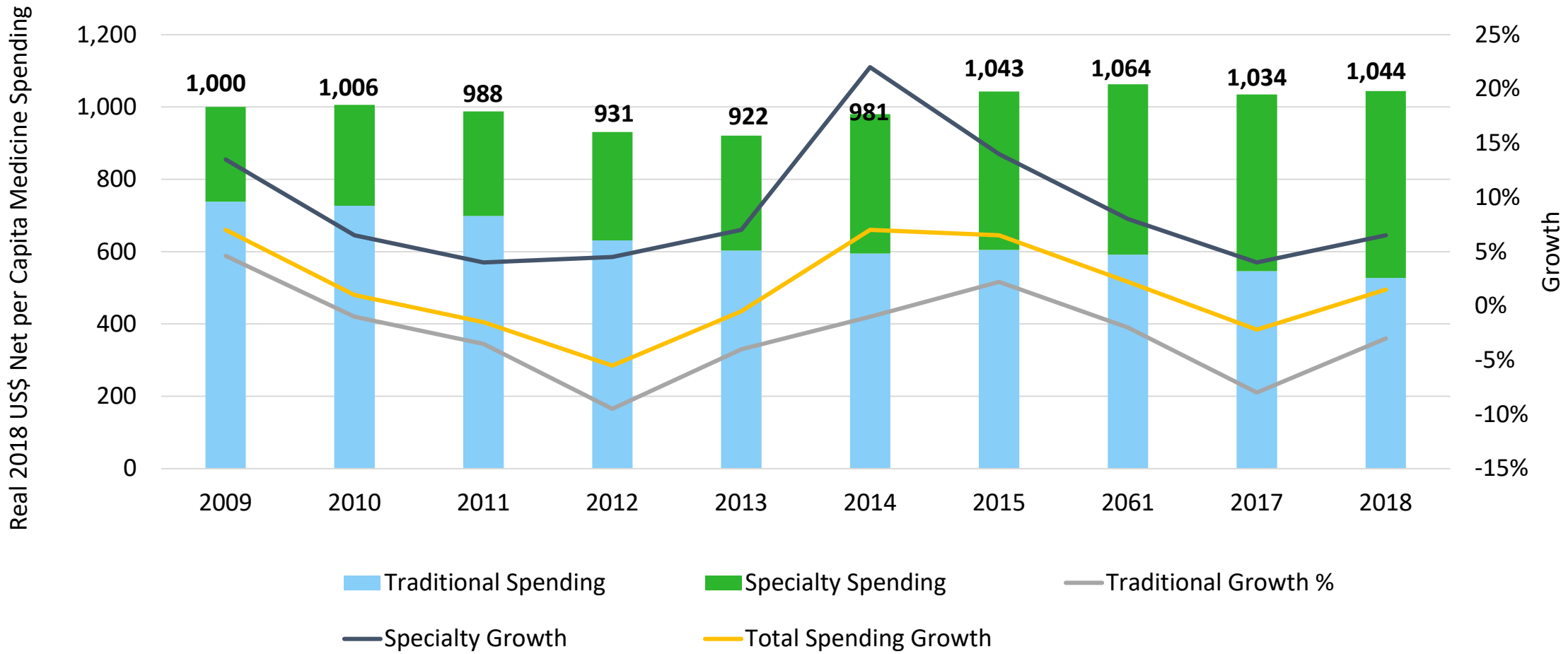
Summary

- Gene therapy aims to restore healthy physiologic function or suppress aberrant activity via gene augmentation, gene suppression, or genome editing
- Somatic cell gene therapies may employ ex vivo or in vivo strategies to introduce genetic material
- Cancer represents a key area in gene therapy, with CAR-T therapies approved and in development
- Rare, monogenic diseases are another notable area for gene therapy, with approved treatments for LCA and SMA and agents in late-stage development for blood disorders

Assessing the Potentially Curative Benefits of Gene Therapy in a Cost-Conscious Environment

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC

Specialty Growth Continues to Outpace Traditional Pharmaceuticals



Medicine Use and Spending in the U.S. IQVIA website. https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023. Published May 9, 2019. Accessed July 2020.

