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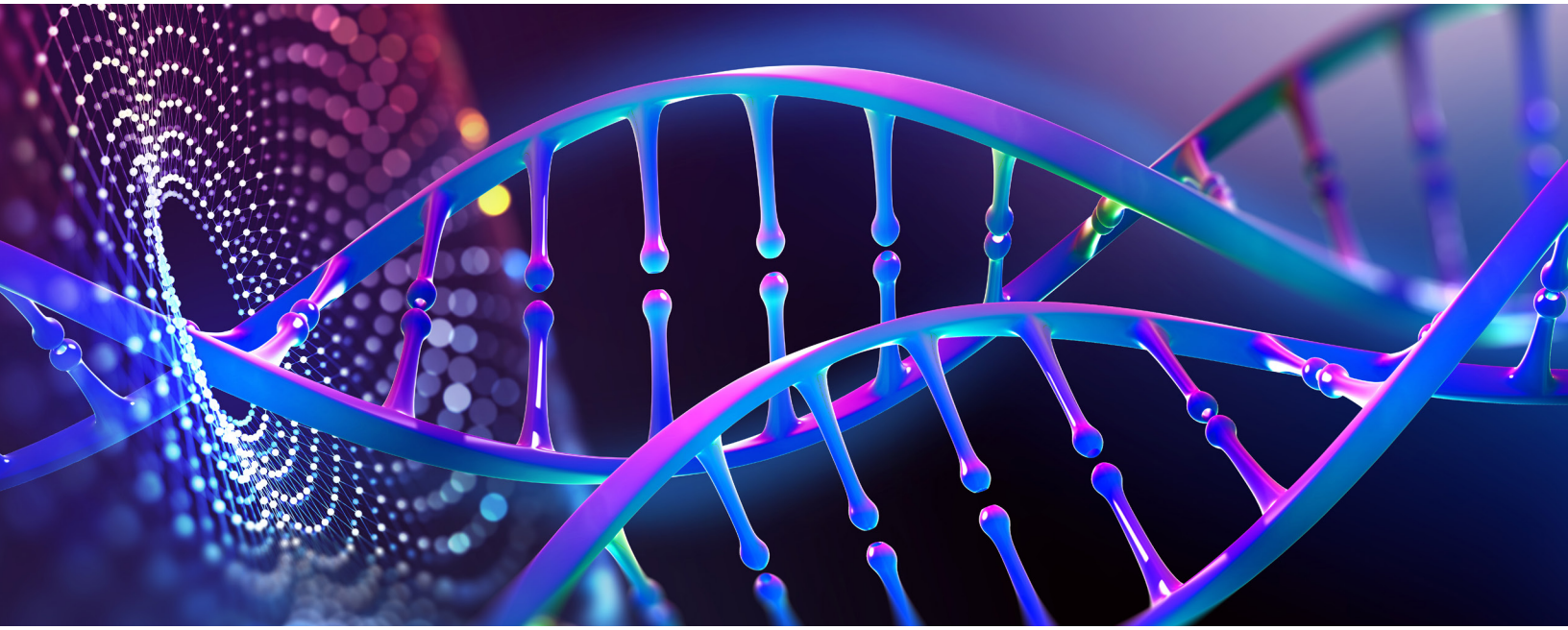
Roaring 20s Redux:
The Next Decade of Gene Therapy Innovation



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Executive Summary

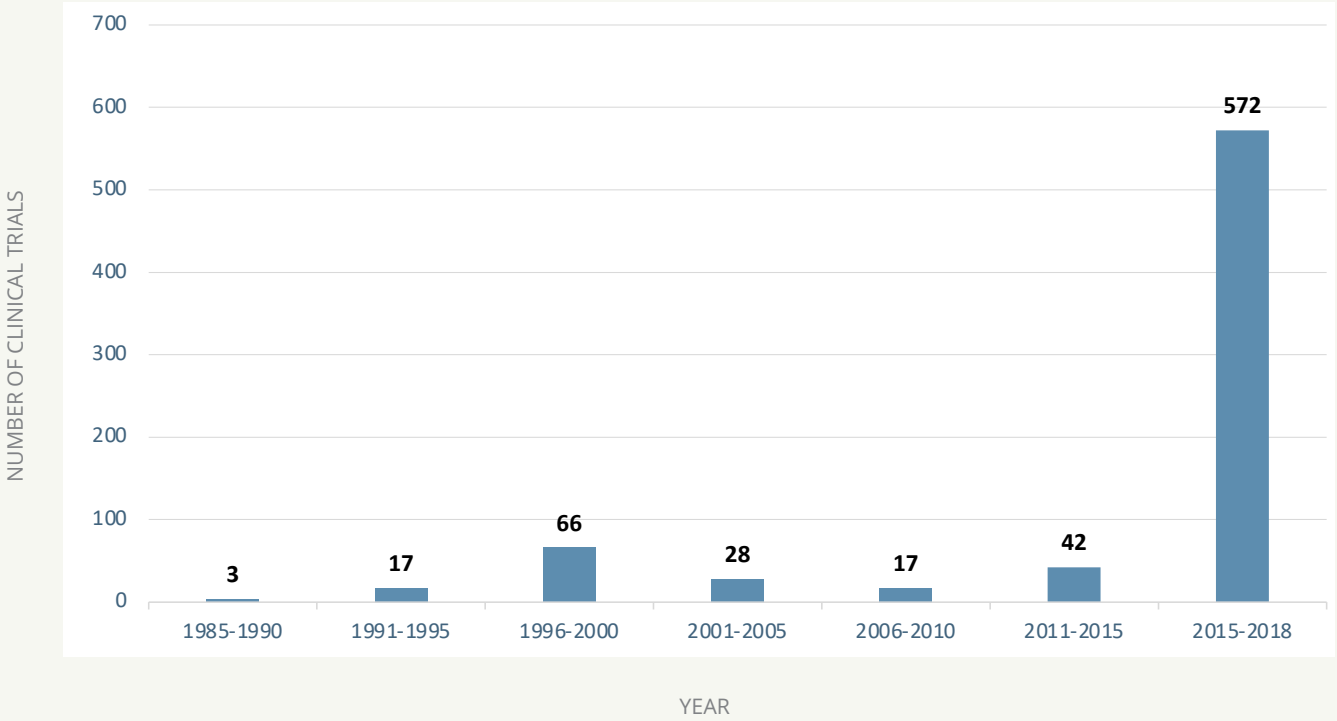
Over the last five years, multiple gene therapies have been approved by regulatory agencies and a bolus of late-stage pipeline assets are approaching the market. As the first few gene therapies realize their potential as transformative treatments for the genetic rare diseases, the space is seen as a crucial part of growth for the biopharmaceutical industry. However, as the first gene therapies began to post early wins, several technical and commercial challenges emerged. With these challenges in mind, leading companies have begun to search for new delivery technologies and commercial models. Only after addressing these roadblocks will gene therapies be able to fully deliver on their longstanding potential to transform patient outcomes, expand into larger diseases, and ultimately provide returns for investors.

THE PAST
Gene Therapy: The First Wave

The premise of gene therapy (i.e., gene replacement, gene transfer) is that monogenic diseases known to be driven by a single genetic lesion can be effectively treated via transfer of a "healthy" gene. Using a delivery vehicle such as a viral vector, an unaltered copy of the mutant gene can be inserted to produce whatever enzyme or other defective protein is the cause of disease pathology to ameliorate the disease. Of course, the nature of the disease pathophysiology can make this more complex, even for monogenic diseases where the underlying biology is well understood.

The gene therapy field already overcame several setbacks to reach initial product approvals. In particular, the death of Jesse Gelsinger in 1999, ~10 years after the first gene therapy clinical trials, handed the field a major setback. With the death related to an adverse event (AE) caused by an adenovirus vector (delivery vehicle), the field initiated a search for safer delivery vehicles such as Adeno-associated viruses (AAVs) in the early 2000s. Similarly, AEs led the field to engineer safer lentiviral vectors in the same period.[1] With first-generation approaches showing clear weaknesses, a precipitous drop in gene therapy clinical trials was observed as academic investigators went back to the drawing board for safer mechanisms of gene delivery (Figure 1). Company formation based on gene therapy platforms also stalled, with scientific advances that would later reinvigorate company formation occurring in academia.[2] Signs of life for gene therapy in the industry emerged with the EU approval of Glybera (alipogene tiparvovec) in 2012 and the founding of Spark Therapeutics in 2013.

