Gene Therapy Landscape

December 2023

Bluestar
BioAdvisors

Applications of regenerative medicine, including GTx, cell-based GTx, and cell therapy, vary greatly depending on the technological approach and drug delivery environment

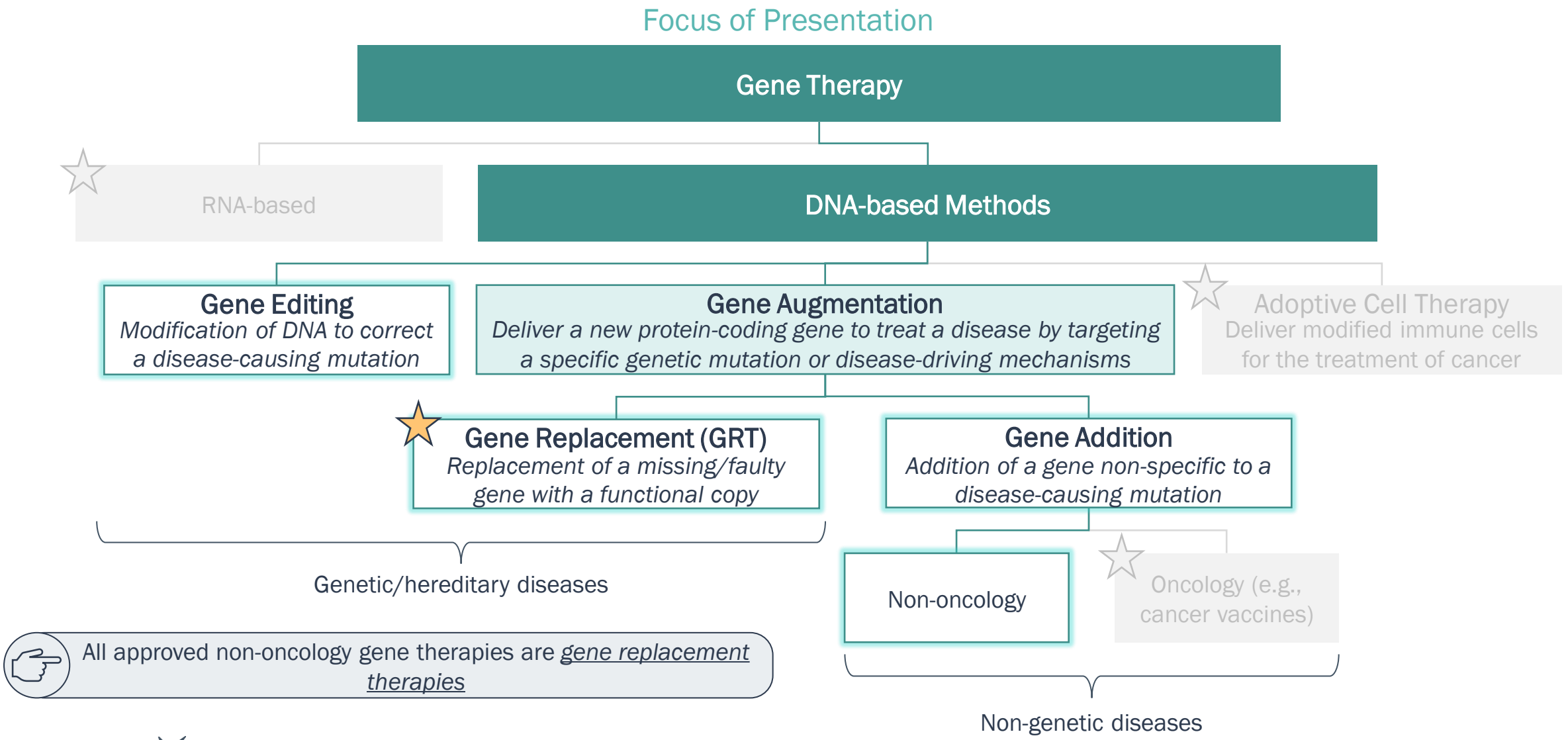
Overview of Approaches to Regenerative Medicine