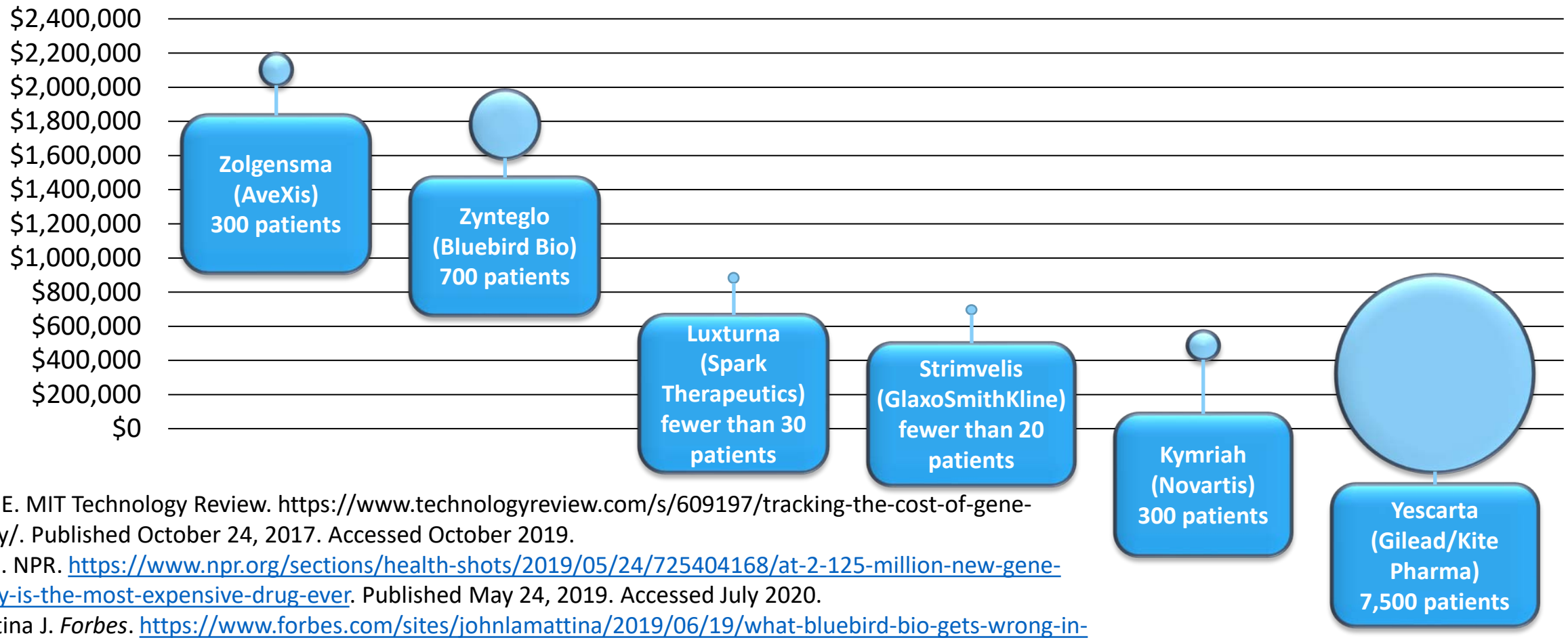
Gene Therapy Forecasts Demonstrate a Significant Cost Impact on the Specialty Trend

			Sales ($m)		
Product	**Company**	**Pharmacology class**	**2019e**	**2024e**	**Status**
Lentiglobin	Bluebird Bio	Beta-globin gene therapy	24	1,758	Filed
AAVrh74.MHCK.Micro-Dystrophin	Sarepta Therapeutics	Micro-dystrophin gene therapy	-	1,659	Phase II
SGT-001	Solid Biosciences	Micro-dystrophin gene therapy	-	1,589	Phase II
Zolgensma	Novartis	Survival motor neuron (SMN) gene therapy	156	1,565	Filed
Valoctocogene roxaparvovec	BioMarin Pharmaceutical	AAV-factor VIII gene therapy	-	1,210	Phase III
AMT-061	uniQure	Factor IX gene therapy	-	741	Phase III
SPK-8011	Spark Therapeutics	Factor VIII gene therapy	-	458	Phase II
Ad-RTS-hIL-12	Ziopharm Oncology	IL-12 gene therapy	-	378	Phase II
HMI-102	Homology Medicines	Liver gene therapy	-	362	Preclinical
NSR-REP1	Nightstar Therapeutics	Adeno-associated viral vector (AAV) encodingREP1 gene therapy	-	358	Phase III
Other			213	5,289	
Total			**393**	**15,368**	

Evaluate Pharma. 2019.

Gene Therapies Carry Extremely High Costs and Address Niche Patient Populations, Parallel to Hemophilia Cost/Prevalence

Gene Therapy Prices by Eligible Patients Per Year



Mullin E. MIT Technology Review. https://www.technologyreview.com/s/609197/tracking-the-cost-of-gene-therapy/. Published October 24, 2017. Accessed October 2019.

