The Promise of Gene Therapy

ACCESS AND COVERAGE FOR INNOVATIVE, HIGH-COST TREATMENTS

insights
INNOVATIONS IN TREATMENT
NATIONAL HEMOPHILIA FOUNDATION

Jointly provided by

NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

Impact Education LLC

MEDICAL EDUCATION RESOURCES

This activity is supported by BioMarin Pharmaceutical Inc., uniQure, Spark Therapeutics, Inc. and Takeda.

AMCP *held in conjunction with* NEXUS2019

Learning Objectives

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

Molecular and Physiologic Principles of Gene Therapy in the Treatment of Hemophilia

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Chief, Pediatric Hematology

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Louisiana Center for Advanced Medicine (LCAM)

Disease Overview

- Hemophilia is a congenital bleeding disorder affecting all racial, ethnic, and socioeconomic groups
- There are ~20,000 persons with hemophilia (PWH) in the US and ~500,000 PWH worldwide

Data & Statistics on Hemophilia. Centers for Disease Control and Prevention website: https://www.cdc.gov/ncbddd/hemophilia/data.html. Accessed October 2019.
Fast Facts. National Hemophilia Foundation website: https://www.hemophilia.org/About-Us/Fast-Facts. Accessed October 2019.

Clinical Features of Hemophilia

Severity of bleeding tendency depends on the factor level

Mild (>5%)

- Bleed only after severe injury, trauma, or surgery
- May not be diagnosed until adulthood

Moderate (1%-5%)

- Bleed after injury, surgery
- May have occasional spontaneous bleeding

Severe (<1 %)

- Frequent spontaneous bleeding
- Diagnosis made in early childhood

Hemophilia A. National Hemophilia Foundation website: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed October 2019.

Results of Innovation in Hemophilia Therapies Over Time

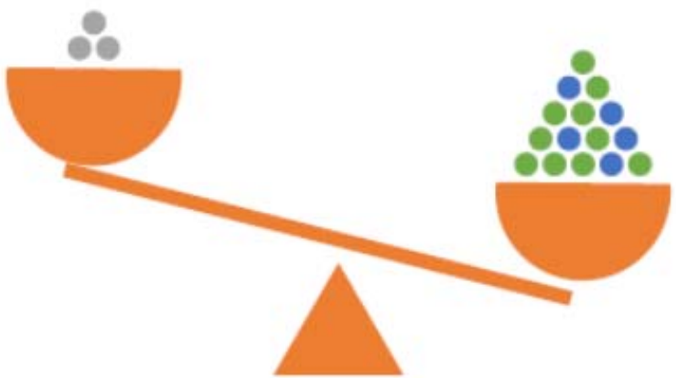
Unmet Need	Resulting Innovation
Bleeds	Plasma-derived factor
Infections (HIV, Hep-C)	Recombinant factor
Spontaneous bleeds and joint damage	Prophylaxis
Inhibitors/limited success of ITI and bypassing agents	Emicizumab

QOL 1960	QOL 2019
• Average life expectancy <20 years • Severe disability • Pain and limited opportunities	• Average life expectancy 70 years • Joint disease virtually nonexistent in young patients without an inhibitor

Remaining Needs	Future Innovation
Venous access, infusion burden, annualized bleed rates are not zero, etc.	Investigational therapies?

The Shifting Paradigm of Hemophilia Treatment

Hemophilia



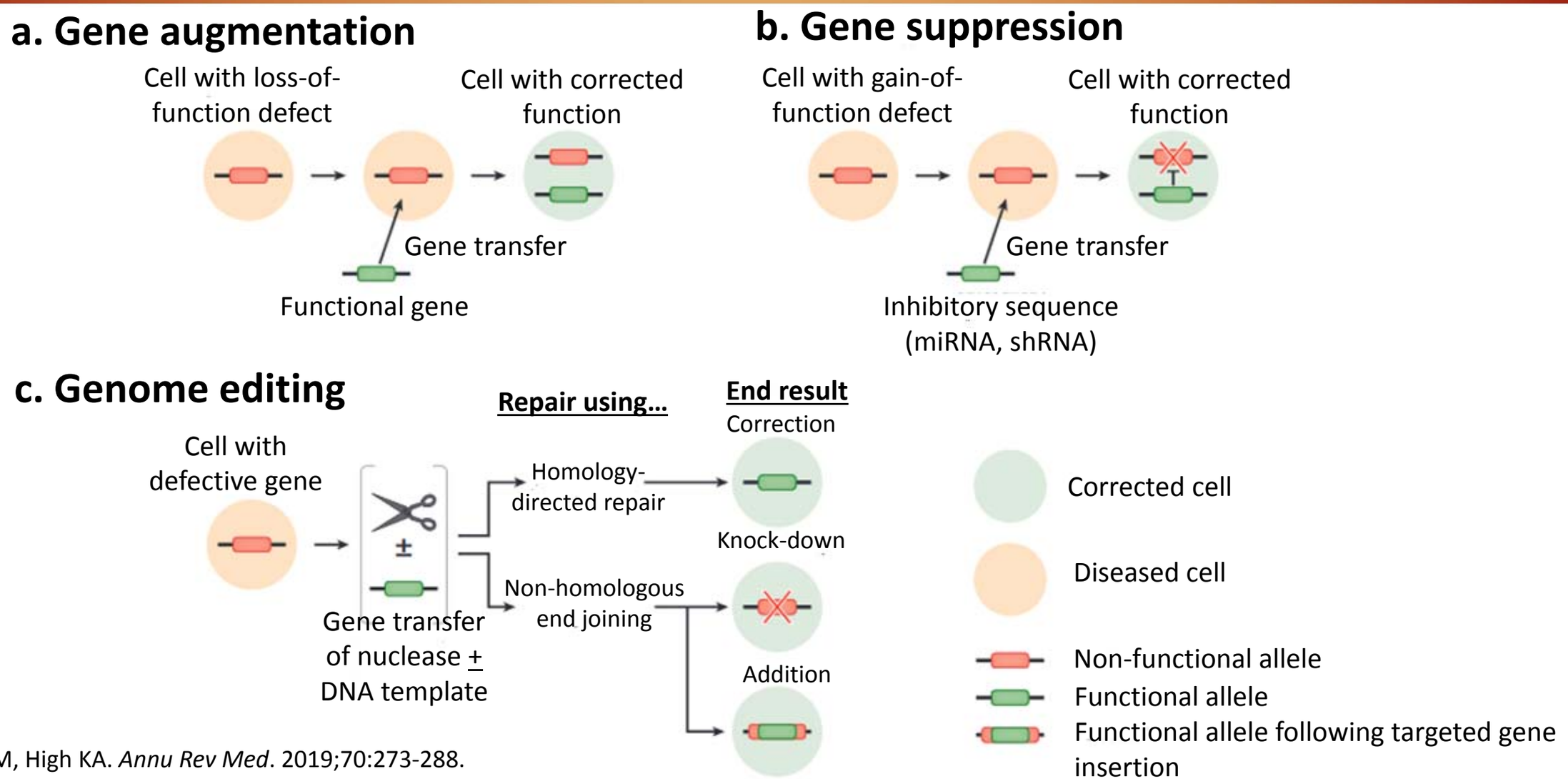
Factor Replacement Therapy Restores the Balance

Standard half-life products
Extended half-life products
Bypass – Xa, FEIBA, VIIa
Substitute for FVIII-Emicizumab
Gene therapy

Anticoagulant Inhibition Treatment is an Approach in Development to Restore Balance

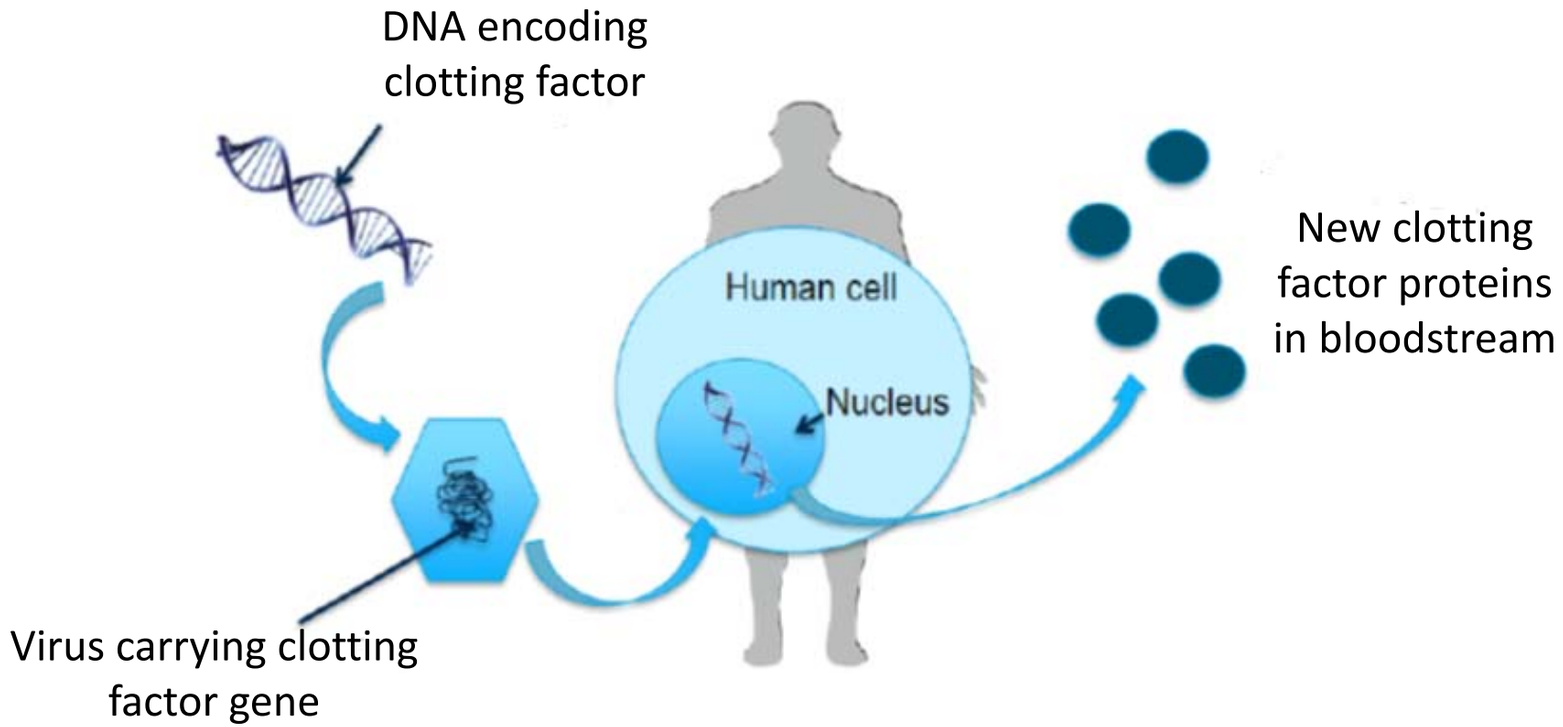
Anti-TFPI
Fitusiran
Bio-engineered α1 antitrypsin (protein C inhibitor)