	Gene Therapy (GTx)	Cell-based GTx	Non-genetically Modified Cell Therapy
Definition	*Transfer of genetic materials to patient cells*	*Transfer of functional living cells which have been genetically modified*	*Transfer of functional living cells*
Drug Delivery Environment	*in vivo*: *Target gene* → *Transgene packaging* → *Deliver to patient*	*ex vivo*: *Donor* → *Allogeneic* → *Collect delivery cells* → *Introduce packaged transgene* → *Genetically modified cells* → *Deliver to patient* (*Autologous*)	
Approaches	RNA-based (e.g., ASO, RNAi, mRNA)	DNA-based: Gene Editing & Gene Augmentation Therapy; Adoptive Cell Therapy	Stem Cell Transplant
Mature Areas of Clinical Development	Rare Diseases	Oncology/Hematology	
Approved Example(s)	Onpattro (ATTR-CM); Zolgensma (SMA)	Zynteglo (β-thalassemia); Kymriah (ALL, DLBCL, FL)	HEMACORD (disorders affecting the hematopoietic system)

*Adoptive cell therapy (ACT) including CAR-T, TCR-T, and CAR-NK explicitly target human immune cells

Sources: Sources: ASGCT; Alliance for Regenerative Medicine, Cell & Gene, GeneHome

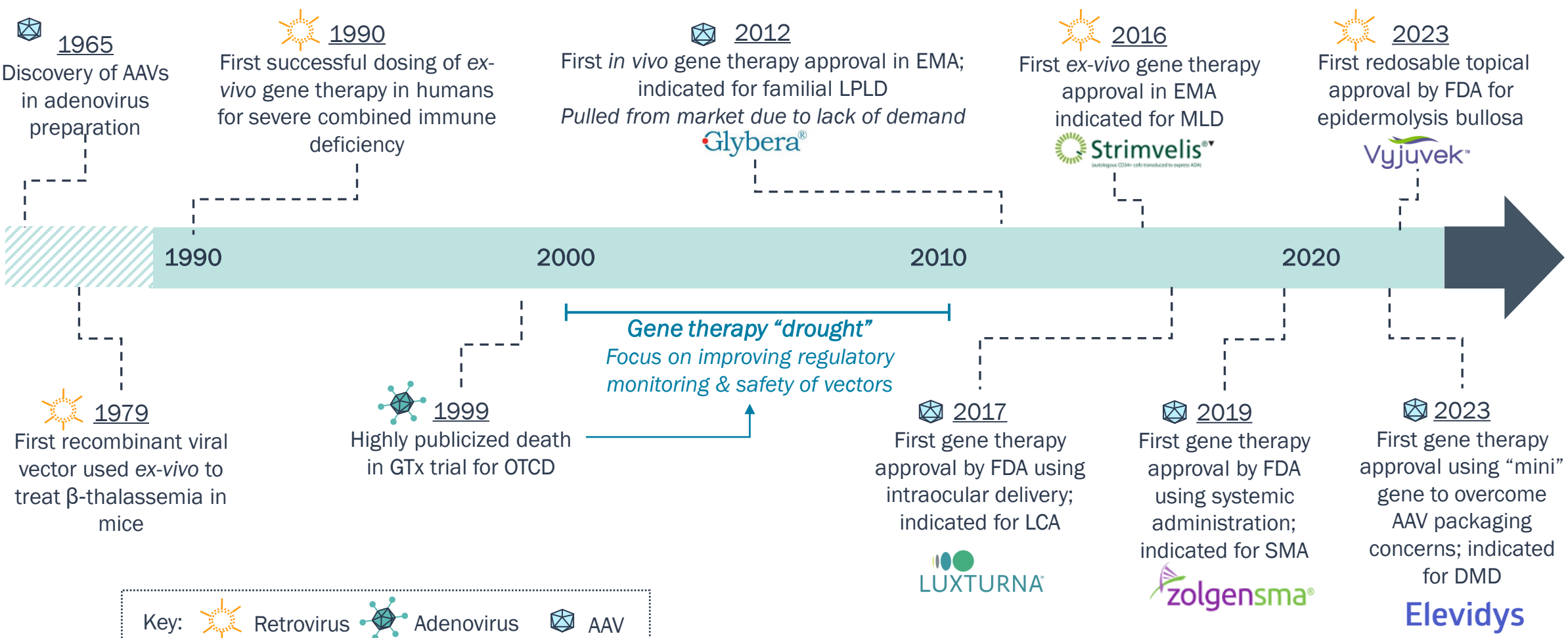
This presentation focuses on non-oncology DNA-based GTx approaches, including gene editing, gene replacement, and non-oncology gene addition