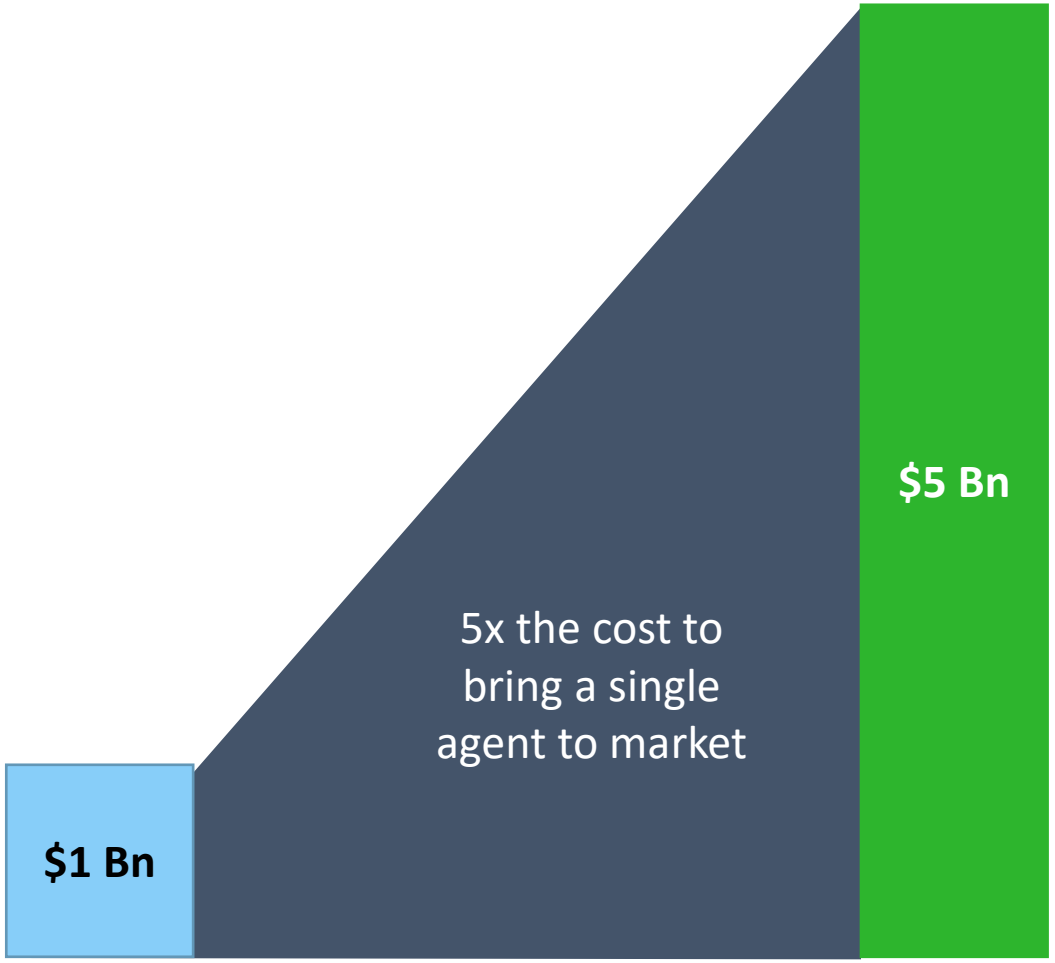
Stein R. NPR. https://www.npr.org/sections/health-shots/2019/05/24/725404168/at-2-125-million-new-gene-therapy-is-the-most-expensive-drug-ever. Published May 24, 2019. Accessed July 2020.

LaMattina J. *Forbes*. https://www.forbes.com/sites/johnlamattina/2019/06/19/what-bluebird-bio-gets-wrong-in-pricing-for-its-1-8-million-drug/#699d506269c5. Published June 19, 2019. Accessed July 2020.

Gene Therapies Are Subject to More Extensive Regulatory Evaluation and Development Costs

Conventional Pharmaceuticals

- First phase of the FDA approval process typically requires twenty to eighty participants
- The third and largest phase usually requires at least 3,000 participants



Gene Therapies

- Tailored to specific individuals
- Completing clinical trials for FDA approval especially challenging and costly
- Fewer patients required, but estimates of nearly $1 million in cost per clinical trial participant
- Subject to the regulatory structure of the FDA as well as the Office of Biotechnology Activities and the Recombinant DNA Advisory Committee

American Consumer Institute. https://www.theamericanconsumer.org/wp-content/uploads/2019/02/Gene-Therapy-FINAL.pdf. Accessed July 2020.
Van Norman GA. *JACC Basic Trans Sci*. 2016;1:170-179.

The Value of Innovation

Scientific:

- Societal value in enhancing knowledge
- Overcoming obstacles to better patient outcomes

Market access/economics:

- More efficient use of scarce resources
- Replacing current therapies
- Reducing total costs of care

It's not the innovation but the result that has value!

How Value is Created

Better patient outcomes

- Clinical endpoints
- Lower toxicity
- Better Quality of Life

Health care system efficiencies

- Refocus of resources
- Cost offsets

Improved societal outcomes

- Increased productivity
- Less reliance on caregivers
- Caring for others

Living longer and better

- Employment
- Productivity
- Self-worth

How should value be measured?