Figure 1:
Gene Therapy Clinical Trials Over Time



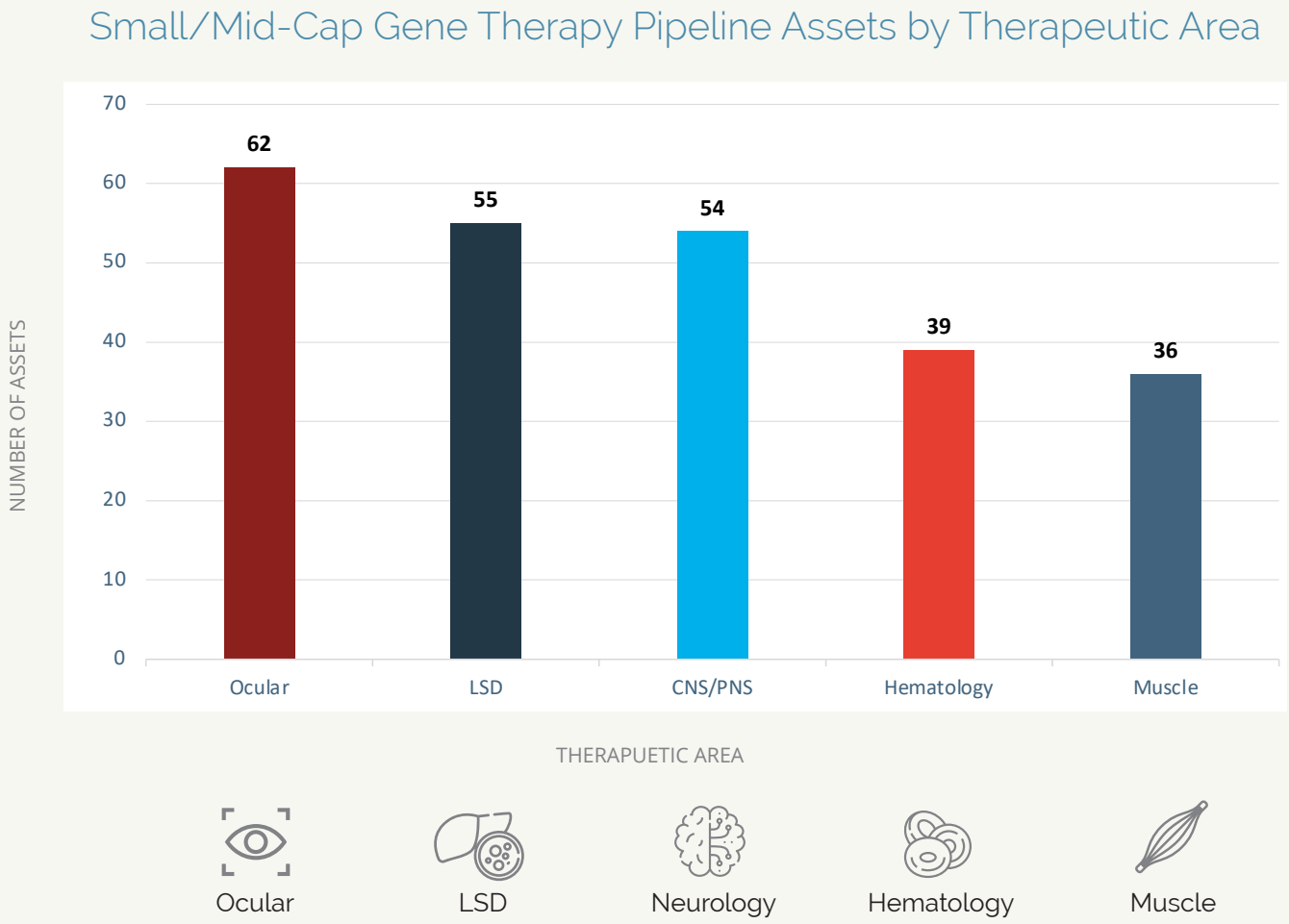
Sources: Back Bay analysis, clinicaltrials.gov

Even more recent advances in gene therapy science and delivery reinvigorated interest across therapeutic areas (e.g., Neurology, Ophthalmology, and metabolic diseases) (Figure 2). Two AAV gene therapies have been approved by the FDA in the last 3.5 years, Luxturna (voretigene neparvovec) for a genetic form of Leber congenital amaurosis (LCA) and Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy (SMA), and a plethora of clinical programs are following closely behind. Reports of the disease-modifying and even curative potential of both Luxturna and Zolgensma have been widely publicized alongside price tags of ~$1M and ~$2M, respectively.

Clinical Challenges

Despite advances, the roll out of these first commercial gene therapies has not been without hiccups. Developers have hit speedbumps reaching the same levels of efficacy demonstrated in clinical trials, achieving durable therapeutic benefit, and establishing a favorable risk/benefit profile, ultimately resulting in substantial regulatory concerns.

Figure 2:
Key Gene Therapy TAs



Sources: Back Bay analysis, Guggenheim 19Mar2020

Four key technical questions have arisen for gene therapies due to the observed challenge of translating therapeutic promise into clinical benefit:

- **Delivery**: How do we deliver a therapeutic gene to the right organs and cells?
- **Safety**: How can we avoid side effects with either delivery or the expression of a new gene?
- **Efficacy**: Even if we can get to the appropriate cells avoiding side effects, what level of durable transgene expression is needed for clinical benefit?
- **Genetic Understanding**: Is expressing a therapeutic gene sufficient to prevent or reverse disease progression or are other factors involved?

Highlighted below are examples of clinical issues seen in the field:

Novartis' Zolgensma (onasemnogene abeparvovec) has not shown safety and efficacy in older SMA patients, who have more advanced disease and require intrathecal, rather than IV, administration

- The required pivotal trial in older patients is on partial clinical hold due to preclinical data integrity issues[3,4]

BioMarin's Valrox (valoctocogene roxaparvovec) for Hemophilia A has yet to demonstrate the durable therapeutic benefit required for regulatory approval[5]

- Valrox's therapeutic benefit decreases over time, with 4-year data from a phase 1/2 study showing a significant decrease in factor VIII levels back toward baseline
- This led the FDA to issue an unexpected complete response letter (CRL) requiring 2 years of additional safety and efficacy data following the completion of the phase 3 clinical trial rather than allowing phase 1 durability as a surrogate

Both Audentes' AT132 for X-linked myotubular myopathy and Solid Bioscience's SGT-001 for Duchenne muscular dystrophy caused serious adverse events (SAEs) resulting in since removed clinical holds due to risk/benefit concerns

- In Audentes' ASPIRO trial, there were 3 patient deaths in the high dose group[6]
- Multiple clinical holds were placed on Solid's IGNITE DMD trial, as 2 patients experienced SAEs[7,8]

Commercial Challenges

In the same vein, the first approved gene therapies have also seen issues achieving meaningful uptake. Concerns across treatment and manufacturing logistics, pricing and market access, and reaching a meaningful number of patients have led multiple therapies to withdraw from the market, despite receiving approval. Many of these concerns have yet to be fully addressed due to the nascent stage of commercialized gene therapies and restriction to relatively few indications to date.

Commercial barriers facing gene therapies are directly related to operating in a structure developed for chronically dosed therapies and can be condensed into 4 areas:

- **Pricing**: What is a reasonable price to charge for a therapeutic that potentially lasts a lifetime/cannot be re-dosed?
    - How do you balance long-term or lifetime efficacy with near-term affordability?

- **Reimbursement**: What alternative payment models exist to help avoid the financial risk of one-time therapies?
- **Commercial Lifespan**: How long will it take to achieve peak penetration into the addressable patient population? How does this compare to traditional, chronically dosed therapies?
- **Competition**: With multiple companies aiming for approval in the same indications due to technical feasibility, can the number of prevalent patients with a disease support the number of potential gene therapy products that will eventually be in the marketplace?
    - Once prevalent patients have received a gene therapy, are there enough incident patients to support multiple products? Are there enough to support one product?