Key: ☆ FDA/EMA approved agents

Despite facing substantial developmental challenges, the gene therapy market has achieved remarkable success in the last 5-10 years

Milestones in Gene Therapy



Sources: Landhuis E, 2021, Nature; What Is Biotechnology: Gene Therapy summary

The majority of the 11 approved agents, which are all gene replacement therapies, in US/EU markets treat hematological or CNS diseases

Overview of Approved Gene Replacement Therapies (Products Approved in US and/or EU Markets)

	TA	Indication	Year First Approved	All Approved Geographies	Delivery		
					ROA	Frequency	Packaging
NOVARTIS Zolgensma	CNS	SMA	2019		IV, IT	Single dose	
Orchard therapeutics Libmeldy		MLD	2020		IV		
bluebirdbio Skysona		CALD	2022		IV		
PTC THERAPEUTICS Upstaza		AADC Deficiency	2022		IC		
SAREPTA THERAPEUTICS Elevidys		DMD	2023		IV		
uniQure Hemegenix	Hematologic	Hemophilia B	2022		IV	Single dose	
bluebirdbio Zynteglo		β-thalassemia	2022		IV		
BIOMARIN Roctavian		Hemophilia A	2023		IV		
Orchard therapeutics Strimvelis	Metabolic	ADA	2016		IV	Single dose	
Roche Luxturna	Ophthalmic	LCA	2017		IVT	Single dose	
Krystal Vyjuvek	Dermatologic	Epidermolysis Bullosa	2023		Topical	Redosable	

All approved drugs are GRTs for the treatment of autosomal recessive, monogenic diseases

