



"One-and-done" gene therapies

A near-term niche?

We are in a new era of scientific innovation where "one-and-done" gene therapies can potentially cure disease. However, headwinds still exist that will limit their use to rare and ultra-rare monogenic diseases for the next 5-10 years. In this paper, we seek to inform biopharma leaders of these ongoing issues and illustrate what they mean in terms of building a sustainable presence in this innovative field.

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Table of contents

2 Introduction

3 State of the industry

5 Three immediate challenges

8 Pursuing monogenic vs. polygenic diseases

10 Competing in rare monogenic diseases

12 Acquire or partner?

13 Conclusion: Spread your bets and stay the course

14 How KPMG can help

The last decade has brought forth a revolution in the pharmaceutical industry with the launch of the first “one-and-done,” or potentially curative, gene therapies.¹ From the launch of Luxturna for an inherited eye disease, to the entry of Zolgensma for spinal muscular atrophy (SMA), we are now in an era of innovation in which certain diseases can potentially be cured. However, the majority of these gene therapies target rare or ultra-rare² monogenic³ diseases with clear genetic drivers. Only a few, like those designed to treat Huntington’s disease, beta thalassemia and hemophilia, are aimed at larger patient populations that could support a number of curative therapies. Gene therapies can potentially transform clinical outcomes in many diseases including, in the long-term, complex polygenic diseases like hypertension, type 2 diabetes and heart disease. However, for the time being we believe the focus will likely remain on rare and ultra-rare monogenic diseases until the field evolves and the major challenges of therapeutic delivery and manufacturing are addressed.

If this is the hand that biopharma companies have been dealt, how should they play it? What does this mean for short- and long-term business models? Should biopharma companies be spending big now in the hope that, in the long term, these therapies and their associated platforms will drive sustainable top- and bottom-line growth from more complex, larger-population diseases? In short, how can companies gain a competitive advantage in what will likely be a near-term niche while also developing a long-term presence in this innovative field?

In this paper, we look at (1) the current state of the gene therapy market, (2) three major challenges facing today’s players, (3) considerations for pursuing monogenic vs. polygenic disease states, (4) strategies for commercial success in monogenic gene therapy, and (5) guidance on pursuing acquisitions vs. partnerships to gain competitive advantage. Our recommendations are based on analyses of more than 100 clinical trials in the U.S. for single-dose “one-and-done” gene therapies across 50 different diseases and eight distinct therapy areas. Given the focus of the paper is on potentially “curative” therapies and the ability of multiple companies to compete for very small patient populations we have excluded oncology from the analysis. Despite recent advances in *ex vivo* autologous therapies, such as CAR-T, many patients are still not cured, and the population sizes for genetically engineered cell therapies are large enough to support multiple companies. Companies are also using gene therapy technologies, such as gene editing, to treat HIV and other diseases that do not have a genetic cause. However, these were also excluded from the analysis as they do not have a genetic driver.

¹ For the purposes of this article, the term “gene therapy” refers to the *in vivo* and *ex vivo* delivery of certain types of nucleic acid technologies by various types of delivery vector, that are single dose and therefore potentially curative after one treatment. This includes nucleic acid technologies designed to replace a defective gene or supplement working genes (e.g., by delivering a functional copy), down-regulate a toxic gain of function gene (e.g., through delivery of RNA modulation technologies) or edit a defective gene (through delivery of a gene editing technology such as CRISPR/Cas9). For the purposes of the article, oncology and HIV are excluded.

² Rare diseases affect less than 200,000 people in the U.S. and less than 1 in 2000 in the EU; although there is no formal FDA definition of an ultra-rare disease, in Europe a disease is generally considered to be ultra-rare if it affects less than 1 in 50,000 patients.

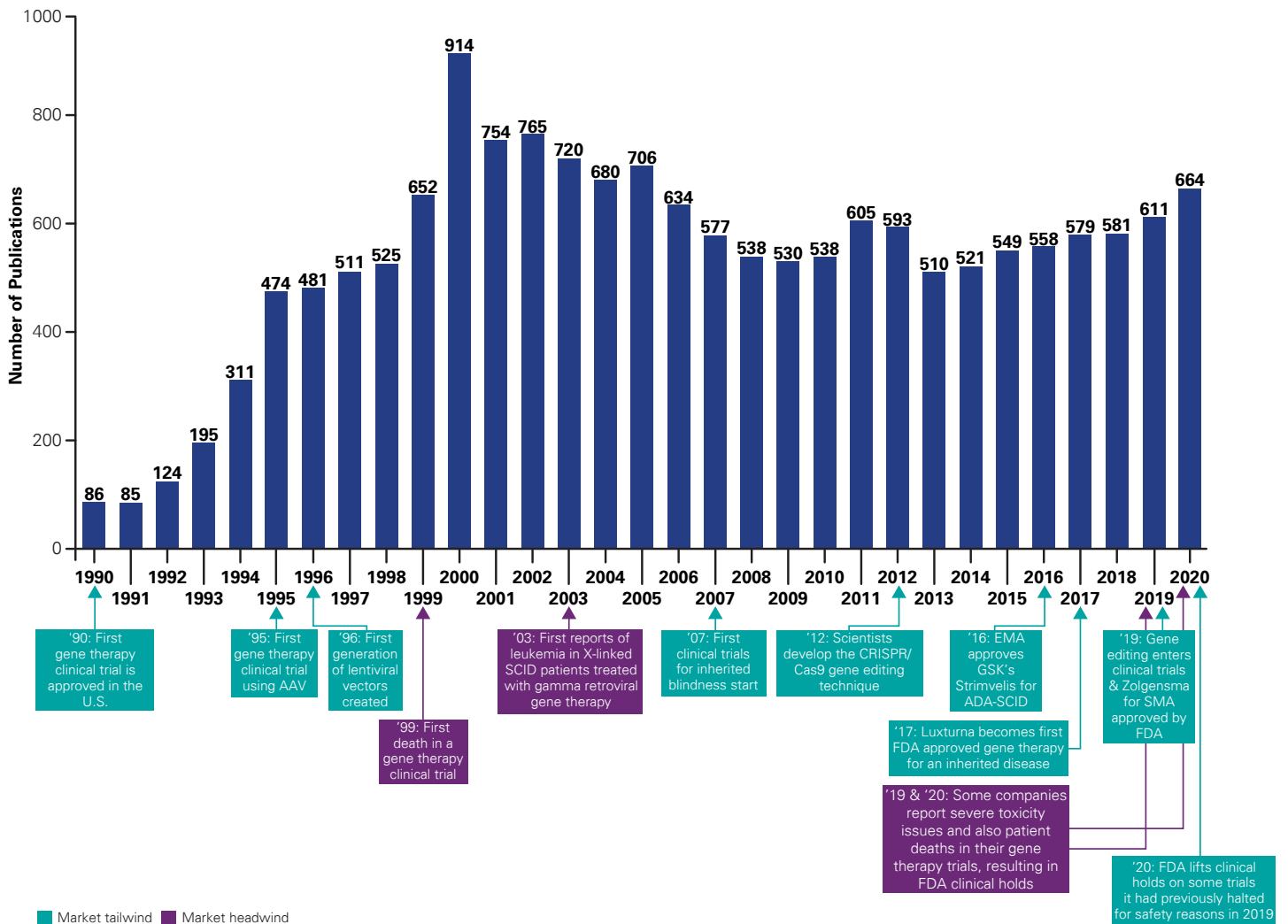
³ Mutations in just one gene are responsible for disease. These diseases run in families and can be dominant or recessive and autosomal or sex-linked. There can be one mutation in the gene or sometimes dozens of different mutations.