Some of the first gene therapy developers, highlighted below, have struggled to tackle these questions:

uniQure's Glybera (alipogene tiparvovec, AAV1), indicated for the treatment of lipoprotein lipase deficiency (LPLD), was pulled from the market in 2017 after treating only 1 patient[9, 10, 11]

- Glybera's price of >$1M was highly scrutinized despite significant clinical benefit, though >$1M price tags are often expected for gene therapies in 2021

Orchard Therapeutics' Strimvelis (γ-retrovirus, acquired from GlaxoSmithKline in 2018), indicated for the rare disease adenosine deaminase-severe combined immunodeficiency (ADA-SCID), is under EMA investigation after being linked to a case of leukemia[12]

- Strimvelis has been used to treat 16 patients since approval in 2016 at a price of ~$650,000, generating ~$10M in total sales

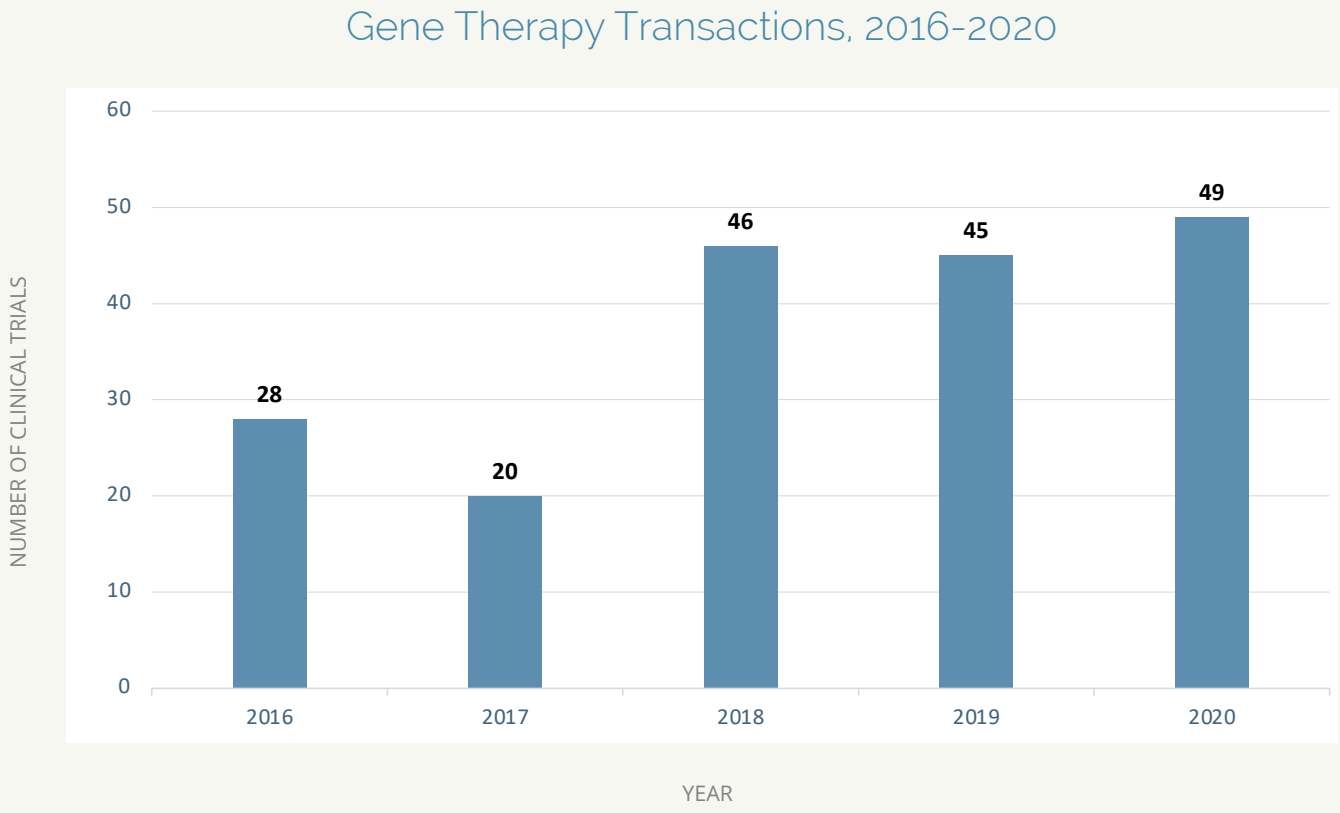
Spark Therapeutics' (now a member of the Roche Group) Luxturna (voretigene neparvovec-rzyl, AAV2) is indicated for patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy; Spark has focused initial commercialization efforts on patient identification

- Luxturna has generated ~$100M in total sales to date at a price of $425,000 per eye and is commercialized by Novartis in the EU
- WW sales are expected to peak at less than $200M, as Luxturna is a niche product

THE PRESENT
The Big Barrier: Delivery

Large consolidator interest in gene therapy soared after the FDA approval of Luxturna in December 2017 despite clinical and commercial challenges facing developers (Figure 3). With this interest and growing evidence of delivery as the Achilles heel of gene therapy, research and funding into the development of improved gene delivery vehicles has also skyrocketed. To date, most gene therapies utilize virus to deliver the gene of interest. Historically, companies have used Adeno-associated viral (AAV) and lentiviral vectors. However, each viral platform comes with drawbacks such as lack of durable gene expression (AAVs), risk of genomic integration leading to oncogenesis (lentivirus), and limited tissue tropism (an issue with both viruses). We have evaluated the advantages and disadvantages of different viral (e.g.,, AAV, lentivirus) and non-viral vectors (e.g.,, lipid nanoparticles, exosomes), including recent innovations improving tissue targeting (e.g., novel AAV serotypes) and reducing oncogenicity (e.g., self-inactivating lentiviral vectors).

Figure 3:
Gene Therapy Transactions by Year



Sources: Back Bay analysis, Cortellis

Figure 4:
Viral and Non-viral Vectors

VIRAL VECTORS	NON-VIRAL VECTORS
• Adeno-associated virus (AAV) • Lentivirus • Sendai virus • Adenovirus • Bocavirus	• Lipid nanoparticles • Polymer nanoparticles • Exosomes • Peptide-based complexes • iTOP • Feldan shuttle

Sources: Back Bay analysis

Viral and Non-Viral Vectors: The Backbone of Gene Therapies

Gene therapy vectors, or delivery vehicles, fit within two broad categories, viral and non-viral, with viral vectors being the most used due to their ability to naturally infect cells (Figure 4). Among these, lentiviruses and AAVs lead the pack, but both have their own unique trade-offs (Figure 5).

Perhaps the most important difference between lentiviruses and AAVs is genome integration. While lentiviruses integrate their payload into the host chromosome, genes delivered by AAVs become an episome, or circular piece of DNA that resides inside the nucleus. Although genomic integration prevents the dilution of genetic material over time due to cell division, it poses a risk of oncogenesis. Therefore, the gene therapy field has identified optimal use cases for both lentiviruses and AAVs.

Lentiviruses are used for *ex vivo* gene-modified cell therapies (including CAR-T), in which the gene of interest is delivered to stem cells collected from the patient outside the body. After target gene integration, the cells are amplified and returned to the patient, usually in an autologous stem cell transplant. In this setting, genome integration is advantageous and not an outsized safety risk since the location where the target gene has integrated can be analyzed in the modified cells, thus removing the risk of introducing a cancerous cell back

Figure 5:
AAV versus Lentivirus

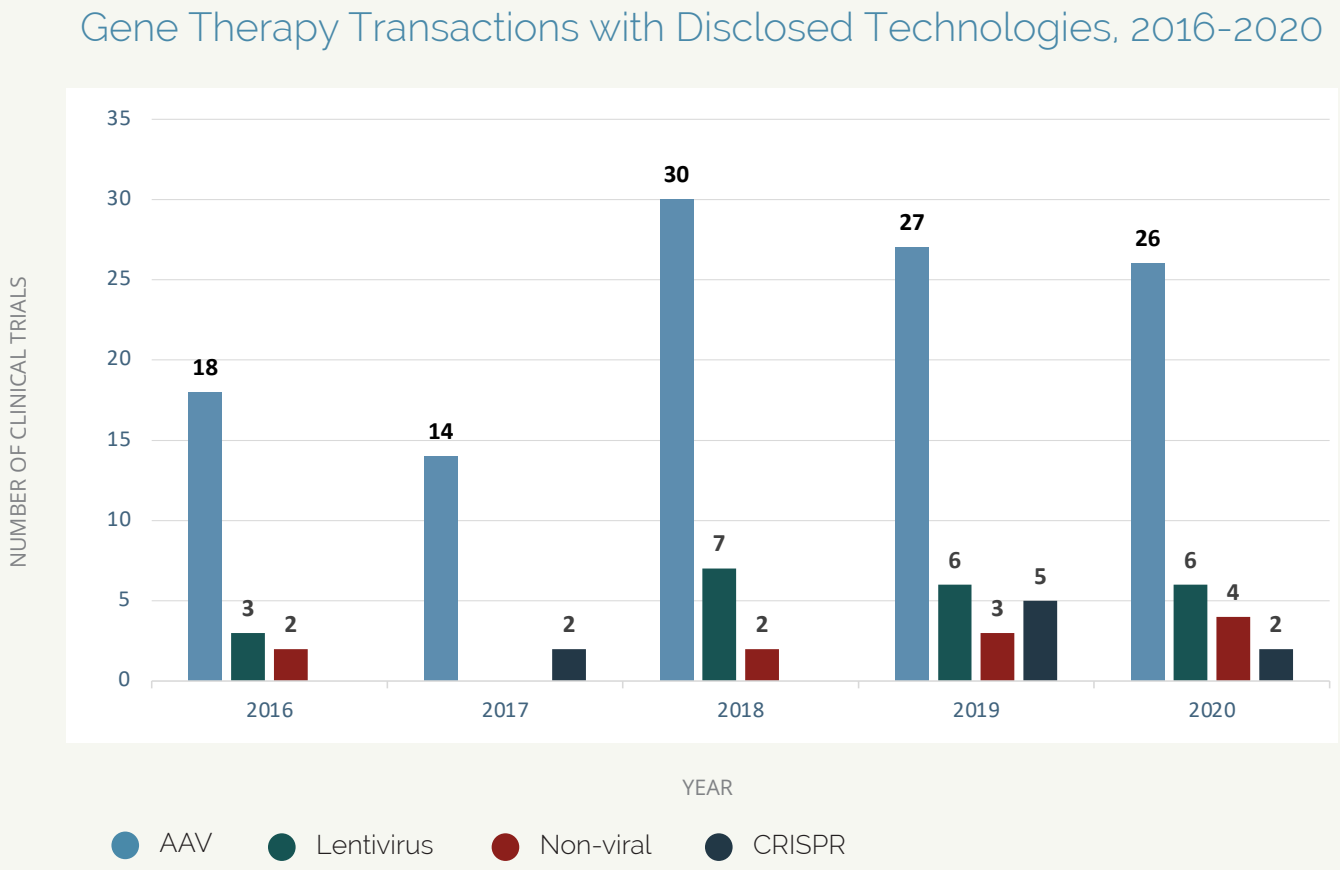
TRAIT	AAV	LENTIVIRUS
Enveloped	No – tropism determined by capsid	Yes – tropism determined by enveloped
Pathogenic	No – stripped of viral genes	Yes – stripped of viral genes
Integrate into the host genome	No – resides in host as episome	Yes – integrates in host chromosome
Genome size	4.8kB	9kB
Use Case	Preferred for in vivo use	Preferred for ex vivo use
Representative Leading Platform Companies	REGENXBIO, uniQure, Roche, Spark, Novartis, avexis, askbio, Pfizer, TAYSHA GENE THERAPIES, SAREPTA THERAPEUTICS, Takeda	OxfordBioMedica, AVROBIO, bluebirdbio, Orchard therapeutics