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



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

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

Considerations Regarding Gene Therapy

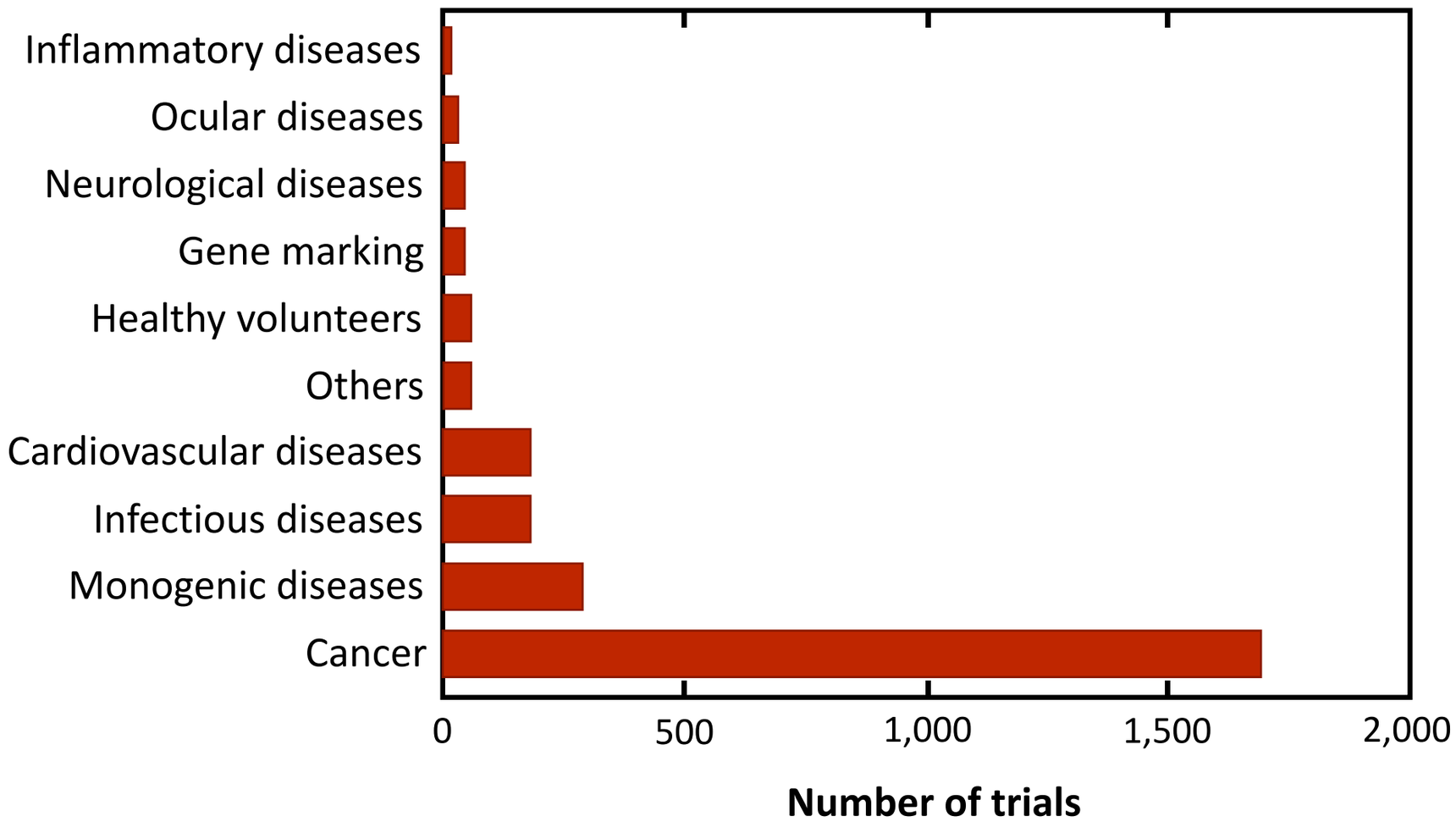
Unmet Needs Addressed

1. Steady, ongoing concentrations of factor
2. Reduction or elimination of spontaneous bleeds
3. Reduction or elimination of dependence on frequent infusions

Potential Limitations

1. Not all Hemophilia A patients will be candidates or will want to receive gene therapy
2. There are viable options for treating patients now
3. Patients who receive gene therapy may not be cured in the sense that they may still need treatment with factor under certain conditions
   - Trauma
   - Surgery
4. Treatment will not reverse joint damage

Hemophilia and Other Monogenic Conditions Represent the 2nd leading Disease Area in Terms of Gene Therapy Research and Development



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

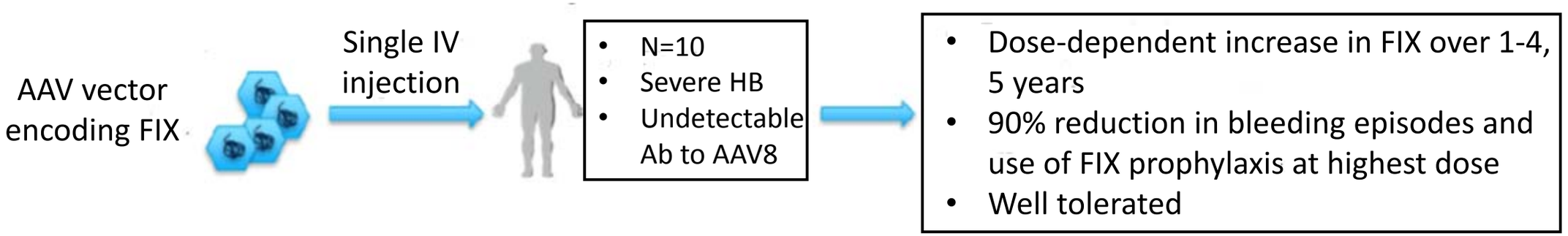
Active Gene Therapy Trials for Hemophilia B

Sponsor	Product	Development Phase
uniQure	AMT-60/61	3
Spark Therapeutics/Pfizer	SPK-9001	1/2
Sangamo Biosciences	SB-FIX	1/2
Freeline Therapeutics	FLT-180	1/2
St. Jude	scAAV2/8-LP1-hFIXco	1
Takeda	TAK-748/SHP648	Preclinical
Bioverativ/Sanofi	Undisclosed	Discovery

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 B: AMT-060

Proof of concept demonstrated using a vector encoding FIX for patients with hemophilia B[1]

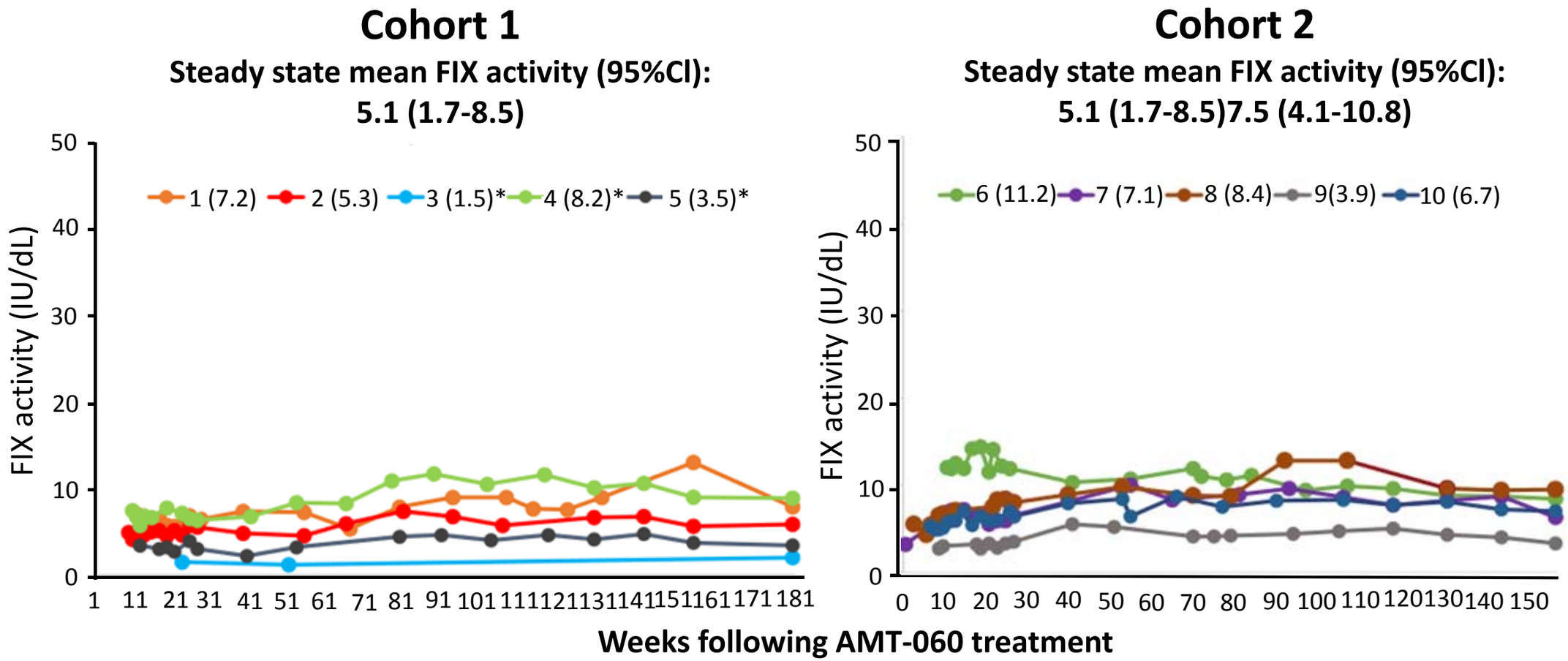


Phase 1/2 study of AMT-060 (AAV vector carry human FIX)[2]

- 10 adult patients treated
- All patients have demonstrated improvements in their disease
- 84% reduction in spontaneous ABR
- 8 patients have discontinued prophylaxis treatment
- 12 months follow-up: mean FIX activity was 8.82%
- AMT-060 was generally well tolerated

1. Nathwani A, et al. *N Engl J Med.* 2014;371:1994-2004; 2. UniQure press release (http://www.uniqure.com/news/283/182/uniQure-Announces-Preliminary-Topline-Results-from-Low-Dose).