1) Treatment costs versus other options
2) Cost of a Qualify Adjusted Life-Year (QALY)
3) Cost of a Disability Adjusted Life-Year (DALY)
4) Overall improvements measured by patient reported outcomes
5) Other

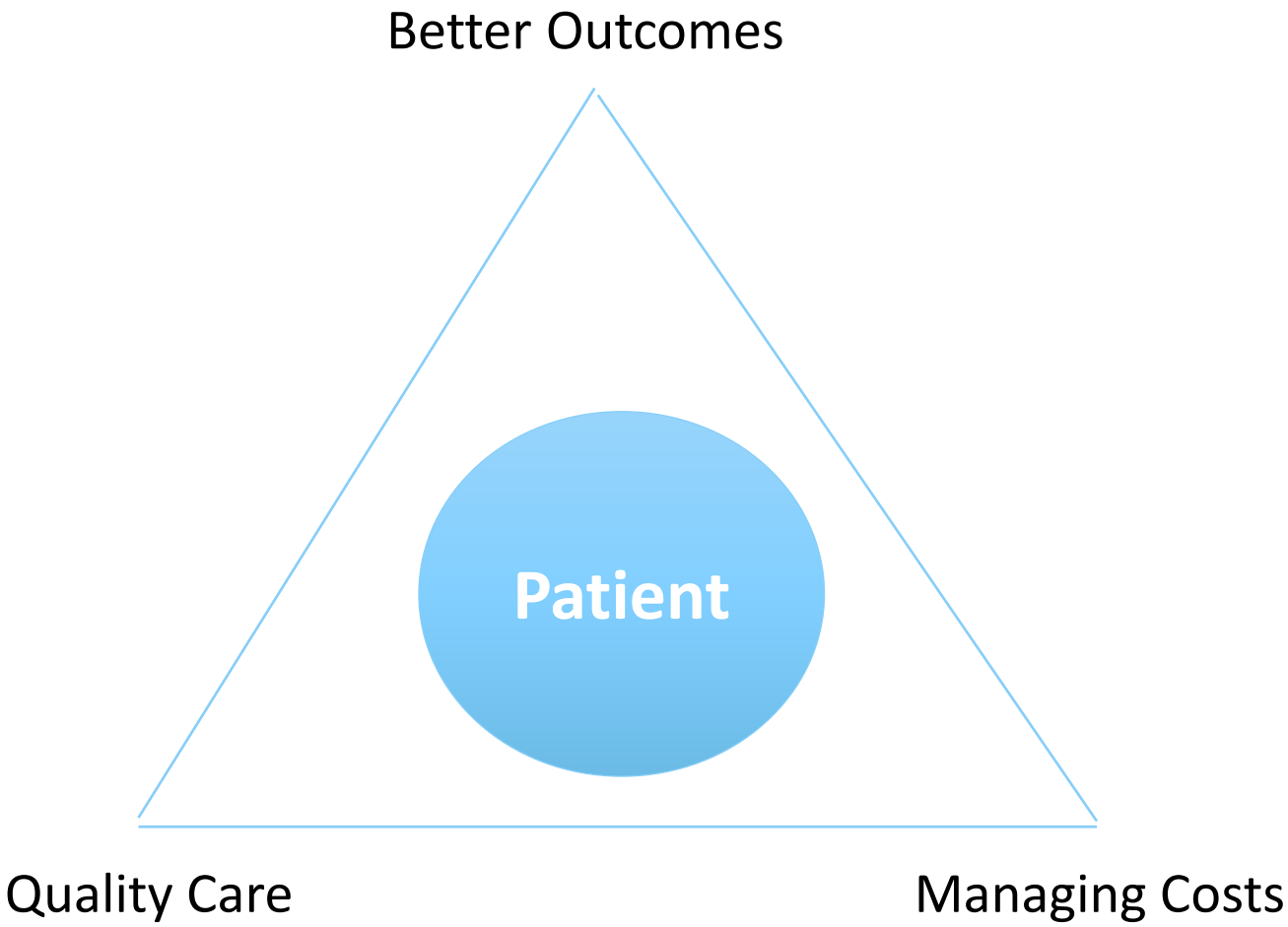
How Value is Measured

- Cost vs. other options – cost benefit
- Utility: cost of a Quality Adjusted Life-Year (QALY)
  - Cost of a Disability Adjusted Life-Year (DALY)
- Overall improvements in patient outcomes

$$V=Q/C$$

Triple Aim

- Better Health
- Better Care
- Lower Cost



The Current System Must Be Adapted to Create a Framework for Safely and Efficiently Integrating Patient-Centered Innovation