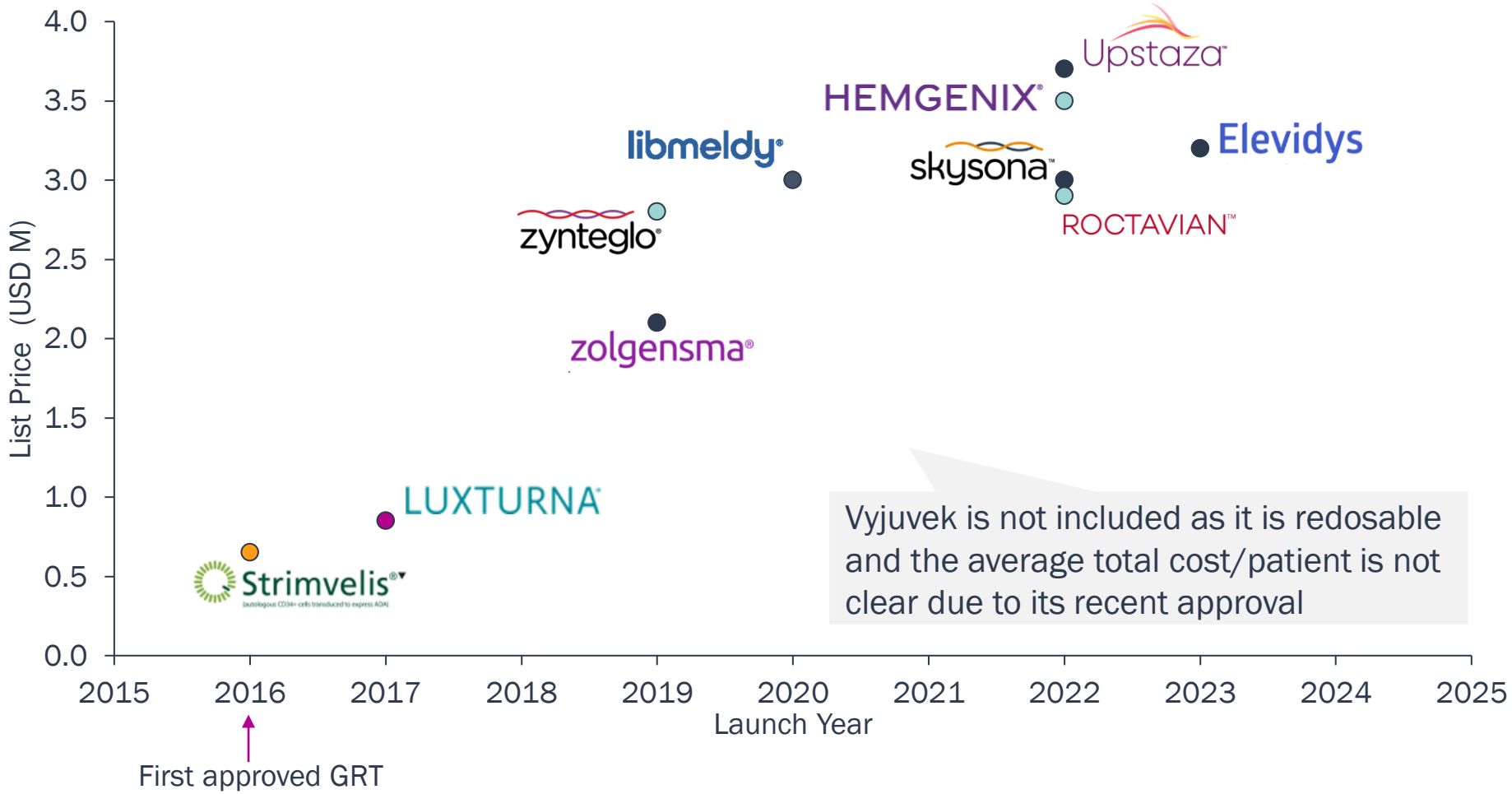
Abbreviations: IT = intrathecal, IV = intravenous, IVT = intravitreal, IC = intracranial
Sources: ASGCT; Alliance for Regenerative Medicine, PharmaProjects

Key: Orphan GTx Cell-based GTx

In the last two years, the number of approved GRTs has doubled; single-dose therapies have an average list price of $3.0M per patient

Market Trends

List Price of Single-dose Gene Replacement Therapies by Year of First Approval*



Vyjuvek is not included as it is redosable and the average total cost/patient is not clear due to its recent approval

European list prices for assets approved only in the EU/UK (Strimvelis, Libmedly, and Upstaza)