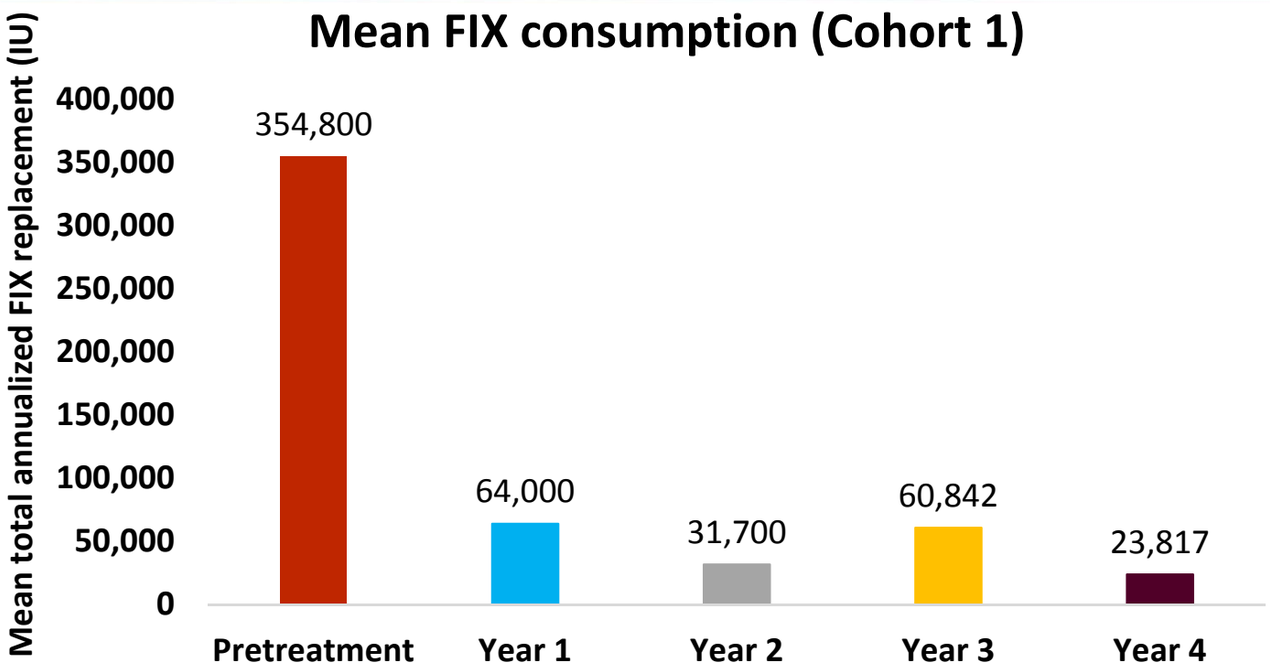
Stable Expression of FIX Following AMT-060 Gene Therapy with up to 3.5 Years of Follow-Up

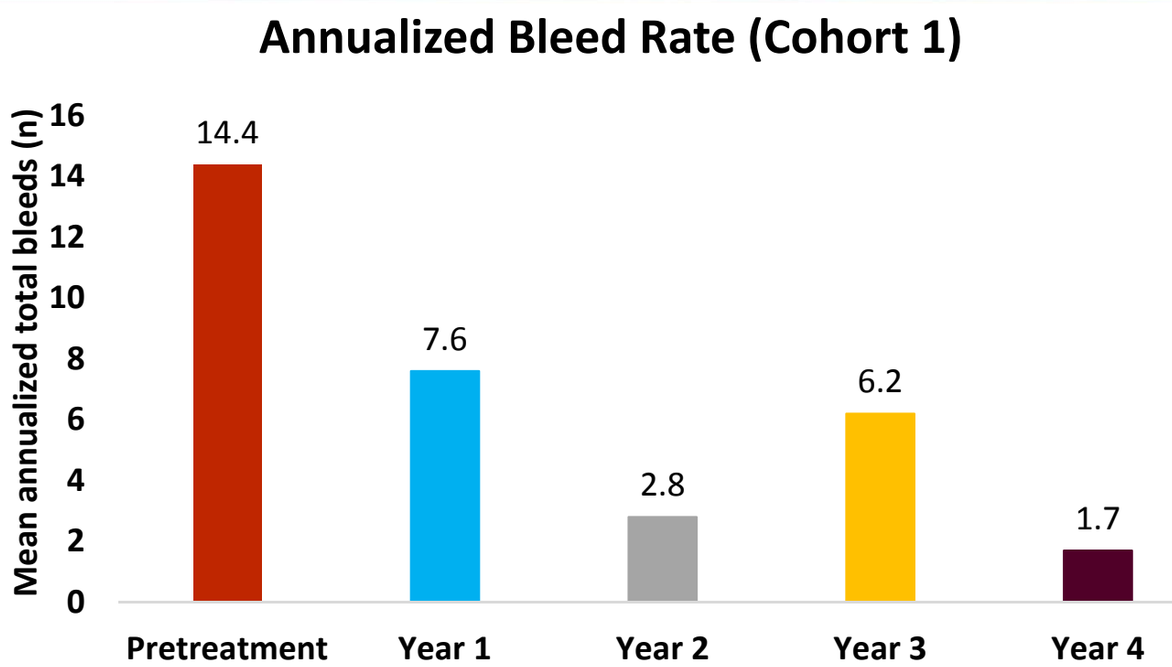


FIX activity levels correlated approximately 1:1 with FIX protein expression

Leebeck F, et al. Oral presentation at ISTH 2019; Saturday July 6, 2019; Melbourne, Australia. https://www.professionalabstracts.com/isth2019/programme-isth2019.pdf

Maintained Reductions in Bleeding and FIX Consumption Following AMT-060 Gene Therapy with up to 3.5 Years of Follow-Up