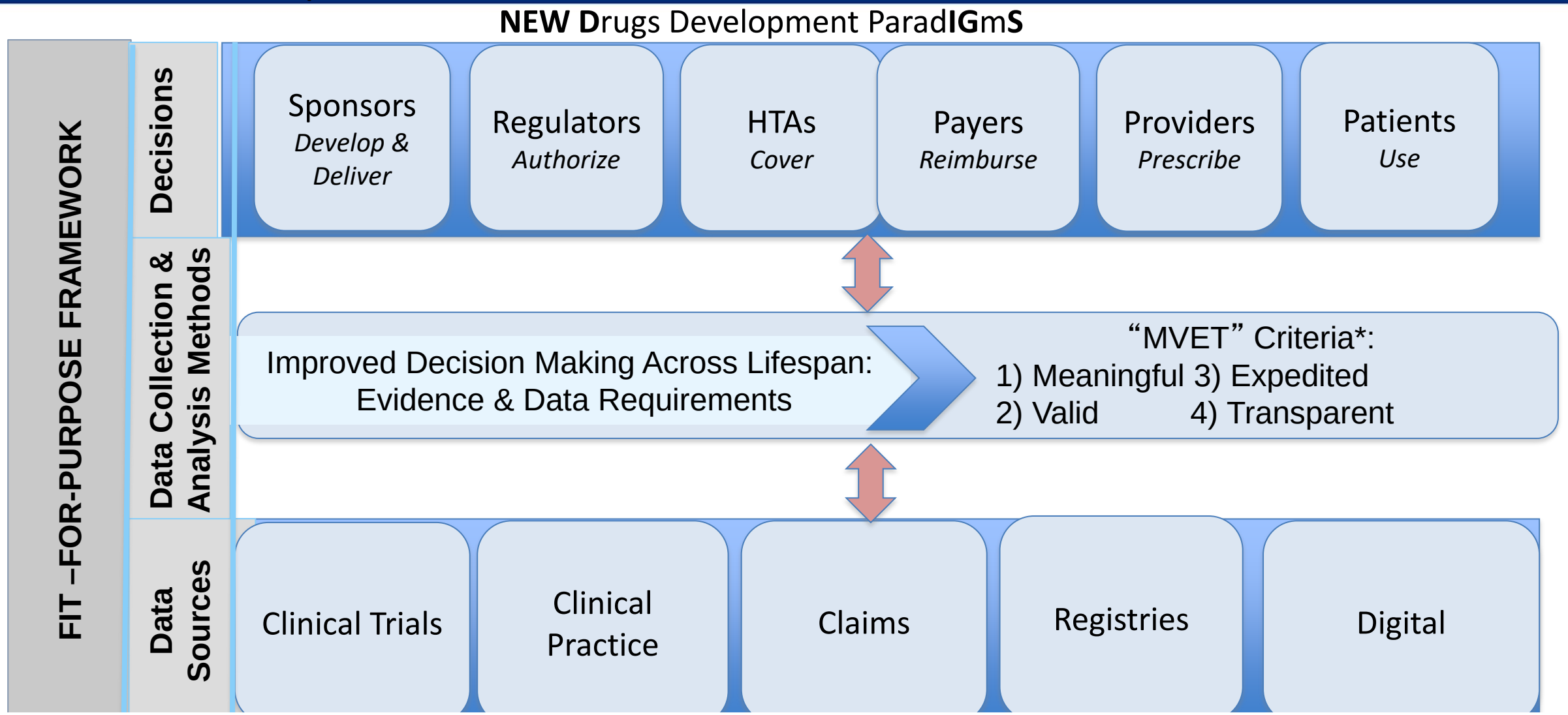
STATE OF THE ART

Adaptive Biomedical Innovation: Evolving Our Global System to Sustainably and Safely Bring New Medicines to Patients in Need

G Hirsch[1], M Trusheim[1], E Cobbs[2], M Bala[3], S Garner[4], D Hartman[5], K Isaacs[1], M Lumpkin[5], R Lim[6], K Oye[1], E Pezalla[7], P Saltonstall[8] and H Selker[9]

The current system of biomedical innovation is unable to keep pace with scientific advancements. We propose to address this gap by reengineering innovation processes to accelerate reliable delivery of products that address unmet medical needs. Adaptive biomedical innovation (ABI) provides an integrative, strategic approach for process innovation. Although the term "ABI" is new, it encompasses fragmented "tools" that have been developed across the global pharmaceutical industry, and could accelerate the evolution of the system through more coordinated application. ABI involves bringing stakeholders together to set shared objectives, foster trust, structure decision-making, and manage expectations through rapid-cycle feedback loops that maximize product knowledge and reduce uncertainty in a continuous, adaptive, and sustainable learning healthcare system. Adaptive decision-making, a core element of ABI, provides a framework for structuring decision-making designed to manage two types of uncertainty – the maturity of scientific and clinical knowledge, and the behaviors of other critical stakeholders.

NEWDIGS Framework for Designing Evidence Generation Plans that Improve Decision-Making for All Stakeholders Across Product Life Span



* Schneeweiss S et al. "Healthcare Databases with Rapid Cycle Analytics to Support Adaptive Biomedical Innovation." CP&T, November 2016.