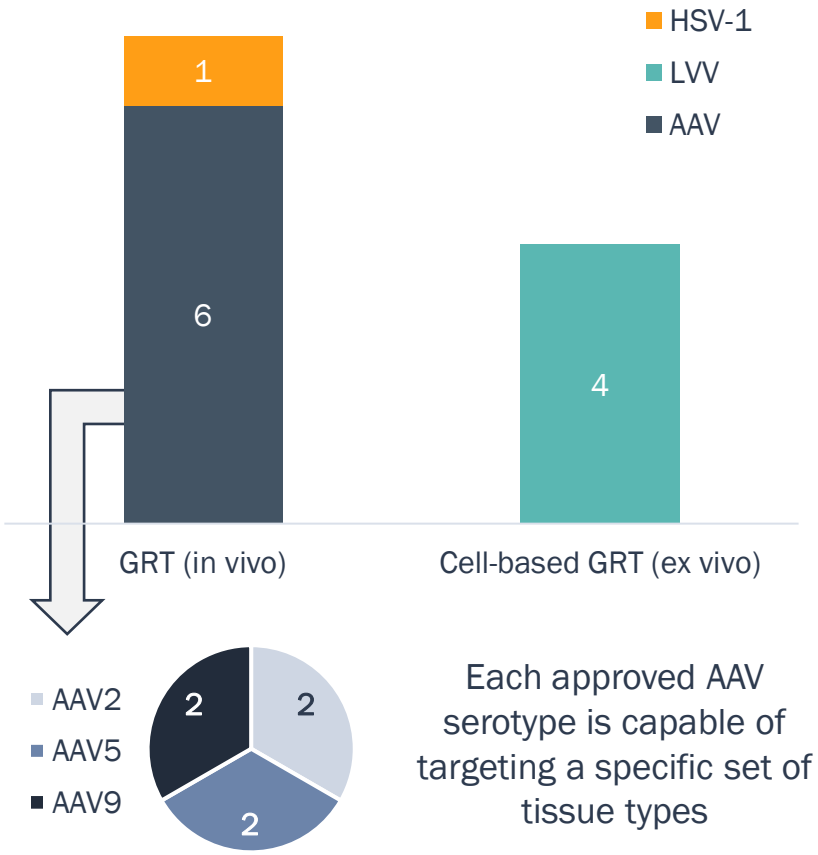
*Vyjuvek not included

Sources: PharmaProjects, ASGCT, Fierce Pharma and Biotech

Key: CNS Metabolic Hematologic Ophthalmic

Viral vectors are the only approved transgene delivery vehicle; *ex vivo* and *in vivo* GRT require different features and predominantly rely on lentiviral or adeno-associated viral vectors, respectively

Transgene Packaging Utilized for GRT



Each approved AAV serotype is capable of targeting a specific set of tissue types

Transgene Packaging Trends

- As the current standard for transgene packaging, viral vectors (e.g., AAV, LV, HSV-1) remain the most effective delivery mechanisms

Cell-based Gene Replacement Therapy (ex vivo)

- LV vectors typically target dividing cells (e.g., stem cells, immune cells) and integrate into the host genome, making them most amenable to *ex vivo* approaches
- Due to high risk for insertional mutagenesis and the associated risk of cancer, *in vivo* use of LV vectors is unlikely

Gene Replacement Therapy (in vivo)

- AAV vector packaging delivery dominates *in vivo* GRT, which most commonly targets non-dividing cells (e.g., neurons, photoreceptors, liver cells)
  - AAVs have limited packaging capacity and are not ideal for larger transgenes; however, GRTs like Elevidys overcome this barrier by delivering a μ-dystrophin gene ("mini" dystrophin)
  - Target tissue type drives AAV serotype selection; AAV9 vectors target at least 5 tissue types and have become prominent in the pipeline
- Vyjuvek, the most recently approved GRT, is the first *topical and redosable* GRT, and employs a novel HSV-1 vector
  - HSV-1 vectors target both dividing and non-dividing cells without integrating into the host genome; topical administration and redosing reduce potential concerns of HSV-1 immunogenicity and transient gene expression