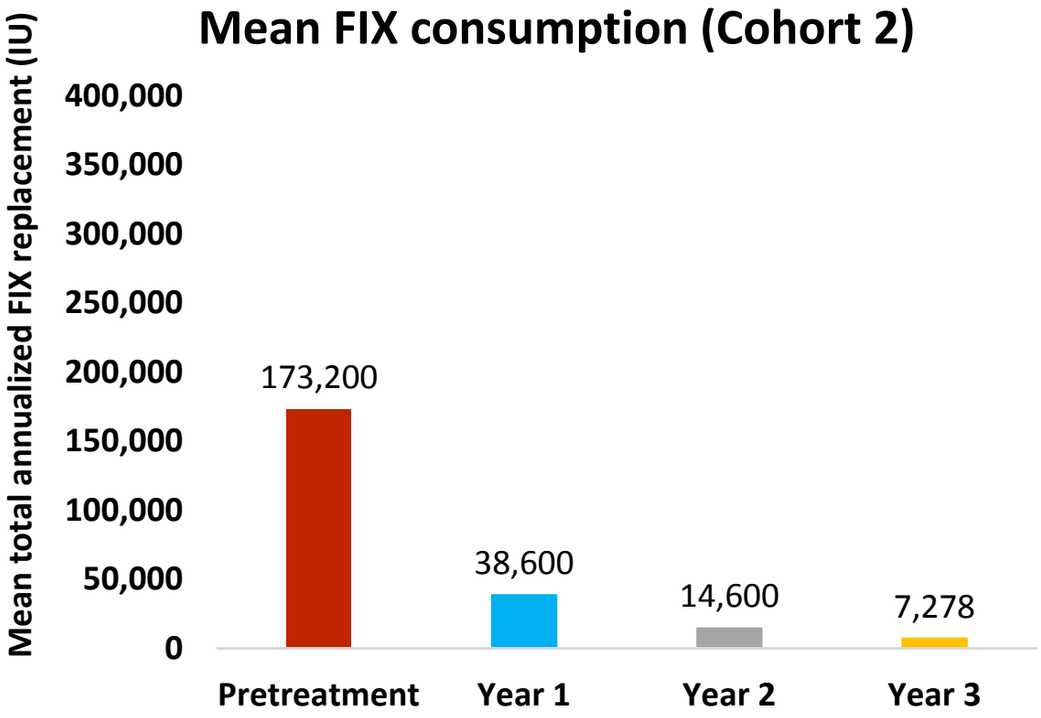


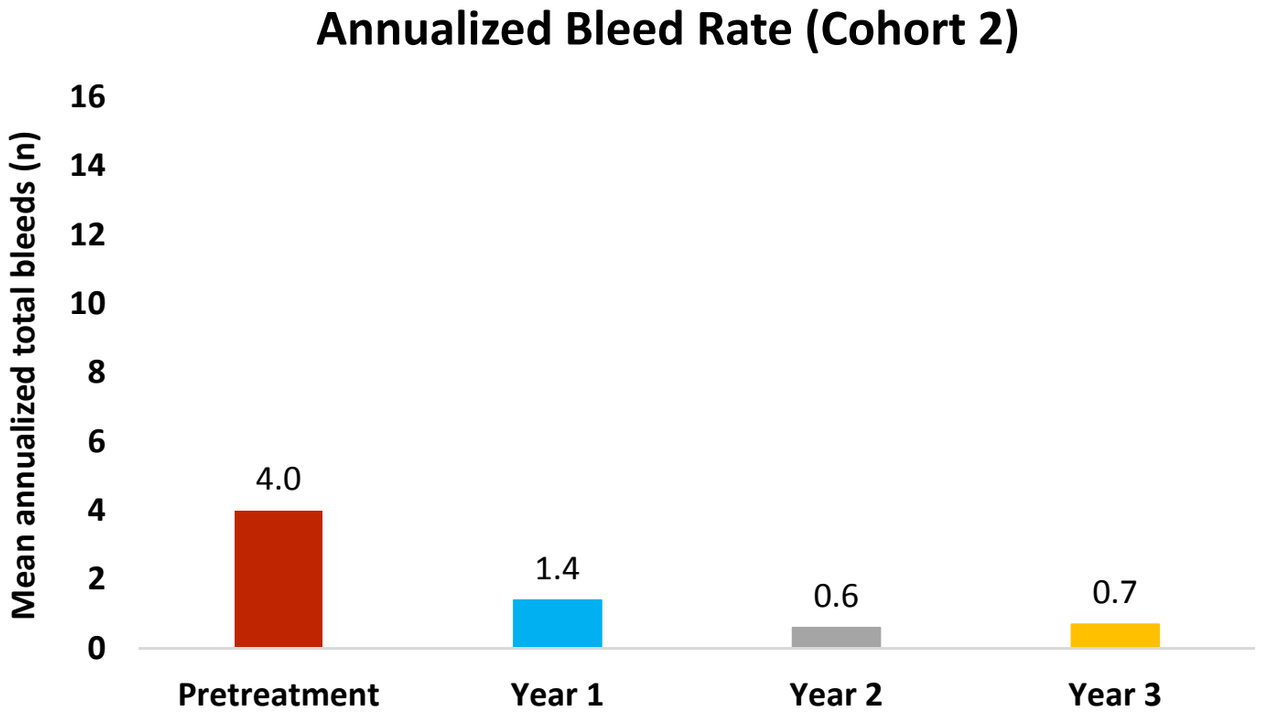


Reduction relative to pre-AMT-060	FIX use	Bleeds
Year 1	82%	47%
Year 2	91%	81%
Year 3	83%	57%
Year 4	93%	88%

Leebeck F, et al. Oral presentation at ISTH 2019; Saturday July 6, 2019; Melbourne, Australia. https://www.professionalabstracts.com/isth2019/programme-isth2019.pdf

Maintained Reductions in Bleeding and FIX Consumption Following AMT-060 Gene Therapy with up to 3.5 Years of Follow-Up (cont.)





Reduction relative to pre-AMT-060	FIX use	Bleeds
Year 1	78%	65%
Year 2	92%	85%
Year 3	96%	83%

Leebeck F, et al. Presented at ISHT. Melbourne, Australia; July 6-10, 2019.

AMT-060 Gene Therapy Was Generally Well Tolerated with up to 3.5 Years of Follow-Up

TRAE	n (E) Cohort 1 (N=5)	n (E) Cohort 2 (N=5)
Any TRAE*	**4 (5)**	**5 (10)**
Liver enzyme increased	1 (1)	2 (3[†])
Pyrexia	1 (1)	2 (2)
Anxiety	1 (1)	1 (1)
Drug ineffective	1 (1)	0
Joint swelling	1 (1)	0
Palpitations	0	1 (1)
Headache	0	1 (1)
Prostatitis	0	1 (1)
Rash	0	1 (1)

TRAE, treatment emergent adverse event reported as possibly/probably related to treatment by the investigator; FIX, factor IX; n, Number of participants with events; (E), number of events; *TRAE reported in last 12 months; [†]2 events reported in the same participant

Serious AE

- 1 participant: short, self-limiting fever in first 24 hours post-AMT-060
- 2 participants (1 in Cohort 1, 1 in Cohort 2): mild, asymptomatic elevations in liver enzymes

Overall

- 1 new TRAE was observed during the last 12 months of observation post-treatment
- No participants developed FIX inhibitors

Leebeck F, et al. Oral presentation at ISTH 2019; Saturday July 6, 2019; Melbourne, Australia.
https://www.professionalabstracts.com/isth2019/programme-isth2019.pdf

Active Gene Therapy Trials for Hemophilia A

Sponsor (Product)	Transgene	Vector
BioMarin (BMN 270)	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: BMN 270

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 BMN 270:
  - 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

BMN 270 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

BMN 270 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 BMN 270 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.*

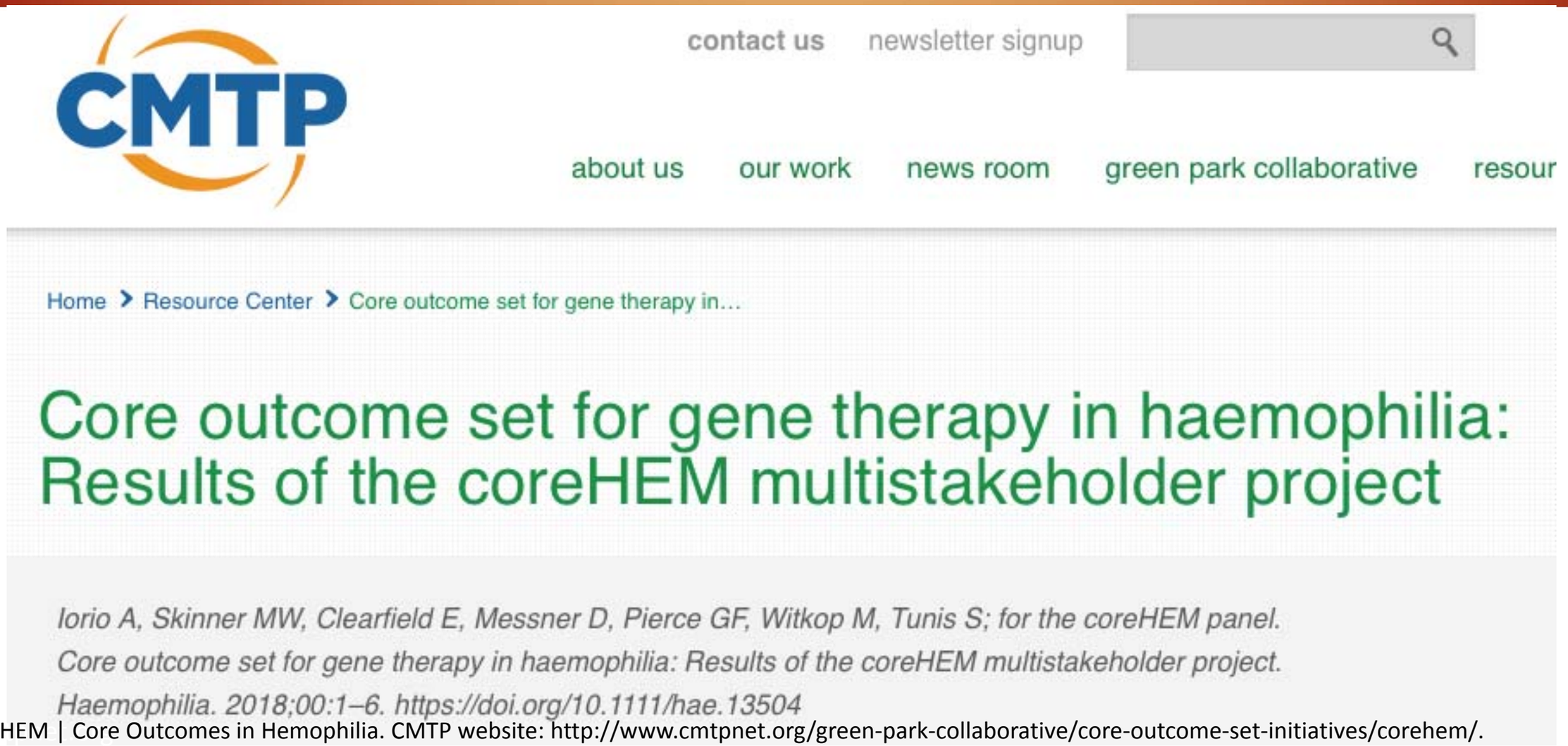
Pasi J, et al. Presented at ISHT. Melbourne, Australia; July 6-10, 2019.

BMN 270 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.

Evaluating Gene Therapy



coreHEM | Core Outcomes in Hemophilia. CMTP website: http://www.cmtpnet.org/green-park-collaborative/core-outcome-set-initiatives/corehem/. Accessed October 2019

The coreHEM Data Set

- Contains multiple domains
  - Physical function
  - Pain
  - Target joints
  - Psychological and social issues
- Intended to help evaluate gene therapies in development
- Subsets of the coreHEM set may be useful in clinical practice to evaluate gene therapy outcomes in individual patients

Summary

- Hemophilia treatment has advanced significantly over the past several decades, but a number of unmet needs remain
- Gene therapy represents an opportunity to meet these needs, with promising results in phase 1/2 trials
- Clinicians must be mindful that not all patients will be candidates or will want to receive gene therapy and may still need treatment with factor under certain conditions
- Continued rigorous disease management is necessary to minimize joint damage prior to initiation of gene therapy, and post-marketing surveillance will be paramount after presumed FDA approvals