Sources: Back Bay analysis

into the patient. Lentiglobin™, Bluebird bio's gene-modified cell therapy for β-thalassemia and sickle cell disease, is one of several *ex vivo* gene-modified cell therapies in development. While largely safe and efficacious to date, the use of *ex vivo* gene-modified cell therapies is limited by manufacturing (e.g., demonstrating product consistency) and administration (e.g., requirement of lymphodepletion) challenges that have repeatedly delayed Lentiglobin™ commercialization in the US.[13] Further, the theoretical risk of oncogenesis has repeatedly slowed developers such as Bluebird.[14]

In contrast, AAVs are used for *in vivo* or systemic treatment, where the virus is directly administered to the patient via IV or injection to the tissue of interest. Since *in vivo* treatment is less complex than *ex vivo* cell manipulation and theoretically safer than autologous stem cell transplant, research, development, and investment in gene therapy has recently focused on AAVs (Figure 6). Both recently FDA approved gene therapies, Luxturna and Zolgensma, utilize AAV vectors. Similarly, Glybera, the first approved gene therapy (by the EMA in 2012), utilized an AAV vector.

Figure 6:
Gene Therapy Transactions by Year



Sources: Back Bay analysis, Cortellis, company websites and press releases

Innovations in AAV Delivery: Early Science

Despite product approvals, AAVs still have major limitations, namely immunogenicity (e.g., an immune response to the AAV vector) and tissue targeting. Both immunogenicity and tissue targeting are AAV subtype, or serotype, dependent. Each AAV serotype has immunogenicity and tissue tropism determined by its protein shell, or capsid, which is made of unique repeating protein subunits, known as variable regions. The variable regions within AAV capsids differentiate the hundreds of described AAV serotypes and alter properties that influence immunogenicity and tissue tropism.[15] Of particular importance is the cell surface glycan that acts as an AAV receptor, which strongly influences tissue tropism and is determined by the AAV variable regions.

AAV immunogenicity can be triggered by either pre-existing antibodies to AAVs or an immune reaction to the administration of initial AAV gene therapy doses. This immunogenicity directly limits the addressable patient population for AAV gene therapies, as approximately 50-90% of the population (depending on the serotype) maintains anti-AAV antibodies. Therefore, a substantial portion of any patient population may not be ideal candidates for AAV-based gene therapies. In the context of a patient with some level of pre-existing immunity or who has already received one AAV gene therapy treatment, AAV gene therapies may be ineffective.

However, immunogenicity is perhaps less important than the issue of constructing an AAV-based gene therapy that will deliver the target gene to the organ system of interest. Since specific AAV serotypes are only able to infect certain tissues, the ability to target specific organs and cells is limited. For example, there are few AAVs that can effectively infect muscle cells. AAV serotypes used in Zolgensma (AAV9) and Luxturna (AAV2) can target neurons and retinal cells following *in vivo* administration. These tissues are generally thought to be easily targeted due to limited immune surveillance and the ability for direct tissue (e.g., retinal or intrathecal) injections.

Figure 7:
Described AAV Vectors and Patents

GENERATION	FIRST						SECOND		
Vector	AAV1	AAV2	AAV3B	AAV4	AAV5	AAV6	AAV7	AAV8	AAV9
Primary IP Ownership	Patent Expired	Patent Expired	Patent Expired	Patent Expired	Patent Expired (from UniQure in 2019)	Patent Expired	REGENXBIO		
Primary Receptor	N-linked sialic acid	HSPG	HSPG	O-linked sialic acid	N-linked sialic acid	N-linked sialic acid	Unknown	Unknown	N-linked galactose
Patent Expiration Date							US: 2026 EU: 2022	US: 2022 EU: 2022	US: 2026 EU: 2024
Tropism	Muscle, CNS	Muscle, Liver, Kidney, Eye, Lung, CNS	Liver, CNS	Eye, Heart	Liver, Eye, Lung	Muscle	Muscle	Muscle, Liver, Heart, Eye	Muscle, CNS
Representative Companies Utilizing		Biogen, Roche, Spark, MEIRAGTx			uniQure			Takeda, AUDENTES, Biogen, ultragenyx	Abeona, NOVARTIS, rocket, avexis, Lilly, Prevail

Sources: Back Bay analysis

Ultimately, with only a few more than ten human and non-human AAV serotypes well described to date and many more uncharacterized in nature, novel AAV capsid generation has become a key part of gene therapy preclinical development. Scientific proof-of-concept for modulating immunogenicity and tissue tropism has been described in academia and industry with changes to both capsid amino acids and post-translational modifications demonstrated to impact AAV profiles.[16, 17] For example, uniQure developed the vector AAV5, which is thought to be less sensitive to antibody neutralization than other AAV vectors.[18] The process of generating new AAV capsids, called epitope mapping, scans and tests the diversity of peptides that may be incorporated into a capsid. In addition to addressing immunogenicity and tropism issues, epitope mapping helps generate novel IP, as AAVs designed via epitope mapping are not naturally occurring. With IP protection having expired or approaching expiration for early AAV vectors, novel AAV capsids provide strategically important IP protection and differentiation for early-stage gene therapy companies (Figure 7).

Players Big and Small

To develop optimal gene therapy products, both public and private gene therapy players are developing next-generation vector technologies in 4 key categories: AAV Capsid, AAV immunogenicity, Lentiviral vectors, and Non-viral vectors (Figure 8).