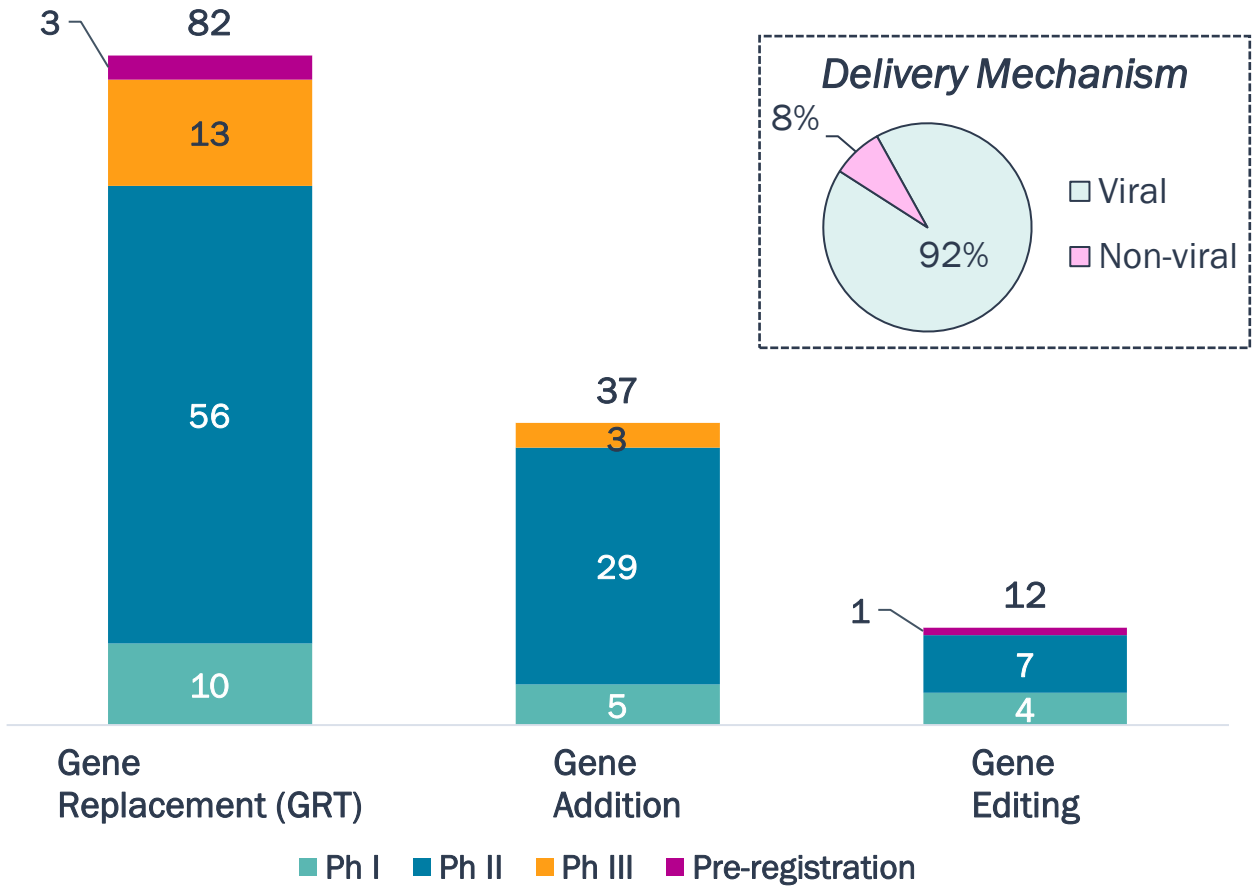
Abbreviations: AAV-Adeno-associated Virus; HSV- Herpes Simplex Virus-1; LV- lentiviral
Sources: Pharmaprojects, Krystal Biotech, Bulcha et al., *Signal Transduct. Target. Ther.*, 2021

Clinical Development for Non-Oncology Gene Therapy

GRT represents the most common and mature approach in the GTx pipeline; a minority of agents employ novel non-viral delivery methods while the majority use classic viral vectors

Summary of Clinical Development for Non-Oncology Gene Therapies

Non-Oncology Gene and Cell-based Gene Therapy Pipeline* (N=131)



The FDA is set to make decisions on pipeline agents in December 2023

Both therapies are for the treatment of sickle cell disease

VERTEX / CRISPR THERAPEUTICS — exa-cel (December 8)

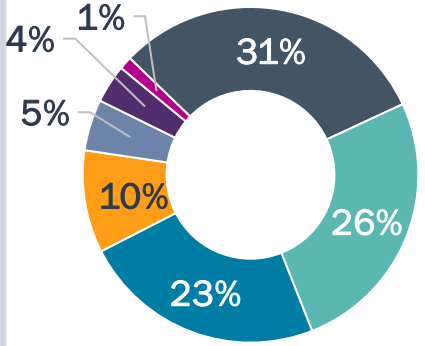
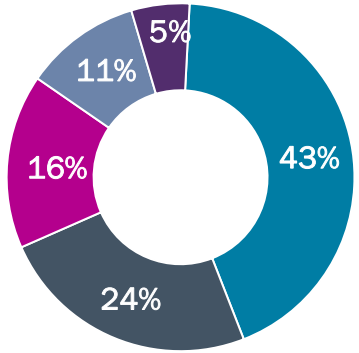
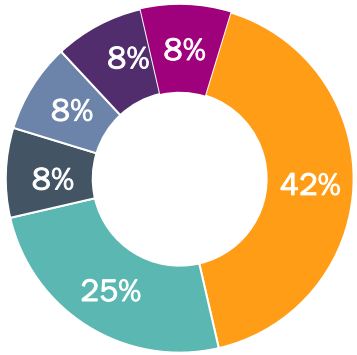
bluebirdbio — lovo-cel, novel GRT (December 20)