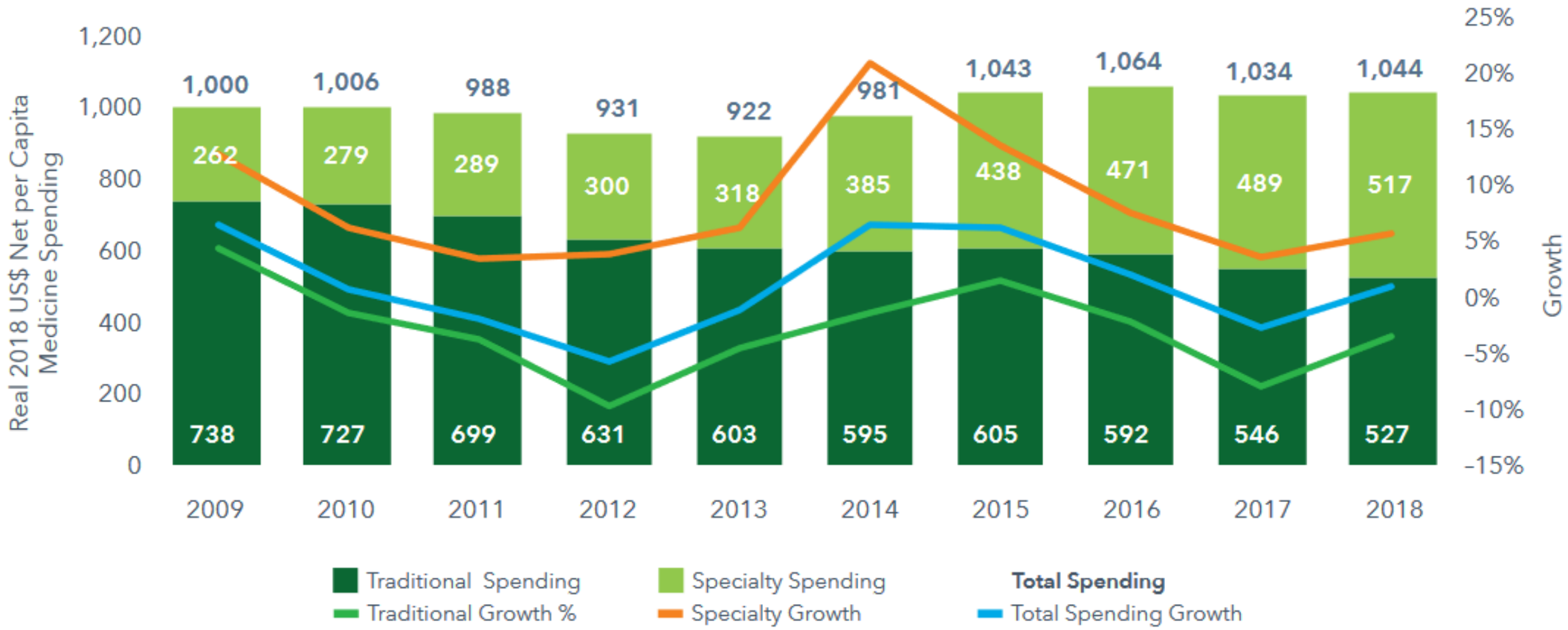
Financial Implications of Gene Therapy and the Potential for Improved Outcomes and Reduced Health Care Service Utilization

Edmund Pezalla, MD, MPH

CEO

Enlightenment Bioconsult, LLC

Specialty Growth Continues to Outpace Traditional Pharmaceuticals



IQVIA. Medicines Use and Spending in the US. 2019

Bleeding Disorders Remain a Key Driver of the Specialty Trend

		TOP DRUG CATEGORIES Listed highest to lowest in terms of plan cost for 2017	2016 RANK	2017 PMPY	NET PMPY TREND	COST TREND	UTILIZATION TREND
1	-	Inflammatory Disorder	1	$227.91	23.6%	9.1%	14.5%
2	-	Oncology	2	$163.19	14.9%	4.0%	10.9%
3	-	Multiple Sclerosis	3	$77.59	4.7%	4.0%	0.7%
4	↑	Immunological Disorders	5	$28.20	9.3%	-1.4%	10.7%
5	↑	Blood Cell Disorders	6	$27.28	4.6%	1.8%	2.8%
6	↓	Hepatitis C	4	$20.88	-22.9%	-4.5%	-18.4%
7	-	Growth Disorders	7	$19.06	15.7%	7.6%	8.1%
8	↑	Enzyme Deficiency	9	$13.32	9.4%	8.1%	1.3%
9	↓	Bleeding Disorders	8	$12.03	-1.2%	-4.8%	3.6%
10	-	Osteoporosis	10	$9.56	18.1%	10.6%	7.5%

↓ Down from 2016 **↑ Up from 2016** **- Same rank from 2016**

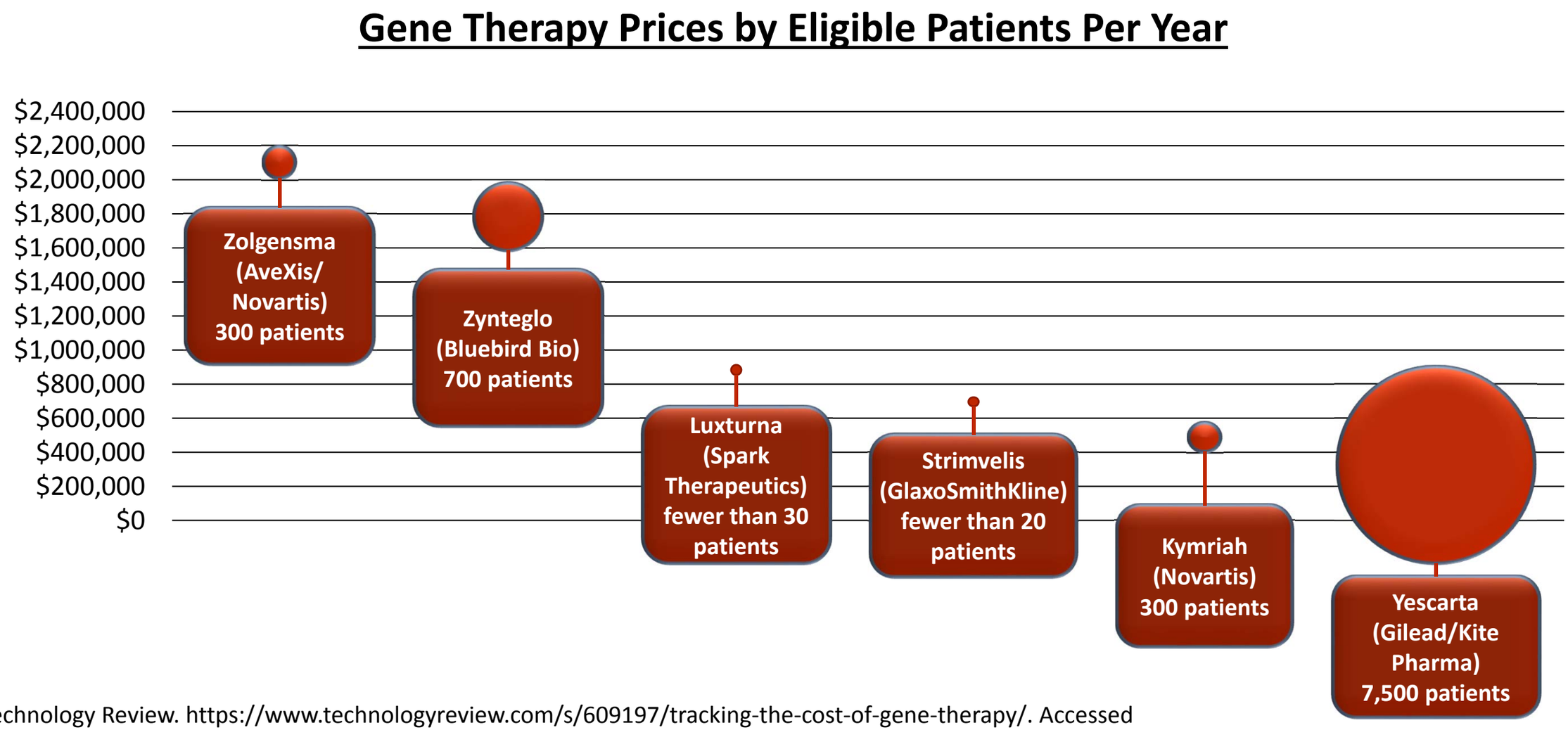
Artemetrx. State of Specialty Spend and Trend. 2018.

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



MIT Technology Review. https://www.technologyreview.com/s/609197/tracking-the-cost-of-gene-therapy/. Accessed October 2019.

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

Healthcare 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

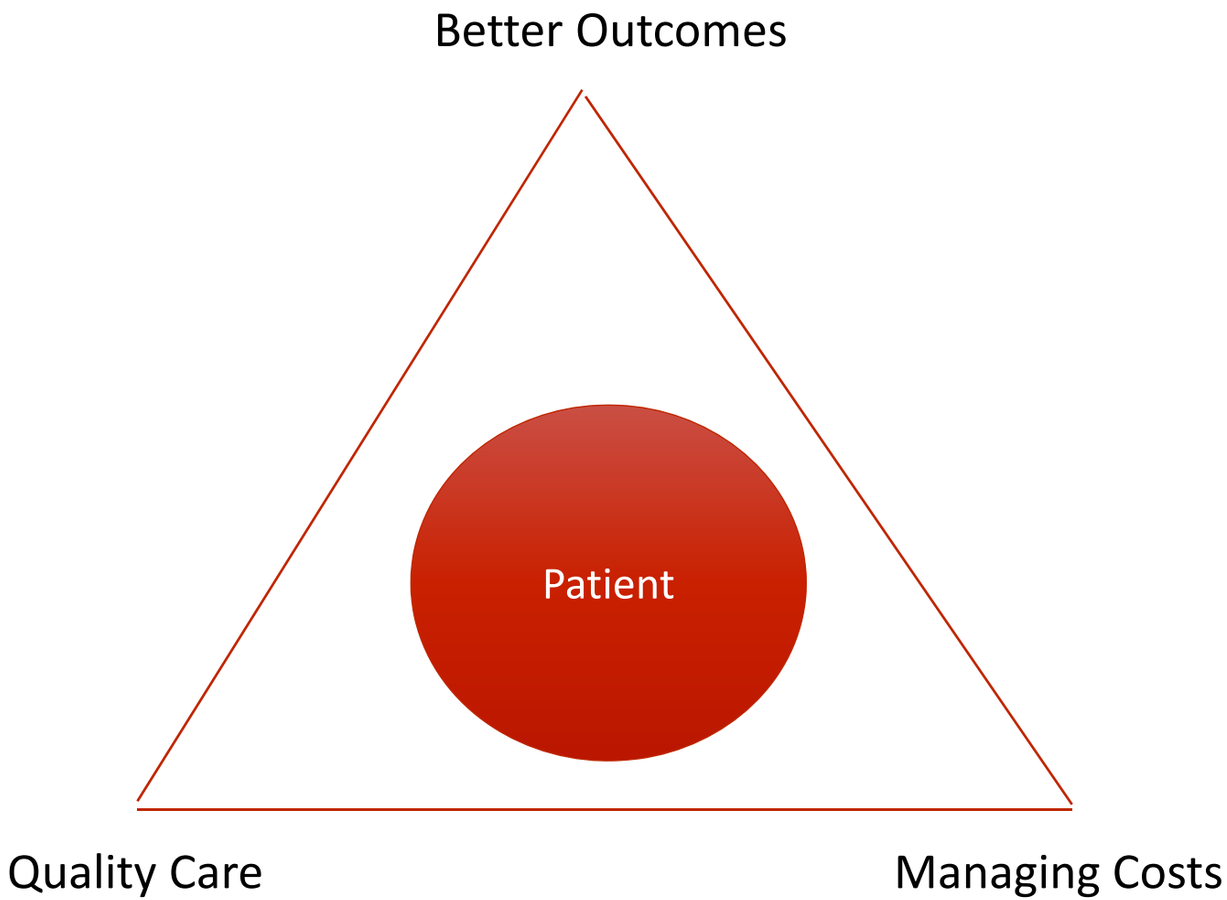
How Value is Measured

- 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



Adaptive Biomedical Innovation as a Holistic Integrating Framework for Sustainable, Patient-Centered Innovation