Financing and Reimbursement **o**f **C**ures in the **US**: FoCUS Objectives

Vision

- Collaboratively address the need for new, innovative financing and reimbursement models for durable/potentially curative therapies in the US, that ensure consumer access and sustainability for all stakeholders

Mission

- Deliver an understanding of the financing challenges created by durable/potentially curative therapies, leading to system-wide, implementable precision financing models

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

FoCUS Stakeholders' Path from Discovery to Delivery

May 2016 FoCUS Begins

April 2017 Option Generation Design Lab

October 2017 Initial Results Design Lab

April 2018 Pilot/Toolkit Planning Design Lab

October 2018 Dissemination & Pilot Planning

Outcome Pilot Plan

August 2019 2nd Edition of FoCUS Research Compendium

Issue discovery & design drivers

Option Modeling by Research Team

Modeling Refinement by Research Team

Research, Pilot Design, Communication, Tools

Dissemination & Recommendations

Design Phase

Dissemination & Implementation

I. Elucidation (April 2017)

II. Pressure Testing

III. Dissemination & Implementation Planning

Select accomplishments to date

- >60 organizations & 170 individuals engaged
- Precision Financing framework created
- FoCUS recognized as 'Player' via publications, pipeline projections & speaking/workshop invitations
- Pilot(s) in development to demonstrate approach and spur policy change

Pilot & Scale
- PAP
- MBC
- Other?

Inform & Influence
- Papers (RBs to WPs to Pubs)
- Conference (Paying for Cures)
- Speaking engagements
- Policy discussions

Measure & Model
- PAM Market Estimates
- Consumer Perspective
- Payer Perspective

Extend, Evolve & Deepen
- New Cases & products
- Risk Pools & Reinsurance
- Consumer & Provider Financing

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

FoCUS Addresses Financing the Value

On—

Creating **precision financing solutions** for durable/potentially curative therapies with large, upfront costs whose benefits accrue over time

Not on—

Assessing or setting value, or negotiating specific prices for specific products

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

Stakeholder Perspectives and Concerns: Consumers

- There is much excitement around the possibility of curative, durable treatments
- Dominant focus areas for consumers
  - Access
  - Treatment Location and Provider
  - Cost
- Perspective changes with the age of the consumer
- Consumers want to have a voice in the development of new therapies

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

Consumer-identified Outcomes In Hemophilia

PROBE project - outcomes identified by consumers deemed relevant to their life[1]

- Pain – chronic/acute, interference, occurrence
- Independence – limitations and impact on activities of daily living
- Education – attainment, attendance
- Employment – duration, underemployment, attendance
- Family life – marriage, children
- Mobility – assistance required, impairment

Skinner MW, Chai-adisaksopha C, Curtis R, et al. Pilot Feasibility Stud. 2018;4:58.

Consumer Perspectives of Potentially Curative Therapies

- Differences among the population relate to perceived value and decision making
  - Personal, cultural, or religious beliefs
  - Health literacy
  - Emotional or mental health
  - Risk tolerance
  - Physical status – comorbidities and mobility
  - Situation – job/income, family, insurance

Stakeholder Perspectives and Concerns: Consumers

- Expectations of high financial burdens due to out-of-pocket costs (copays, deductibles, possible loss of income due to treatment and travel costs, housing at site, childcare for siblings)
- Will my provider change?
- Will I have to travel for treatment?
- How much time will be needed for post treatment monitoring?
- Are these new treatments safe and effective?
- Will I be eligible to undergo treatment due to restrictions?
- Who can help me navigate existing resources (copay and deductible assistance, educational resources)?
- Will my provider be able to answer all my questions?

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

Stakeholder Perspectives and Concerns: Providers

- There is much excitement around the promise of these new treatments for individuals who have none
- Face challenges with redefining existing service offerings and operations
- Face new financial risks
  - Will these new therapies drive the need to find new income streams? i.e. will the provider be accredited to administer the new therapies?
- Shifts in financing solutions will require:
  - New contracts – with potentially different entities
  - Contracts with milestones or outcome requirements add consumer follow-up and record keeping overhead
- Modifying existing provider operational models:
  - Potential loss of revenue (buy and build models)
  - Potential that timing of new billing codes will slow down reimbursement
  - Potential for new cost burdens to gear up for accreditation

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

Stakeholder Perspectives and Concerns: Policy and Regulatory

- Affected legislators and staff (State and Federal)* are more well educated on the topic of gene therapy than other colleagues
- Thoughts from the Hill
  - Value-based contracting could be the solution but needs more study
  - We need to figure out effective reimbursement strategies
  - Desire to support consumers
- Agencies:
  - FDA: Strong support of the consumer, supportive of moving gene and cell therapy ahead (expedited reviews, updated and new guidelines, etc.)
  - CMS: Focus on fiscal responsibility

*Affected – A consumer, family member, friend with a rare disease or cancer.

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

Stakeholder Perspectives and Concerns: Policy and Regulatory

- Hill:
  - Concerns over costs to the US healthcare system
  - What will happen with drug pricing legislation?
  - Some distrust of pharmaceutical companies
  - Will long-term contracts increase costs of gene and cell therapies over time?
- Agencies:
  - FDA: Safety and efficacy of these therapies
  - CMS: Need for more data to determine if the therapies (CAR-Ts are the test case) are being utilized and impact on budgets

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

Concerns Summarized Across Stakeholders

- Financial
- Effectiveness or Performance
- Regulatory
- Operational
- Access (either to receive or deliver)

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

One-Size-Fits-All Approaches Cannot Work

- Diseases and therapeutic approaches vary
- Payers differ by funding sources, size, and constraints
- Providers and developer financial needs and capacities vary
- Patient ability to financially participate could inhibit access to care

NEWDIGS Initiative. MIT Center for Biomedical Innovation website. https://newdigs.mit.edu Accessed July 2020.