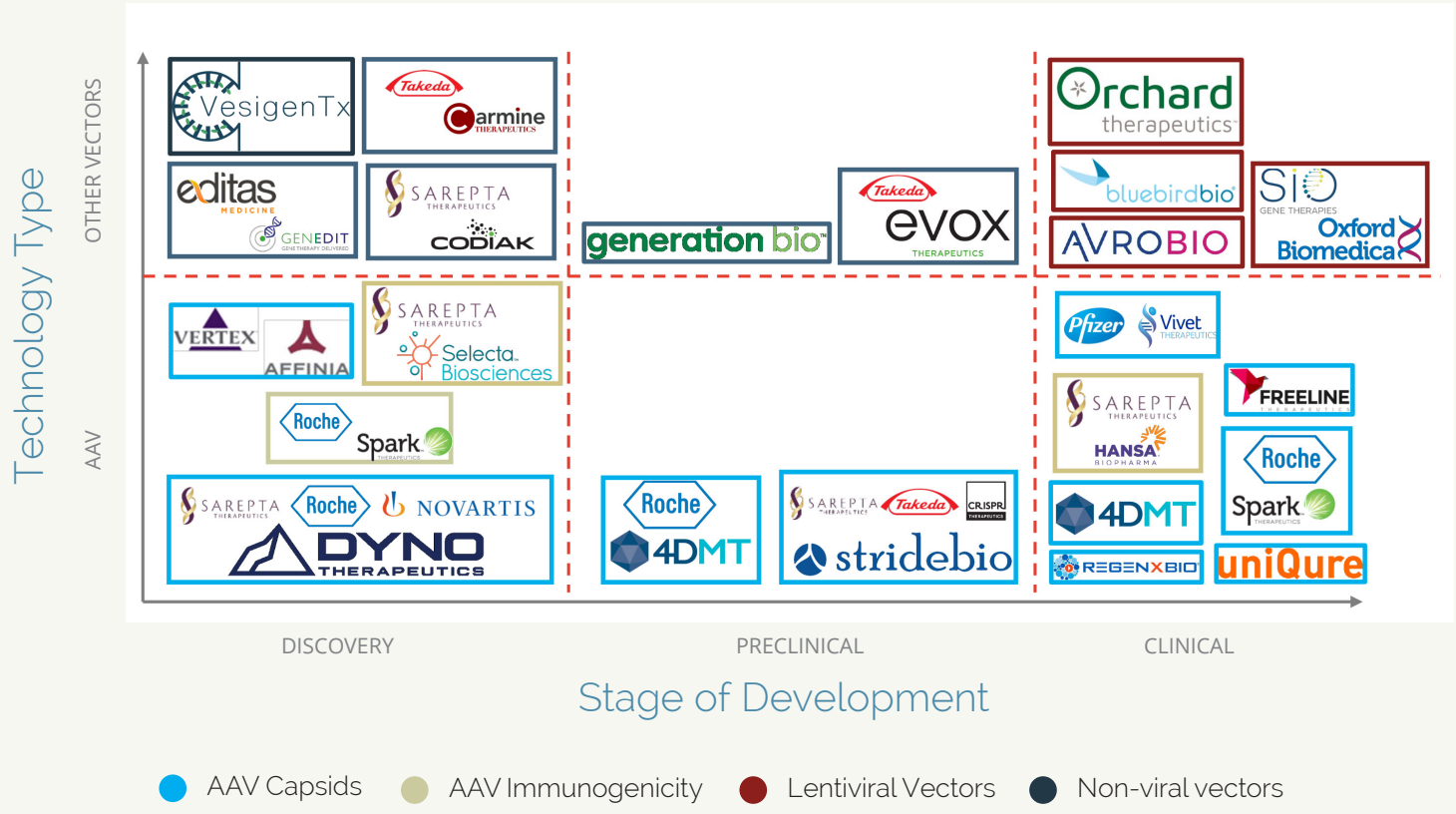
AAV TECHNOLOGIES

First and second-generation AAV Capsids developed by companies including **uniQure**, **Freeline**, **Vivet Therapeutics**, **Spark Therapeutics**, and **REGENXBIO** have already shown initial promise by moving toward commercialization. For example, AAV9 was developed by REGENXBIO's NAV Technology and has been out licensed >5 times since 2015 (including for Zolgensma), ultimately becoming the most widely used Capsid across the gene therapy landscape due to its ability to transduce neurons.

Therefore, business development focus has shifted towards third generation AAV Capsid approaches. **Dyno Therapeutics (**CapsidMap™ platform**)**, **4DMT (**Therapeutic Vector Evolution platform**)**, and **StrideBio (**structure inspired AAV vector engineering; STRIVE™ platform**)** have all entered collaborations for targets associated with their next-generation AAV Capsid platforms. Partners seeking these next-generation AAV Capsid technologies include **Sarepta**, **Roche/Spark**, **Novartis/Avexis**, **Takeda**, and **CRISPR Therapeutics.** In the same space, **Vertex** established a multi-year collaboration with **Affinia** for novel AAV Capsids ~1 month after their $60M raise in March 2020.[19]

Despite the preponderance of AAV Capsid technologies aiming to improve AAV delivery and immunogenicity, few companies have developed technologies/ therapies that modulate the immune response to AAV vectors. While improved AAV Capsids directly enhance gene therapy safety and efficacy, immunology-

Figure 8:
Selected Vector Technology Players by Stage and Technology Type



Sources: Back Bay analysis, company websites and press releases

based technologies improve gene therapy safety and efficacy by altering the body's immune response to gene therapy administration. **Selecta Biosciences** and **Hansa Biopharma** have both signed deals with **Sarepta** for these immunology targeted agents.[20, 21] Selecta's ImmTOR Immune Tolerance Platform may permit redosing with AAV therapeutics, while Hansa's Imlifidase may remove pre-existing neutralizing antibodies to AAV. A similar solution to Imlifidase comes from **Spark Therapeutics**, who recently published research showing immunoglobulin G-degrading enzyme of *Streptococcus pyogenes* transiently cleaves neutralizing antibodies to AAV in the bloodstream.[22]

OTHER VECTORS

Non-viral vector technologies are rapidly evolving and have attracted significant public and private investments over the last year, including for exosomes, vesicles, and polymer nanoparticles (Figure 9). Further, many non-viral platforms have been recently out licensed including large partnerships with **Takeda**, **Sarepta**, and **Editas.** [23, 24, 25, 26]

Figure 9:
Non-Viral Platforms and Financings

COMPANY	DATE	MOST RECENT FINANCING TYPE	TOTAL RAISED ($M)	VALUATION ($M)	PLATFORM
evox THERAPEUTICS	February, 2021	Series C	$95	Not disclosed	DeliverEX™ exosome platform
CODIAK	October 2020, February 2021	IPO and Secondary IPO	$141	$360	engEx™ exosome platform; initial focus on oncology
generation bio	June 2020, January 2021	IPO and Secondary IPO	$396	$1,900	Close-ended DNA construct platform
GENEDIT GENE THERAPY DELIVERED	November 2020	Series A	$26	$56	NanoGalaxy™ polymer nanoparticle platform
VesigenTx	July 2020	Series A	$29	$44	ARrestin-domain 1 Mediated Microvesicle platform
Carmine THERAPEUTICS	June 2020	Partnership with Takeda	$6	Not disclosed	Red Cell Extracellular Vesicle Gene Therapy, REGENT® platform

Sources: Back Bay analysis, company websites and press releases, Pitchbook

In contrast, the development of Lentiviral vector technologies has largely consolidated into 4 major companies valued at >$4B by the public markets, including platform-focused companies **Oxford Biomedica** and **Bluebird bio** and product-focused companies **Orchard Therapeutics** and **Avrobio**. While Oxford Biomedica has developed its platform largely in-house and out-licensed a variety of products, Bluebird bio has brought in enabling Lentiviral technologies from institutions such as Généthon and executed multiple product-focused collaborations to grow. Unlike product-focused AAV collaborations, where most technologies are being licensed from companies, Lentiviral products are often developed in academia before being out-licensed. A recent collaboration between Avrobio and the University of Manchester serves as an example of this approach alongside early agreements between Orchard Therapeutics and the Universities of Manchester and SR-Tiget.[27]

Questions (and Answers) for the Future

As the gene therapy field has tackled looming delivery questions, clinical and commercial setbacks have lowered expectations for gene therapy sales, leading sell-side forecasts to fall more than 50% since 2018.[28] However, more than $6.5B in 2026 projected gene therapy sales remain across DMD, Hemophilia A/B, Sickle Cell Disease, Fabry Disease, Huntington's Disease, and LCA10 alone, putting pressure on industry leading gene therapy companies to deliver.[29] We highlight six key questions and recommendations for the future of gene therapy.

1. WHAT TECHNOLOGIES SHOULD GENE THERAPY COMPANIES EVALUATE BEYOND DELIVERY VEHICLES?

Despite significant investment in AAV vector technologies, very few companies have looked beyond modulating the ability of AAV capsids to reach (or be re-dosed to) target organs/cells. An area for future consideration is within the AAV lifecycle. Enhancing the AAV lifecycle may enable improved efficacy by increasing the number of nuclei infected with AAV encoding the transgene, ultimately increasing sustained gene expression.[30] Further, novel gene sequences, such as those created by **Codexis'** protein engineering platform (partnered with **Takeda** in Fabry Disease), may enhance efficacy by leading to increased transgene activity. Another approach to increasing transgene activity is highlighted in a 2021 deal between **Spark/Roche** and **Senti Bio** for synthetic promoters.[31] Both increasing transgene activity and enhancing the AAV lifecycle may help lower the AAV doses required for therapeutic benefit, improving safety by preventing potential adverse reactions to large amounts of AAV.