Exa-cel has potential to be the first FDA- approved gene editing therapy

*Includes clinical stage assets with trials in the US and/or EU+UK; Abbreviations: Exa-cel- exagamglogene autotemcel; lovo-cel- lovotibeglogene autotemcel
Sources: PharmaProjects

Gene replacement/editing approaches tend to focus on monogenic diseases with known etiologies; gene addition offers potential in diseases with unknown disease-causing mutations

Clinical Development Trends

	Gene Replacement (n=82)	Gene Addition (n=37)	Gene Editing (n=12)
Ex vivo/in vivo	in vivo 78 ex vivo 4	in vivo 35 ex vivo 2	in vivo 6 ex vivo 6
Therapeutic Area	 *CNS, metabolic, and ophthalmic related diseases represent 83% of the GRT pipeline*	 *Ophthalmic and CNS related diseases represent 67% of the gene addition pipeline*	 *Hematologic and metabolic disorders represent 72% of the gene editing pipeline*
Disease Frequency	100% rare diseases	14% rare diseases 86% common diseases	73% rare diseases 27% common diseases
Commentary	GRTs exclusively target rare diseases with the majority being autosomal recessive and monogenic	Frequently target common diseases and have broader applicability due to their mutation-independent approach	The gene editing pipeline is relatively small and predominately focuses on rare, hematologic disorders

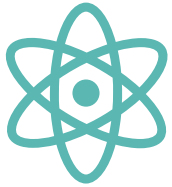
Definitions: rare disease- prevalence ≤200K; common disease- prevalence >200K
Source: PharmaProjects

Key: Autoimmune, Cardiac, CNS, Hematologic, Metabolic, Ophthalmic, Other

As the gene therapy space continues to rapidly evolve, it is important to monitor current market challenges/considerations and the potential impact of proposed solutions

Key Market Considerations

Technical



Transgene packaging options remain limited and implicate clinical utility of gene therapy products

- How will non-viral delivery methods impact the gene therapy?
- What strategies are drug developers using to overcome AAV capacity issues?

Clinical

Significant clinical unknowns exist due to limited historic benchmarks and a lack of long term data

- Are there inherent challenges to clinical trial design?
- How will the availability of long-term efficacy/safety data impact the development of gene therapy?

Commercial

Market access dynamics, manufacturing logistics, and accurate forecasting are top concerns in the gene therapy space

- How will payers influence GTx utilization?
- How will high upfront costs and early depletion of addressable populations impact uptake curves

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Source: Bluestar Analysis

Abbreviations

Term	Abbreviation
Spinal Muscular Atrophy	SMA
Metachromatic Leukodystrophy	MLD
Ornithine Transcarbamylase Deficiency	OTCD
Lipoprotein Lipase Deficiency	LPLD
Cerebral Adrenoleukodystrophy	CALD
Duchenne's Muscular Dystrophy	DMD
Adenosine Deaminase Deficiency	ADA
Leber's Congenital Amaurosis	LCA

Glossary

Term	Definition
Transgene	Gene that has been deliberately introduced into the genome of an organism
Viral Vector	Modified virus used as a delivery vehicle to transfer genetic material into a host cell
Non-viral Vector	Non-viral delivery system or method used to transfer genetic material into host cells
Autologous	Derived from an individual's own body
Allogeneic	Derived from a donor other than the patient