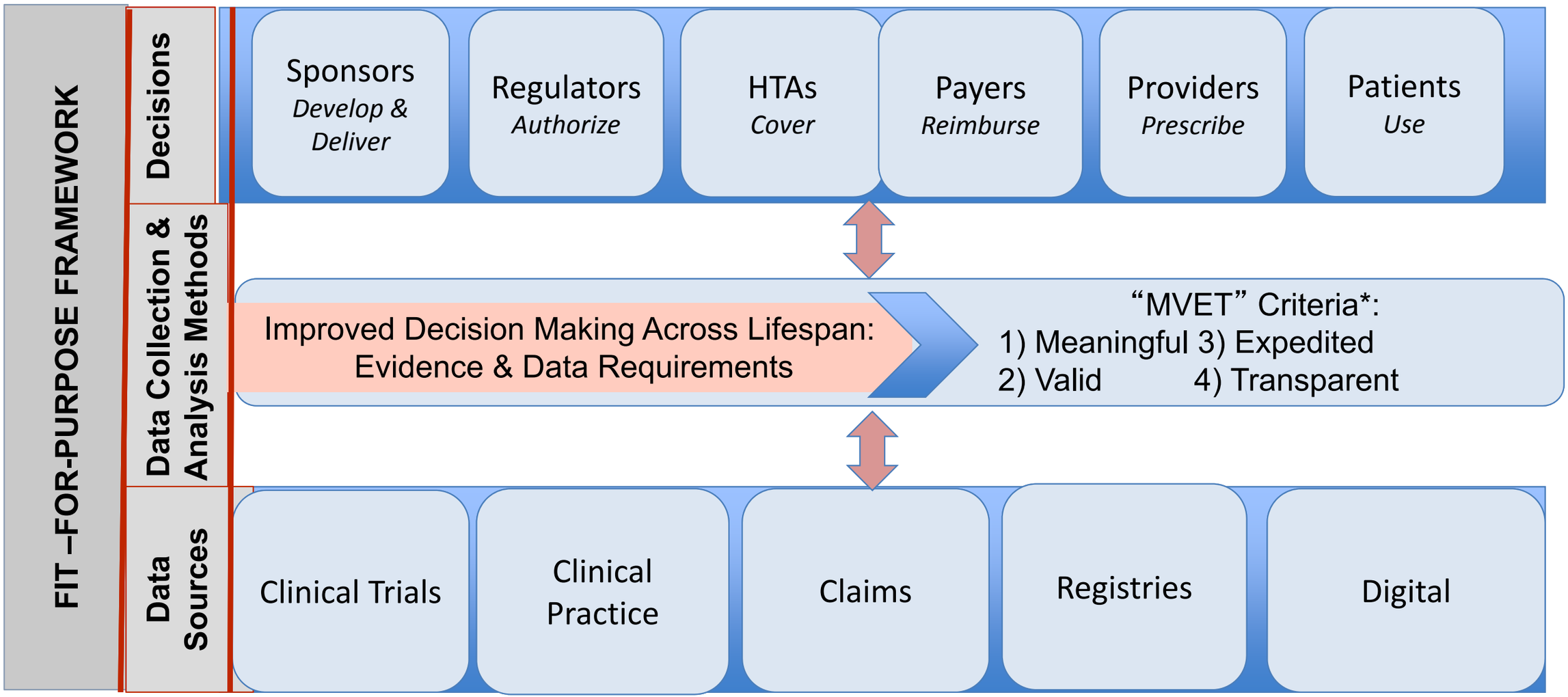
STATE OF THE ART

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.

FoCUS Objectives

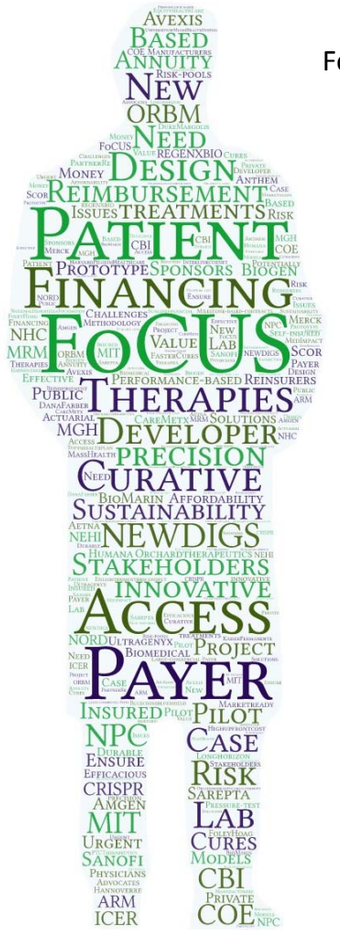
Vision

- 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

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

Dissemination & Recommendations

Issue discovery & design drivers

Option Modeling by Research Team

Modeling Refinement by Research Team

Research, Pilot Design, Communication, Tools

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

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

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

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

1. Skinner, M. W., Chai-Adisaksopha, C., Curtis, R., Frick, N., Nichol M., Noone, D., O'Mahony, B., Page, P., Stonebreaker, J. S. and Iorio, A. (2018). The Patient Reported Outcomes, Burdens and Experiences (PROBE) Project: development and evaluation of a questionnaire assessing patient reported outcomes in people with haemophilia. Pilot and Feasibility Studies, 2018 4:58. doi: 10.1186/s40814-018-0253-0.

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?

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
- I will need to modify my existing operational models:
  - Potential loss of revenue (buy and build models)
  - Potential that timing of new billing codes will slow down reimbursement
  - Potential for new costs burdens to gear up for accreditation

Stakeholder Perspectives and Concerns: Payers

- Payer perspective is dependent upon the segment:
  - Commercial : Fully insured, self insured, individual market or exchanges, ACOs , managed care
  - Public: Medicare, Medicaid
- Organizations paying for health care have different reasons why they pay for health
  - Commercial : Member satisfaction, employee recruitment
  - Public: Societal obligations

- The challenges they face will vary dependent upon size, financial strength and ability to absorb risk at multiple levels
- Reimbursement options are dependent upon their member population and legal or regulatory restrictions
- Acknowledge current financing mechanisms were not designed to address the financial demands of these therapies
- Financing strategies to allow consumer access to durable therapies must be tailored to the preferences, processes, and constraints of each payer segment
- Cumulative effect of curative therapies for multiple conditions will put increasing strain on the current structure

Stakeholder Perspectives and Concerns: Payers

- Financial
  - Actuarial Risk – self-insured and Medicaid plans especially
  - Payment Timing – milestone or performance-based contracts and delayed payments
- Consumer Mobility
  - How to track consumer outcomes required for payments when they move between plans or states
  - Novel treatments can have significant financial consequences – how will we survive the financial impacts of these new, innovative therapies?
- Medicaid and varying state regulations
- Self-insured plans and stop-loss
  - One large payment for rare and unforeseen conditions reduces incentive for alternative reimbursement strategies
  - Risk of laser for predictable or identifiable conditions: cystic fibrosis, hemophilia
  - Increased stop-loss premiums
- Measuring Performance
  - Objective metrics relatively undefined
  - Operational changes and costs to monitor outcomes

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.

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

Concerns Summarized Across Stakeholders

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

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

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, including in hemophilia
- 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 coverage of gene therapy in future care interventions

Proposed Payment Models Aligned with Appropriate Use for Hemophilia Gene Therapy

Mari-Pat Pusey, MBA
Senior Product Director
OptumRx

Payers Face Different Challenges Based on their Size, Financial Strength, and Regulations that Govern their Operations

Actuarial Risk (A):
Small payers face a larger impact from actuarial risk, as individual high-cost events represent a significant fraction of income

Performance Risk (P):
Limited clinical evidence creates performance risk for all payers, across all therapy types

Payment Timing (T):
Conditions with large patient backlogs create a risk of cost surge for all payers.