Summary

- The specialty drug trend continues to outpace that of traditional pharmaceuticals and remains a key priority of payer management
- Gene therapy forecasts demonstrate a significant cost impact on the specialty trend
- Value in health care innovation lies in the result of the innovation rather than the innovation itself
- The juxtaposed needs and concerns of payers, providers, and patients must all be carefully weighed when evaluating the role and value of gene therapy in future care interventions

Medical and Pharmacy Management Strategies for Optimal Gene Therapy Outcomes

Mari-Pat Pusey, MBA
Senior Product Director
OptumRx

Which of the following financial considerations are most important to payers?

1) Managing Therapy Price
2) Managing Treatment Cost
3) Managing Volatility
4) None of the above
5) All of the above
6) Unsure

Gene Therapy Represents an Emerging Area of Focus for Payers

Coverage

- What does the appropriate patient look like?
- Should inclusion/exclusion criteria for clinical trials be applied to utilization management?

Sustainability

- Does treatment afford a lifetime of disease-related morbidity mitigation?
- How should consumer mobility/subscriber retention factor into long-term cost considerations?

Payment

- How should these high-cost therapies be funded in a manner that is sustainable to the healthcare system?
- What new payment models can be applied efficiently and effectively?

Payer Financial Considerations for Gene Therapies

Manage Price

Ensure that patient outcomes are commensurate with the price paid for therapy

83% consider it very beneficial **to only pay for therapy that works***

Manage Cost

Ensure high quality delivery of care, while minimizing mark-ups through the delivery system

64% consider Centers of Excellence Networks are part of their management strategy*

Manage Volatility

Manage the volatility of ultra-high cost therapies on plan economics

47% consider it very beneficial to **smooth payments over time***

Survey Results: Payer perspectives on financing and reimbursement of one-time high-cost durable treatments. New Drug Development Paradigms Initiative/MIT website. https://newdigs.mit.edu/sites/default/files/MIT%20FoCUS%20Payer%20Perspectives%202019F210v044.pdf. Published October 2019. Accessed July 2020.

Payer Perspectives and Approaches to Gene Therapy

The challenges payers face will vary dependent upon size, financial strength and ability to absorb risk at multiple levels

Segment	Awareness	Top Concerns	Current Risk Mitigation	Future Considerations
National FI Plans	Watchful Waiting -> Actively Managing	• Cost Management	Cash Reserves	COE Networks Outcomes-Based Contracts
Regional FI Plans	Watchful Waiting	• Volatility • Cost Management	Reinsurance	Risk Pooling Managed Services
Self-Insured Employers	Early Awareness -> Watchful Waiting	• Volatility • Cost Management	Coverage Decisions Stop-Loss Insurance	Risk Pooling Managed Services
Managed Medicaid	Watchful Waiting	• Volatility • Cost Management	Limited Access	Pooled Subscription Models Outcomes-Based Contracts
Medicare Advantage	Watchful Waiting	• Cost Management	Coverage Decisions New Tech Add-On Pymts	New MS-DRG payments

Most of the market is still in a “wait & see” approach… expect that to change by 2022

To Effectively Manage Gene Therapies, Payers Will Need a Unique Set of Tools & Solutions

	Issues to be addressed	Tools/Solution that are Needed
Manage Cost	• Ensure appropriate patients are treated • Minimize Mark-ups through supply chain • Ensure high-quality care… minimize adverse events and maximizing positive outcomes	• Uniform Coverage Criteria / Utilization Management Process • Centers of Excellence Networks • Negotiated contracts with Providers
Manage Volatility	• Payers: Understand Risk Exposure, Engage appropriate Excess Risk strategies to smooth volatility • Excess Risk-Takers: Price risk, manage adverse selection	• Risk Exposure Analytics, Predictive Models • Pricing & Underwriting Tools • Sizable Risk Pools
Manage Price	• Variation in endurance of treatment • Variation in clinical response to treatment • Differing value based by timing of treatment • Adverse events or unforeseen costs of treatment	• Therapy Valuation Tools • Outcomes-Tracking Capabilities

Recent Market Solutions

Risk Pools

Embarc Program for Self-funded employers.