Several additional companies have developed AAV and lentiviral platforms aiming to improve upon the gene therapy business model beyond simply an improvement in delivery. **AskBio** and **Taysha Gene Therapies** have platforms across the three components of an AAV therapeutic: novel vector development, improved gene expression, and optimized manufacturing (Figure 10, 11). Lentiviral companies such as **VIVEbiotech** and **Vectalys** have changed the lentiviral lifecycle by developing non-integrating lentiviral vectors to reduce the risk of oncogenesis. **Sana Biotechnology, Interius BioTherapeutics,** and **Umoja Biopharma** have developed *in vivo* lentiviral vectors that remove the need for transplant and the associated white blood cell depleting chemotherapy currently required for the delivery of lentiviral gene therapies, while **Ensoma** is developing Engenious™ adenoviral vectors for the same purpose. Interius, Ensoma, and Umoja have raised ~$200M across their 2021 Series A fundraising rounds.

Interest in gene editing technologies such as CRISPR has spurred the need to search for larger and more flexible viral and non-viral vector technologies. With a recent Nobel Prize for CRISPR and early applications advancing towards commercialization, the interest in novel packaging technologies that can deliver all the components of CRISPR is increasing. **GenEdit** and **ProBioGen** have struck

Figure 10:
AskBio

Company Overview

AskBio

- **Inception**: Research Triangle, NC; founded 2001
- **Founders**: Dr. R. Jude Samulski, the first to clone AAV, Sheila Mikhail and Xiao Xiao, PhD
- **Background**: Company dedicated to advancing AAV technologies for rare genetic disease
- **Fundraising**: Private; Raised $235M in April 2019 from Vida Ventures and TPG Capital prior to a Bayer acquisition for up to $4B

Pipeline

Indication (TA)	Phase	Partner?
Pompe (NMD)	1/2	
Parkinson's (CNS)		
Congestive heart failure (cardiac)		
Methylmalonic acidemia (metabolic)	Pre-IND	Selecta Biosciences
Multiple system atrophy (CNS)		
LGMD 2i/R9 (NMD)		
Huntington's (CNS)		
Angelman (CNS)		

Platform Overview

AskBio has an integrated gene therapy platform includes a high-yield cell line, an expansive capsid library, and synthetic promoters and DNA

- **Capsids:** Have designed both mosaic (ex. AAV2.5 vector with properties of AAV1 and AAV2) and chimeric (ex. AAV2g9 vector with alterations to the capsid structure of AAV2) AAV vectors to achieve improved therapeutic properties
- **Promoters:** Acquired Synpromics Ltd., the leader in gene control synthetic promoter technology, in August 2019
- **Manufacturing**: Spun out Viralgen, a CDMO that uses Pro10™ technology to ensure high yield AAV produced in a suspension manufacturing process
- **Next-generation technology:** Partnered with Touchlight Genetics to advance Doggybone™ DNA (dbDNA™), closed-linear constructs that eliminate bacterial sequences and improve expression characteristics

Partner	Platform Technology	Date	Overview
Pfizer	Pro10™ cell line	August 1st, 2016	**Enables high yield suspension AAV manufacturing in collaboration with AskBio spinout Viralgen**
Novartis / AveXis	Duplex vectors	June 17th, 2015	**Enables faster onset and higher level of therapeutic expression for Zolgensma**
Takeda	Biological Nano Particle AAV	April 2nd, 2014	**Enables more targeted delivery of the FIX therapeutic "cargo" into the natural site of FIX synthesis**

Sources: Back Bay analysis, company websites and press releases

Figure 11:
Taysha Gene Therapies

Company Overview

TAYSHA GENE THERAPIES

- **Inception**: Dallas, TX; founded 2020
- **Founders**: Former leaders of AveXis
- **Background**: Focused on monogenic CNS diseases in partnership with UT Southwestern experts Steven Gray, Ph.D. and Berge Minassian, M.D.
- **Fundraising**: Public, $940M market cap (April 2021); raised $125M across two rounds prior to a September 2020 IPO

Platform Overview

Taysha has 3 next-generation platforms for AAV redosing, regulated transgene expression, and novel capsids

- **Redosing:** Utilizing delivery through the vagus nerve and other techniques to subvert the immune response
- **Regulated transgene expression**: Have developed a novel miRNA targe panel called miRARE that allows gene therapies to hit the optimal "therapeutic level/window"
- **Novel capsids**: Utilizes machine learning/directed evolution to improve targeted delivery to neurons, astrocytes, or oligodendrocytes

Clinical and Preclinical Pipeline

TA	Modality	Asset	Indication	Phase
Neurodegeneration	Gene replacement	TSHA-120	Giant axonal neuropathy	Phase 1/2
		TSHA-101	GM2 gangliosidosis	
		TSHA-118*	CLN1	
		TSHA-119	GM2 AB Variant	Preclinical
		TSA-104	SURF1-Associated Leigh Syndrome	
	miRNA	TSHA-112	APBD	
		TSHA-111-LAFORIN	Lafora disease	
		TSHA-111-MALIN	Lafora disease	
Neurodevelopment	Regulated gene replacement	TSHA-102	Rett syndrome	
	shRNA	TSHA-106	Angelman	
Genetic Epilepsies	Gene replacement	TSHA-103	SLC6A1	
		TSHA-105	SLC13A5	

***formerly ABO-202**

Sources: Back Bay analysis, company websites and press releases

deals with **CRISPR Therapeutics** and **Editas Medicine**, respectively, to explore novel packaging technologies. If gene editing is to become a reality, packaging and delivery of large vectors with multiple components will be required, which is currently not feasible with existing technologies.

2. WHAT IS THE FUTURE OF RARE MARKETS WITH LAUNCHED GENE THERAPIES?

Under the assumption that patients may not be able to receive multiple gene therapies, we must also consider that there are a finite number of patients to be treated. Given that the risk-benefit profile of gene therapies has for now prioritized rarer, debilitating diseases, the number of prevalent patients in any disease amenable to treatment may only support a single gene therapy manufacturer. This issue is exacerbated if there are multiple ongoing clinical trials that further remove treatable patients from the pool.

If there are a significant number of prevalent patients and multiple gene therapies are available, the eventual depletion of the prevalent patient reservoir will quickly lead to only incident patients supporting the commercial case. For some of the more common genetic diseases such as **DMD** or **Sickle Cell Disease** that may affect several hundred births per year in the US, such a birth incidence may be supportive of more than one gene therapy competitor. However, many diseases have much fewer incident patients (e.g., **MPS IIIA/B**) each year, which limits the long-term viability of a single gene therapy, let alone multiple. Further, epidemiology in these populations is often poorly understood, limiting confidence in the commercial opportunity.

Even in indications where gene therapies have been highly successful (e.g., **Libmeldy** in metachromatic leukodystrophy), clinical data is limited to select patient segments and gene therapy is not fully curative. In the case of **Zolgensma** in SMA, there is clear residual unmet need. **Biogen** treated the first patient in the RESPOND study in January 2021, which is testing **Spinraza** (nusinersen) in patients already treated with Zolgensma. Given Zolgensma's $2.1M price tag and Spinraza's yearly cost of ~$375,000, this approach may be cost prohibitive.

In contrast to the promising efficacy demonstrated by Libmeldy and Zolgensma, gene-targeted therapies in **DMD** and **Huntington's Disease** have shown limited clinical benefit.[32,33] This may be because downstream pathways beyond the underlying genetic mutation are contributing to disease progression that replacing the altered gene will not fix. In these indications, scientists and investors should explore combination approaches, as they will likely be needed to halt or reverse disease progression.

3. IS THERE AN OPPORTUNITY FOR GENE THERAPIES IN NON-ORPHAN MARKETS?

Due to the limited whitespace in rare indications, gene therapy companies are beginning to explore non-orphan market opportunities. **Parkinson's Disease** is one indication being explored by multiple companies. Parkinson's affects

almost 1 million US patients and results in progressive neurodegeneration (primarily from the loss of dopaminergic neurons in the substantia nigra) that shortens life expectancy by 5-10 years. Notably, most gene therapy programs are aiming to restore lost motor function by replacing neurotransmitters with genetic material or promoting cell survival, rather than replacing an altered gene. Examples of clinical-stage programs include **Oxford BioMedica's/Sio Gene Therapies'** AXO-Lenti-PD, **AskBio's/Brain Neuropathy Bio's** AAV2-GDNF, **Voyager Therapeutic's** VY-AADC, and **MeiraGtx's** AAV-GAD. In contrast, **Prevail Therapeutics** (recently acquired by Eli Lilly for ~$900M) has a clinical-stage program aiming to replace the *GBA1* gene, which is altered in ~5-10% of Parkinson's patients.