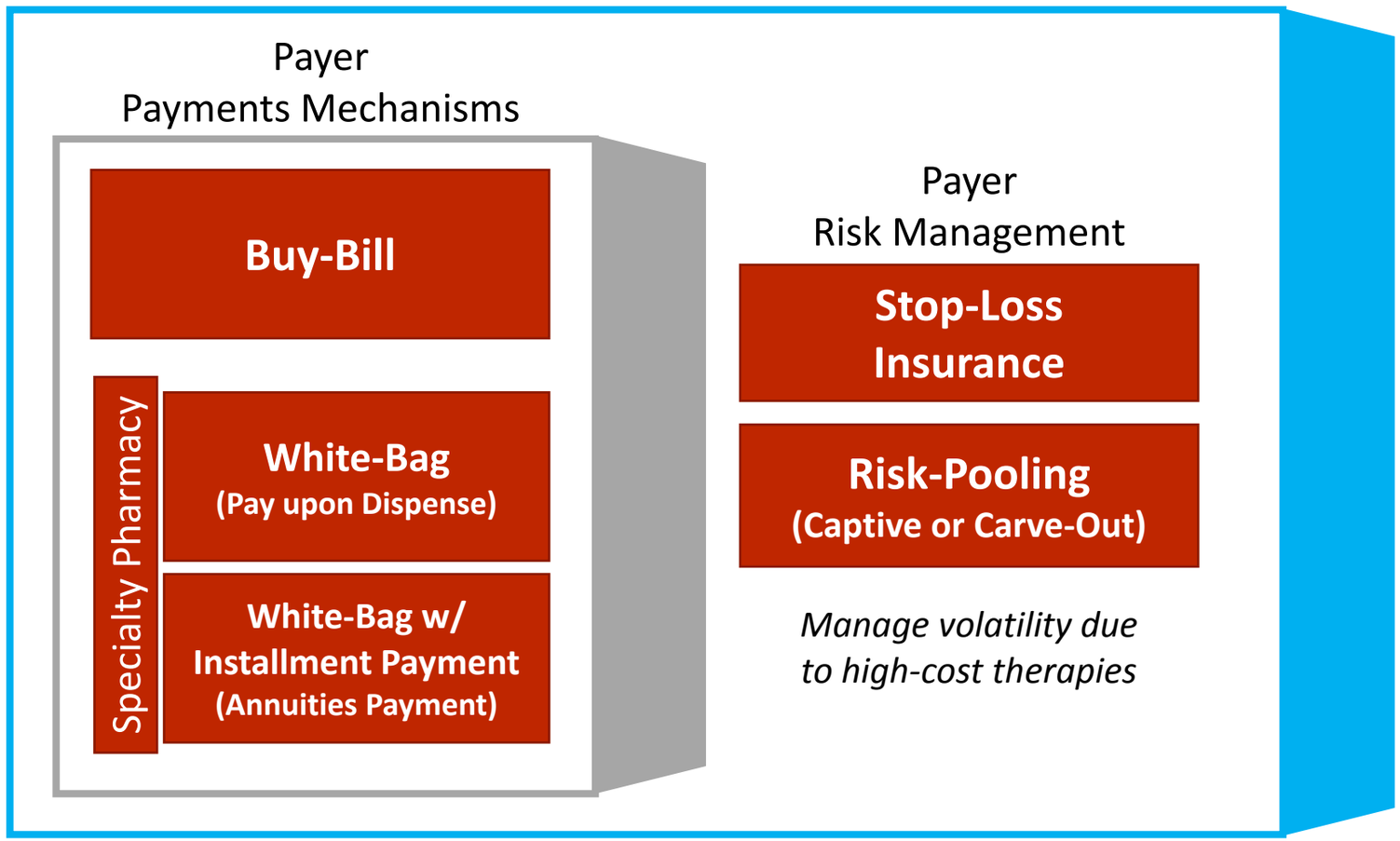
Payment solutions will need to consider both the type of therapy and the type of payer…multiple solutions will likely be needed

	Fully Insured Plans	Medicare	Self-Insured Employers	Medicaid
Orphan Disrupters	P	P	A / P / T	A / P / T
Novel Breakthroughs	P	P	A / P / T	A / P / T
Oncology Therapies	P	P	A / P	A / P
Quantum Leaps	P / T	P / T	A / P / T	A / P / T

- Primary interest is managing performance risk
- Scale reduces the impact of actuarial risk

- Greatest exposure to actuarial risk; conditions with strong genetic inheritance can exacerbate risk
- Payers or employers with small populations, high member turnover or both may be more concerned about over-absorption of the costs
- Ability to spread cost over time helps to mitigate the impact of actuarial risk

Current Mechanisms for Funding High-Cost Therapies



Pricing/Coverage Management Tools

- Performance Rebates
- Performance Guarantee
- Value-Based Agreements

Executed at the Patient or the Population Level

Innovative Access Schemes (IASs) Can Be Divided into Two Groups: Outcome-based and Financial Agreements

Outcomes-Based Agreements		
Performance Guarantee (PG)	Manufacturer pays a rebate based on individual patients that fail to meet predefined outcome measures	Reduced risks around variability of response
Population Performance Rebate (PPR)	Manufacturer pays a rebate/discount for all patients based on the rate of clinical performance within the population	Reduced risks around variability of response in a population
Payment of Costs (PoC)	Manufacturer pays for a portion of costs associated with non-response or suboptimal response to therapy	Limits additional costs related to use of treatment
Performance Pay Over Time (PPT)	Payment executed after patients have reached a predefined outcome measure(s)	Reduced risks of lack of long-term sustainability

Payment Models		
Annuity Payments (AP)	Payment per patient made in installments over a fixed timeframe	Aids in budget management
Stop-Loss	Payers pay a 3rd party a PMPM to assume risk for unexpected events above a certain cost	Aids in budget management
Risk-Pooling	Payers pay a 3rd party a PMPM payment to assume risk for their population	Aids in budget management
Subscription Pricing (SP)	Multi-year agreement for unlimited access to therapy for a defined population	Allows certainty of spending

Additional pricing agreements

- *Pricing capped at a total cost per patient (independent of the amount of drug used)*

Outcomes-Based Agreements

PRO

- Makes sense as it addresses uncertainty
  - Response
  - Durability
- Hedges risk associated with treatment that is not as effective as claimed
- Enables pricing and/or coverage adjustments over time as outcomes data is generated

CON

- Doesn't address short-term budget issues; particularly for small payers
- Medicaid Best Price regulations limit manufacturer willingness to share risk
- Based on clinical failure…need clear definition of outcome measures
- Requires data collection infrastructure and analytics capabilities to reliably measure outcomes
- Need a mechanism to follow patients even as they migrate across plans

Requires data and analytics infrastructure; 3rd-party adjudication services

Payment Models
Annuities (Installment Payments)

PRO

- Reduces budget hit in first year or two
- May help smooth payments for small payers
- Potentially securitizable transferring some risk to the financial markets

CON

- Does not address overall cost
- Adds to the cost of the therapy
- No mechanism for annuity following patient (or expires)
- Accounting challenges
- Medicaid Best Price Rules impede manufacturer from directly administering programs

Limited uptake to date due to financing costs…

Payment Models
Stop-Loss vs. Risk Pooling

Stop-Loss

- Intended to cover UNEXPECTED risk based on an individual plan's population
- Requires annual disclosure of potential high-cost claimants
  - Members with total claims > 50% of proposed deductible
  - Known expected high-cost condition: Members on transplant lists, hemophilia, oncology patients, etc
- Members with expected high cost often "lasered" out of policies
  - Apply high deductible to members with expected high-cost claims
  - Coverage denial based on risk of high-cost claims

May be appropriate for certain gene therapies that address incident populations like Type 1 SMA

Risk Pooling (Captive/Carve-Out)

- Intended to manage risk associated with known high-cost conditions by spreading across a larger population
- Manage population costs through distribution, utilization management, network and quality of care
  - Ensure the right patients are treated with the most effective therapy at the right time and by the right type of provider
  - Pool population to gain leverage with manufacturers and providers

Appropriate for gene therapies that address diagnosed (prevalent) patient pools

Payment Models
Subscription Pricing … part of the future?

Payer Coalition

- Ideally includes: state government, private insurers, agencies covering federal employees
- Pays an **annual subscription** fee to manufacturer for fixed # of years
- Patient outreach

Manufacturers

- **Bid for business:** bids outline duration, annual fee, public health performance targets & bonus payments, patient outreach initiatives
- Selected manufacturer provides **unlimited access to its therapies**

Conditions for Success	Hepatitis C	Gene Therapies
Competition among drug manufacturers	HIGH	LOW – but will increase for certain conditions like CAR-T & Hemophilia as multiple drugs for same indication are approved
Ability to aggregate patients and predict financial risk	HIGH	MEDIUM – Will need to aggregate payers
Understanding of expected clinical performance	HIGH	LOW – addressable with population outcomes-based agreement
Per unit manufacturing costs relative to price	LOW	HIGH – patient-specific therapies are difficult to scale (CAR-T) MEDIUM/LOW – In Vivo therapies are easier to scale as volume increases, manufacturers benefit from guaranteed payments

New Provider/Administrator Entities likely to Emerge

Gene Therapy Administrator

- Negotiate therapy pricing on behalf of Payer Coalition
- Negotiates Outcomes-Based Agreements that ties 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

NEHI Recommendations

1. Stakeholders should address challenges in collecting and analyzing data for VBC
2. A cross-sector group should develop outcome measures including PROs
3. FDA should finalize draft guidance on communication between developers and payers
4. CMS should provide reasonable accommodation for best-price and other reporting
5. OIG has to develop an appropriate safe-harbor
6. HHS Office of Civil Rights should develop HIPAA guidance
7. Stakeholders should continue discussion of new long-term financing arrangements

NEHI: Network for Excellence in Health Innovation

Public Policy and Regulatory Issues

- Impact of outcomes-based payments on best-price and other calculations
- Patient responsibility: what is the impact of these initiatives on patient OOP?
- Pay-Over-Time: Perverse incentives created by fragmentation
- HIPAA
- Anti-kickback

Payment Model Review….

Solution	Payer	Benefit	Barriers
Outcomes-based	Large plan/employer	Reduce cost for ineffective therapy	Need data infrastructure and analytics capabilities
Annuity	Small plan	Manage budget	Financing costs…
Stop-Loss	Small plan	Manage budget	Plan specific, so won't work for all therapies due to lasering
Risk-Pooling (Captive, Carve-Out)	Small plans, Stop-Loss	Manage budget	Need a large pool to appropriately price….
Subscription Pricing	Medicaid Payer Coalitions	Reduce cost for ineffective therapy and manage budget	Need competition

Expect new provider/administrator entities to emerge as the market evolves

Summary

- 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 have been proposed to this end:
  - Outcomes-Based Agreements
  - Alternative Payment Models: Annuities and/or Risk Pools
- 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

Patient Perspective from the National Hemophilia Foundation

Brendan Hayes
Director of External Affairs
National Hemophilia Foundation

2019 NHF Goals

- Community education
- Relationship building – rare disease organizations
- Increase knowledge of the science of gene therapy
- Raising the profile of NHF as an important voice in the rare disease and policy and regulatory space

insights
INNOVATIONS IN TREATMENT
NATIONAL HEMOPHILIA FOUNDATION

Educating the Community

- Established an External Working Group
  - 4 HTC physicians, 2 patients, 1 caregiver and 1 social worker
- Frequently Asked Questions (FAQs)
- In-depth lexicon of gene therapy terms
- *All About Gene Therapy* Video
- Website strategy outlined
- 3 Sessions at NHF's Bleeding Disorders Conference on Gene and Innovative Therapy
  - Multiple sessions in provider track

insights INNOVATIONS IN TREATMENT

National Hemophilia Foundation

FREQUENTLY ASKED QUESTIONS ON GENE THERAPY

GENE THERAPY DEFINED:

What is gene therapy?
Gene therapy is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. If a mutated gene causes a necessary protein to be faulty or missing, gene therapy may be able to introduce a normal copy of the gene to restore the function of the protein. https://ghr.nlm.nih.gov/primer/therapy/procedures

What is a vector? Are there different types of vectors?
A vector is a carrier; the DNA of an agent (virus of plasmid) used to transfer the desired gene to a cell. There are a variety of different types of vectors currently used in gene therapy including retroviruses, adenoviruses, adeno-associated viruses & the herpes simplex virus.