- Collects $0.99 PMPM fee to purchase and provision therapies; Zolgensma & Luxturna

PreserveRx: Reinsurance product for BCBS FI lives

- Collects PMPM fee to cover portion of therapy cost : $250K deductible; capped at WAC

Carve-out risk pool / stop loss

- Self-Insured employers without stop-loss
- Covers costs above a deductible

Management Services

Pipeline analytics, Policy & Coverage guidance, Utilization Management, Provider Contracting, Claims Administration

- Co-promotion with Tokio Marine/HCC to stop-loss carriers & reinsurers
- Step-down deductible program

Outcomes-Based Programs

Performance-Based Rebates

- Designated “clinical failure” criteria tracked over defined timeframe (5 years)
- Manufacturer agrees to rebate a % of therapy price to payer per patient that that meets “failure” criteria
- 3rd party used to track patient outcomes (paid for by manufacturer)

Warranty Programs

- Defined “clinical failure” criteria
- Ongoing conventional treatment paid by manufacturer for a defined period for patients who meet failure criteria
- Burden on the payer to demonstrate patient meets “clinical failure” criteria

Regulatory Progress

New CMS proposed rule to support value-based purchasing helps pave the way for meaningful Outcomes-Based Programs

- Defines value-based purchasing as an arrangement or agreement intended to align pricing and/or payments to an observed or expected therapeutic or clinical value in a population
- Enables manufacturers to report Best Price as the average net price, taking into account all sales prices, including failures and successes
- Allows modifications to Best Price after more than three years for changes related to value-based purchasing agreements
- Creates a pathway for “pay-over-time” models in which payment occurs when a certain benchmark is hit

Significant Questions to be Resolved as the Gene Therapy Pipeline Accelerates

Gene Therapy Management Services

- How to establish coverage criteria with limited clinical evidence?
- How to establish a COE network? What criteria? How many are appropriate to serve the needs of small eligible populations?
- Therapy Acquisition: Buy-Bill vs. White-Bagging

Risk Pooling

- How will stop-loss carriers and reinsurers react to therapies for conditions with predictable/identifiable conditions?
- What size risk pool and how many on market therapies are necessary to effectively be able to price risk?
- How to address adverse selection?

Outcomes-Based Contracts

- What performance measures to track? How will they be decided on? Uniform or differ by payer?
- How will outcomes be tracked as patients migrate between payers and states?
- What infrastructure and/or services are required?
- Which entity(s) should pay for the cost of tracking outcomes?

New Provider/Administrator Entities Likely to Emerge

Gene Therapy Administrator

- Negotiate therapy pricing on behalf of Payer Coalition
- Negotiates Outcomes-Based Agreements that tie population performance with rebates or bonuses
- Offers alternative payment models
- Provides the data and analytics infrastructure to measure and adjudicate outcomes
- Additional services to manage cost and quality:
    - Benefits Management
    - Utilization Management
    - COE Network

PROS

- Specialization allows for more effective and efficient care
- Takes responsibility for all patients regardless of what intervention they will receive
- Can manage over longer time period

CON

- No entity exists now
- Requires investment and clarity of business model

Summary

- Payers are challenged to manage the appropriate utilization of gene therapies
- The anticipated high cost of gene therapy, in addition to the potential for patient migration between health plans, necessitates innovative payment models
- A number of strategies are being tested in the marketplace today:
  - Alternative Payment Models: Risk Pools
  - Outcomes-Based Agreements
- New types of administrator entities are likely to emerge
- The eventual choice of innovative access scheme will ultimately depend on individual health plan environment and characteristics

Faculty Idea Exchange and Q&A Session

John Petrich, RPh, MS
Manager, Investigational Drug Service
Cleveland Clinic

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC

Mari-Pat Pusey, MBA
Senior Product Director
OptumRx

How to Claim Credit

Option 1: Complete the online post-survey and evaluation form immediately following the live webcast. The link to the survey will appear on your screen at the conclusion of the webcast. If you are unable to fill out the evaluation immediately following the live webcast, please note that a personalized evaluation link will be emailed to you following the live webcast at the account you registered with. Once you fill out your evaluation, your certificate will be emailed to you.
For Pharmacists, in order to submit your credit to the CPE Monitor:

Please go to www.impactedu.net/cpe
Enter code: **0716**
You will then need to log in or create an account ensuring your NABP and DOB information is entered and correct. Be sure to enter today's date, **July 16, 2020**, as the date of participation. You will be immediately notified if your submission has been accepted or if there are any issues. Once accepted, the record of your participation will appear in the CPE Monitor within 48 hours. **Credit must be uploaded to CPE Monitor within 30 days.**

Option 2: Print the 'Fax Evaluation Form' in the *Handouts* section and turn in the completed version via fax or email to the number or email address located at the top of the form. A certificate will be emailed to you within 3-4 weeks.
For Pharmacists: upon receipt of the completed evaluation form, you will receive an email within 3 weeks with a link and directions to submit your credit to the NABP CPE Monitor Service. **Pharmacists have up to 30 days to complete the evaluation and claim credit for participation so that information can be submitted to CPE Monitor as required.**

The Gene Therapy Transformation:
A Guide for Managed Care Decision Makers

Jointly provided by

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Professional Excellence in Medical Education

Impact Education LLC

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