Other non-orphan indications that have attracted gene therapy interest include **Crohn's disease** and **Multiple sclerosis. Orchard Therapeutics** is developing an *ex vivo* lentiviral gene therapy for NOD2-altered Crohn's, which affects up to 200,000 patients in the US and EU. Similarly, **Sarepta** has partnered with the University of Florida for a gene therapy in multiple sclerosis, which affects 2 million US patients. In these indications, differentiation from the standard of care will be critical due to existing therapies available at prices much lower than gene therapies. Without clinically significant efficacy demonstrated in large trials or savings for the healthcare system, achieving market access will be challenging for expensively priced gene therapies in non-orphan indications.

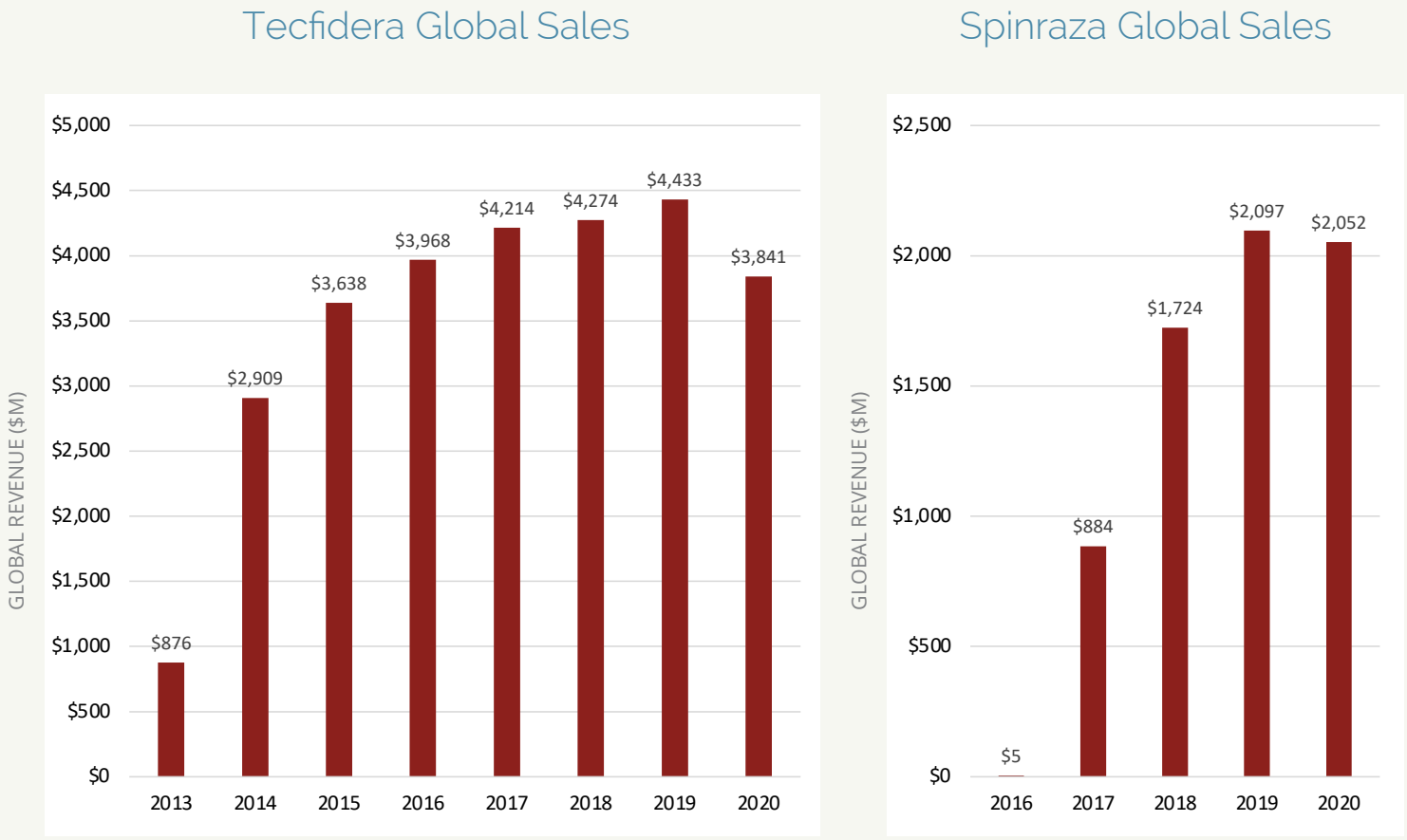
4. HOW SHOULD A GENE THERAPY BE PRICED?

Zolgensma's price in the US has been set at $2.1M, commensurate to the level of benefit Novartis believes it provides to patients and the healthcare system. In fact, during its market research prior to product launch, Novartis was considering prices upwards of $4-5M per patient, and likely tested prices above that range to understand price sensitivity across US payers. While landing on a price of $2.1M per patient, in line with the top end of what ICER considers reasonable based on its impact to life-years gained, that figure still represents a significant upfront payment for health plans.[34]

To help reduce the cost burden to payers, several different payment models have been considered, most notably **outcomes-based contracts** and **mortgage-based models**. Outcomes-based contracts would involve giving rebates to payers if patients do not meet certain pre-defined long-term efficacy metrics,[35] whereas mortgage-based models would spread smaller, fixed payments to the manufacturer over an extended period. Both models also allow payers to avoid a scenario in which they pay fully upfront and then the patient transfers to another plan with the initial plan footing the entire bill.

Novartis currently offers forms of both payment models for Zolgensma, though it is unclear what the specific clinical criteria are for the outcomes-based contract.[36] According to UBS Equity Research, to this point, payers largely have not used either of these payment models and have instead opted to pay the full cost upfront. This is likely reflective of the resources and effort required to implement these payment models and track what amounts to a small number of patients under a specific plan.[36]