What are the differences among the various approaches to gene therapy: gene editing, gene transfer and cell therapy? Gene therapy involves the transfer of genetic material utilizing a vector. Cell therapy refers to the transfers of cells with the necessary function into the patient. Gene editing targets a specific gene in order to correct its mutation. For more information please go to: https://www.asgct.org/education

What is CRISPR?
Clustered Regularly Interspaced Short Palindromic Repeats is a term used to describe a gene editing technique that can identify and modify specific DNA sequences in the genome of an organism. There is a wide variety of uses for this type of technology including repairing specific disease-causing gene mutations as well as the ability to increase a plant's nutritional value and resistance to climate change.

What vectors are being used in gene therapy for hemophilia?
Gene Therapy that is focused on treating hemophilia currently utilizes viral vectors. The most commonly used are the adeno-associated viruses or AAV. These viruses are modified so they don't cause viral infections and are able to safely deliver the gene of interest into specific cells so that they can start producing factor.

WHAT CAN I EXPECT:

Is gene therapy a cure for hemophilia?
Gene therapy holds the potential for longer term, durable treatments for hemophilia and gives promise for improvements to quality of life. Clinical trials are still underway so there is no definitive answers to length of durability which could determine if it is a cure.

Are there gene therapy treatments for both Hemophilia A and Hemophilia B?
Yes, currently there are several different clinical trials underway at various stages for both types of hemophilia.

What can I expect my factor level to be once I undergo gene therapy?
This depends on many factors. Response to gene therapy is very individual and it can vary over time. Clinical trials to date have demonstrated an increase in baseline factor levels. However, it is hard to predict if it will work on everybody and, if it does, how much it will increase and for how long.

Will my factor level fluctuate in the future if I undergo gene therapy?
Current clinical trials data have shown fluctuations in factor levels over time.

When is gene therapy for hemophilia realistically going to happen?
Currently there are several ongoing clinical trials underway for both Hemophilia A and B which are showing promising results. These trials will continue to be closely monitored to determine safety and efficacy of the therapy. At least one of these trials is nearing completion and is expected to file an NDA New Drug Application with the FDA which means the therapy could be available to patients as early as late 2020.

How long can I expect the effects of gene therapy to last?
At this time, no one really knows the answer to this question. There are several clinical trials underway with data that suggests the possibility of some factor expression in excess of 7 years.

Will I still need factor if I receive gene therapy? What if I have an accident, injury or need surgery?
The need for factor post gene therapy will be dependent upon the amount and duration of factor expression. Each person's response to gene therapy will likely be different and will require an individualized approach. This is a question best discussed with your provider.

If I am deemed ineligible for a particular gene therapy will this mean I am ineligible for any type of gene therapy in the future?
There are many reasons why a person could be deemed ineligible for gene therapy. Current clinical trials do not include males under 18, women, or those with an active inhibitor. Some trials exclude those who have developed antibodies to the vector used in the gene therapy. As the technology matures we will learn more about ways to make this technology available to more patients.

If I undergo gene therapy and it stops working can I try again in the future?
Currently, gene therapy for hemophilia is indicated as a one-time intravenous infusion. There is a possibility that the science will advance and increase options for the future.

Once I receive gene therapy will I still need annual checkups at my HTC?
Yes, you still need to follow up with your health care team after having completed gene therapy at least yearly.

Can I stop or turn off gene therapy?
No, gene therapy is a one-time intravenous infusion which once administered cannot be reversed or undone.

RISKS ASSOCIATED WITH GENE THERAPY:

What is vector shedding?
It is the process by which the viral vector leaves the body through bodily fluids after it is no longer needed by the body.

What are the risks associated with gene therapy?
Some possible risks associated with gene therapy include but are not limited to: an unwanted immune system reaction, targeting of the wrong cell, an infection caused by the virus and the possibility of hepatic carcinomas.

What happens if I undergo gene therapy and my resulting factor levels are higher than the normal range?
In some cases, gene therapy has resulted in factor levels well over the normal ranges. Although this may be associated with increased clotting risks no adverse effects have been reported. However, you need to know that this can happen and if it does you will need to be closely supervised by your hemophilia treatment center.

GENE THERAPY AND REPRODUCTION:

Can I pass the effects of gene therapy to my children?
No. Gene therapy for hemophilia is designed to correct the genetic defect only in the person who receives it. That is, it delivers a functional (or working) copy of the factor VIII or factor IX gene to the liver cells providing them with the instructions of how to produce the missing factor. Gene therapy does not correct the genes that are passed onto the next generation.

Should patients who undergo gene therapy bank sperm?
After the administration of gene therapy the body takes several weeks to months to get rid of the vector used in gene therapy through different bodily fluids including semen, blood, urine, feces and saliva. Although the risk for the vector to integrate into the sperm cell is low, men who undergo gene therapy are being asked to use a barrier contraceptive method (such as condoms) to prevent pregnancies for an extended period of time after the infusion. If you are considering having a baby in the near future, it might be reasonable to think about banking sperm before undergoing gene therapy.

Will I still have hemophilia if I have normal factor levels?
Gene therapy for hemophilia is a relatively new concept as a treatment option and is still in the clinical trial phase. This means that we don't know how durable it will be (aka how long will it last) and the level of factor expression will vary among individuals. Factor levels may be in the moderate, mild or normal range and may fluctuate over time.

These gene therapies are targeted to somatic cells (ex. cells that control biological processes within your tissues, organs, blood) not germline or reproductive cells so you can still pass hemophilia to your offspring. While you may rarely need to do infusions or maybe not at all, you will need to remain diligent with your healthcare to ensure you are on top of things.

Will I still be able to go to the HTC?
Most definitely, in fact please do. It will be important to continue to be monitored to assess any changes in overall health including emotional health as well as factor levels. Any underlying issues you had prior to gene therapy (ex. joint issues) will need to be monitored as well. Your HTC will be an important partner in your follow-up care post gene therapy.

ELIGIBILITY:

Who is eligible for gene therapy?
Currently gene therapy for Hemophilia A and B are in the clinical trial phases. Eligibility criteria varies somewhat between studies but for the most part the criteria is as follows: healthy (no diabetes, history of malignancies, heart disease, glaucoma, high blood pressures etc.) males, age 18 and older, with severe Hemophilia A or B, without inhibitors, no evidence of hepatitis or HIV, no evidence of liver dysfunction and no detectable neutralizing AAV antibodies. Your healthcare provider can explain the exclusion criteria in more detail.

At what age can my child have gene therapy?
Currently gene therapy for hemophilia is not indicated for individuals under 18. Gene Therapy for Hemophilia is targeted towards the liver which continues to grow in humans until they reach at least age 12. As the science is perfected the age could be lowered in the future.

Can females with Hemophilia receive gene therapy? If not why?
Currently gene therapy for Hemophilia is not indicated for female patients. Most female patients who are affected are classified as carriers with mild hemophilia and their factor levels are not low enough to qualify.

GENERAL INFORMATION:

How is gene therapy administered?
Similar to a factor infusion, gene therapy is a one-time intravenous infusion which can last anywhere from minutes to a few hours. However, unlike factor, it is currently being done in a medical facility by healthcare providers.

Where will I receive gene therapy? An HTC?
Gene therapy is currently being offered to eligible participants who are enrolled in a clinical trial. Currently, infusions occur only in pre-determined sites participating in the clinical trial.

Will my insurance company pay for gene therapy?
This is an important question and much work is being done to determine alternative financing and reimbursement strategies to enable patients to access these promising therapies. The current healthcare system as we know it is not equipped to handle large one-time payments. Additionally, these new treatment options have short treatment regimens (one-time infusion) and benefits that create challenges. These challenges include uncertainty around how long the therapy will last (insurance plans don't want to pay for things that don't work long-term) and uncertainty around an individual remaining on a given insurance plan (think about how often you might change insurance plans - new job, employers change types of plans offered, etc.). We have seen some gene therapies for rare diseases being reimbursed by insurance companies and that is great news for hemophilia patients. The creation of other conditions or comorbidities due to the gene therapy is also an unknown.

We do not currently know if the out-of-pocket costs will continue to be a challenge for the consumer like it is now in our current health care system. For those consumers with comorbidities or lasting physical effects of their primary disease, the out-of-pocket costs could and probably will continue to pay on an ongoing basis as out-of-pocket costs from high deductible health insurance continue to rise year over year.

Some suggested strategies include milestone-based contracts (payments are made when milestones are achieved) and performance-based annuities (a plan would pay an agreed upon amount if the therapy continues to perform well year to year) to name a few. This will require significant changes to our existing healthcare system. Additionally, there will be a need for policy changes at the Federal level to enable these strategies to work. NHF and other rare disease organizations are working with payers and policy makers to ensure access to these therapies becomes a reality. First dollar coverage is one component being discussed to address the affordability from the patient's side of things. Academic entities like the MET NEWDIGS consortium bring together stakeholders that are working collaboratively (payers, providers, patient advocacy organizations, pharmaceutical developers, academics and others) to come up with innovative solutions.

For more in-depth information please contact:
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NHF #NHF2019 Bleeding Disorders Conference

Relationship Building

- It is IMPERATIVE that we collaborate with others in this space:
  - Global Genes
  - NORD
  - World Federation of Hemophilia – WFH
  - Alliance of Regenerative Medicine (ARM)
  - ARM Foundation
  - ASGCT
  - ASH
  - MIT NEWDIGS – FoCUS Initiative
  - Sickle Cell, SMA, DMD, PKU
  - Faster Cures

Global Genes™
Allies in Rare Disease

NORD®
National Organization for Rare Disorders

NEWDIGS
FoCUS
Financing and Reimbursement of Cures in the US

ARM Foundation *for* Cell & Gene Medicine

2020 NHF Goals

- Develop educational resources (2.0) based on feedback from the Gene Therapy Stakeholder Summit
- Continue to raise the profile of NHF in the gene therapy space through building partnerships and collaborations with other national organizations
- Research – Longitudinal data collection, survey patients on their perspectives on innovative therapies
- Communications – Social media outreach
- Access Challenges — Payer/Policy obstacles