Figure 12:
Highly Successful Chronic Therapies



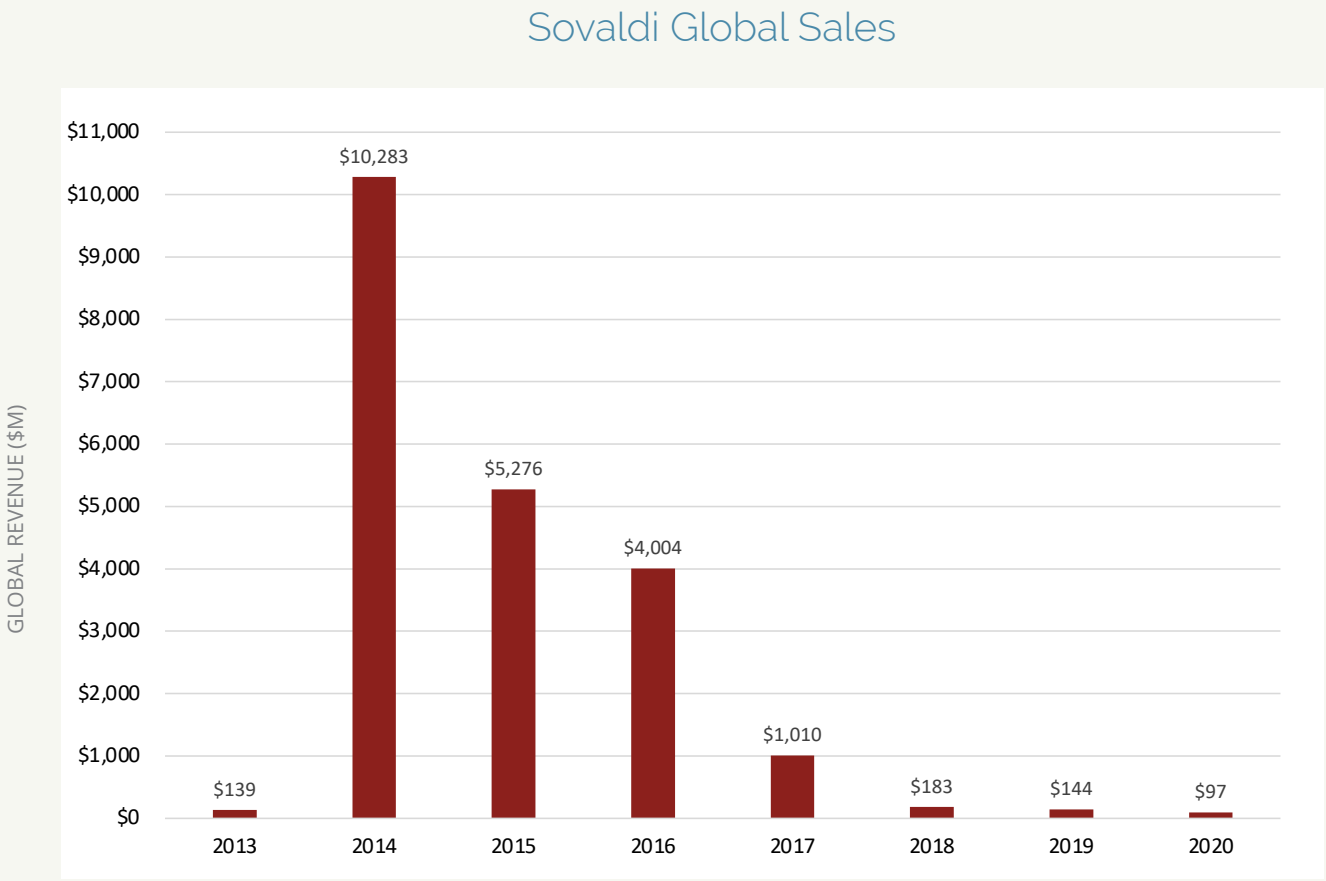
Sources: Back Bay analysis, Evaluate

5. WHAT IS THE EXPECTED COMMERCIAL LIFESPAN FOR GENE THERAPIES?

Given the potentially single dose required to achieve long-term efficacy, a normal pharma sales curve is not expected. Notably, for highly anticipated products that have paradigm-shifting therapeutic potential, time to exceptionally high sales, even if not peak, can be extremely fast. In these cases, we see a "warehousing" effect wherein physicians and patients hold off on treatment in anticipation of a curative or highly effective therapy. The impact on uptake is significant.

Tecfidera (dimethyl fumarate) and **Spinraza** are representative chronic, lifetime therapies that had rapid adoption close to time of launch due to such a warehouse effect (Figure 12). Both became blockbusters within 2 years of launch and are widely considered to be transformative therapies in their respective indications. While the commercial life for Spinraza still has years to play out, the

Figure 13:
Sovaldi Sales

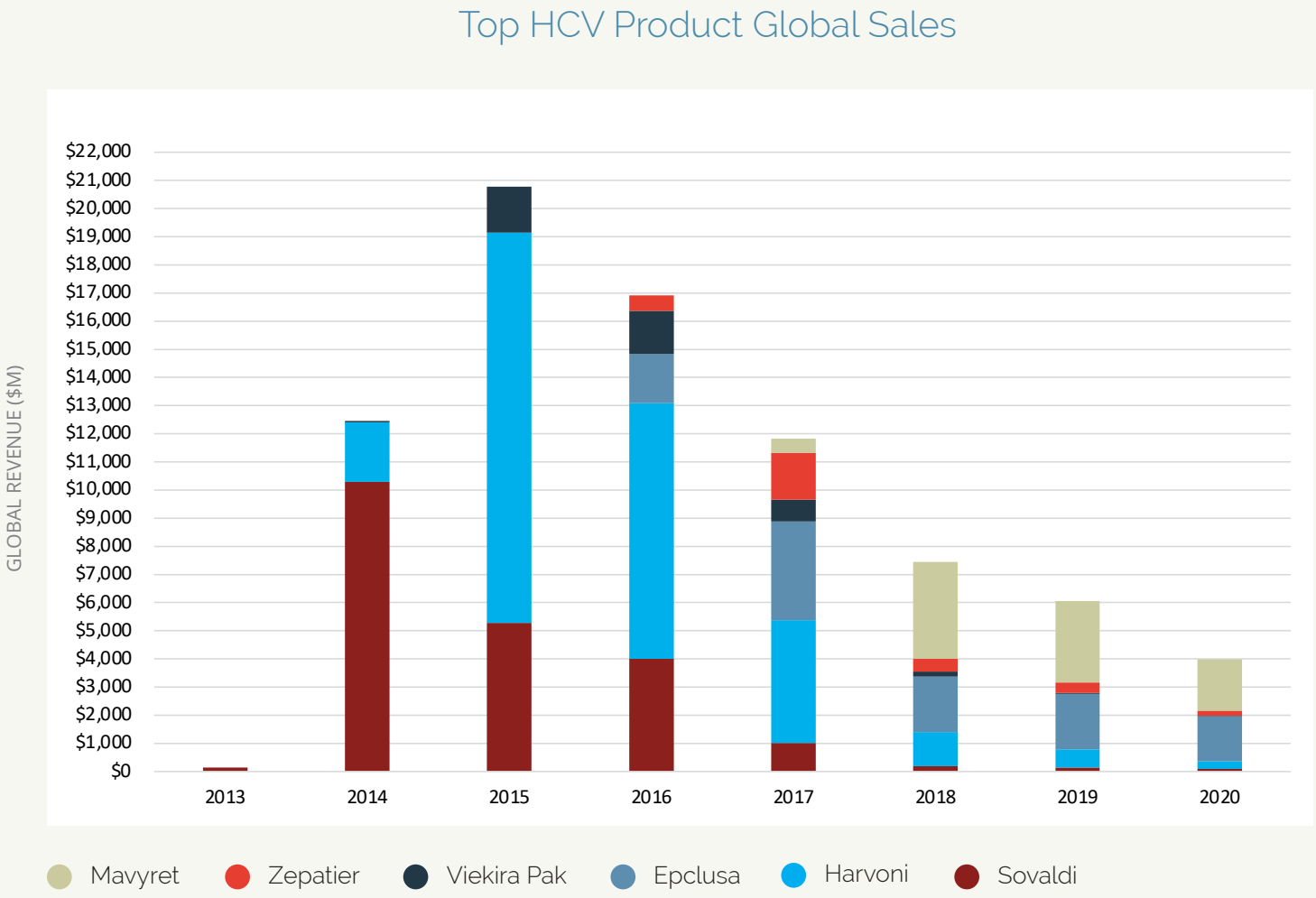


Sources: Back Bay analysis, Cortellis

story of Tecfidera has shown that such therapies can maintain high levels of sales for many years before loss of exclusivity and sales erosion are seen.

However, for products with curative potential such as **Sovaldi (sofosbuvir)** and gene therapies, the entire product lifecycle is condensed into a handful of years. Raising controversy with a cost per course of therapy at $84,000, Sovaldi (Gilead) cured many patients of Hepatitis C virus (HCV) and was rapidly adopted (Figure 13). In its first full year after launch, it captured over $10B in sales, with sales dropping precipitously within several years after the initial bolus of patients was cured. Despite several other factors at play, including additional competitors in the HCV space, follow-on fixed-dose combinations from Gilead, and aggressive contracting strategies, this rapid uptake followed by subsequent rapid decline is illustrative of the shortened commercial lifespan of one-dose, curative therapies. The entire HCV market peaked within 2-3 years of launch and has substantially contracted in the years since (Figure 14). Ultimately, this limits the valuation of

Figure 14:
HCV Market Sales



Sources: Back Bay analysis, Evaluate

gene therapy programs in indications without large incident or prevalent patient populations, as rapid time to and at peak potentially leads to lower valuations than expected with chronically dosed products.

6. HOW DOES THE COMMERCIAL LIFESPAN OF GENE THERAPIES IMPACT A PRODUCT PORTFOLIO?

While there are several smaller, pure play gene therapy biotechnology companies, larger companies with both existing marketed products and substantial gene therapy pipelines face a unique set of challenges. Namely, when maintaining a portfolio, the traditional drug development model of chronically dosed non-gene therapies with 7-10 years of meaningful sales potential turns

into one in which one is likely to capture gene therapy sales within a 2–5-year time window, followed by a period of lower, maintenance sales from the incident population.

Well sequenced gene therapy programs are needed to maintain relatively stable revenues across an entire portfolio and avoid cannibalization of chronic therapies. Further, resources must be allocated to consider if chronic therapies become obsolete once gene therapies launch or if they are likely to be used in combination. It is likely that chronic and gene therapies will coexist in indications and investments will need to be made in both to fully "win" any given indication. However, messaging this approach while still pitching the "curative" potential of gene therapy to both stakeholders and investors requires careful planning.

Conclusion

With new gene therapy delivery technologies and payment models approaching proof-of-concept following large investments, there are significant implications for the viability of the gene therapy business model. Key questions remain around the therapeutic benefit and value offered by gene therapies, with a "cure" unlikely to be achieved for most indications due to the challenges of complex biology. Nonetheless, multiple paradigm-shifting blockbuster gene therapies are likely to reach market over the next decade. With a multitude of companies large and small hoping to commercialize these winners, finding whitespace in larger indications and technologies to control transgene expression and the viral lifecycle may be crucial for differentiation. Assuming the science can meet these critical challenges, a series of commercial questions and considerations must equally be met to ensure a viable business. With most of Big Pharma already invested in gene therapy technologies, the clinical and commercial potential of gene therapy is clear. If the value proposition of gene therapies is realized widely across more diseases, these investments will pay off and usher in a new era of genomic medicine, transforming patient care.

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