State of the industry

The sequencing of the human genome at the beginning of the 21st century gave scientists unparalleled insights into the genetic drivers of disease. This accomplishment – combined with improvements in the design and packaging of genetic payloads, enhancements to delivery vectors and manufacturing processes, and optimization of both *in vivo* and *ex vivo*⁴ approaches – has led to a renaissance in the gene therapy field over the last two

decades. This advancement is all the more remarkable given that it appeared the field had been dealt a fatal blow in the late-90s and early-2000s. During that time period, experimental treatments resulted in the first death in a gene therapy clinical trial, as well as development of leukemia in other investigational studies (Exhibit 1).

Exhibit 1: Publication trends and major milestones in gene therapy, 1990- 2020



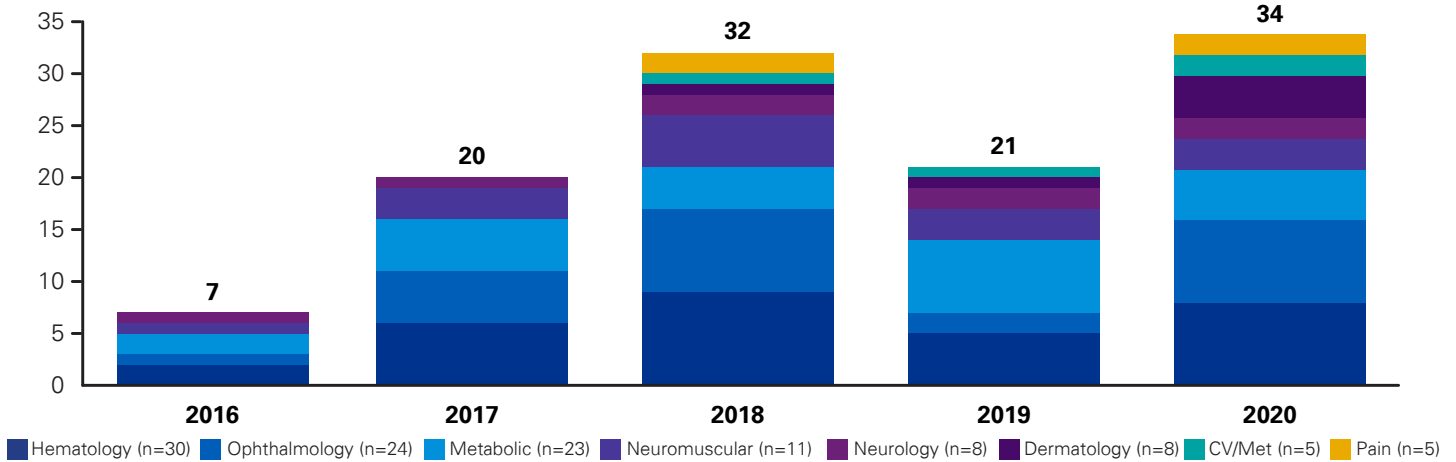
Source: Pubmed search (using the term "gene therapy" in the title of the paper), CureSMA, FDA, genethrapy.net, Human Gene Therapy, *Journal of Clinical Investigation*, *Molecular Therapy*, *pharmaphorum*, *ScienceMag*, *ScienceNews*, *thegenehome*, *Xconomy*

⁴ *In vivo* delivery involves the direct delivery of the vector containing the gene therapy into the human body, while *ex vivo* involves removal of specific cells from the patient and introduction of genetic material in the lab via a vector before re-administration to the patient.

These scientific and technological advances led to an explosion in the number of clinical trials for treatments purported to be curative. Analyses⁵ of U.S. clinical trials for single-dose gene therapies reveal that 114 trials across approximately 50 different diseases and eight distinct therapy areas were initiated between the start of 2016 and the end of 2020 (Exhibit 2). Highlighting the

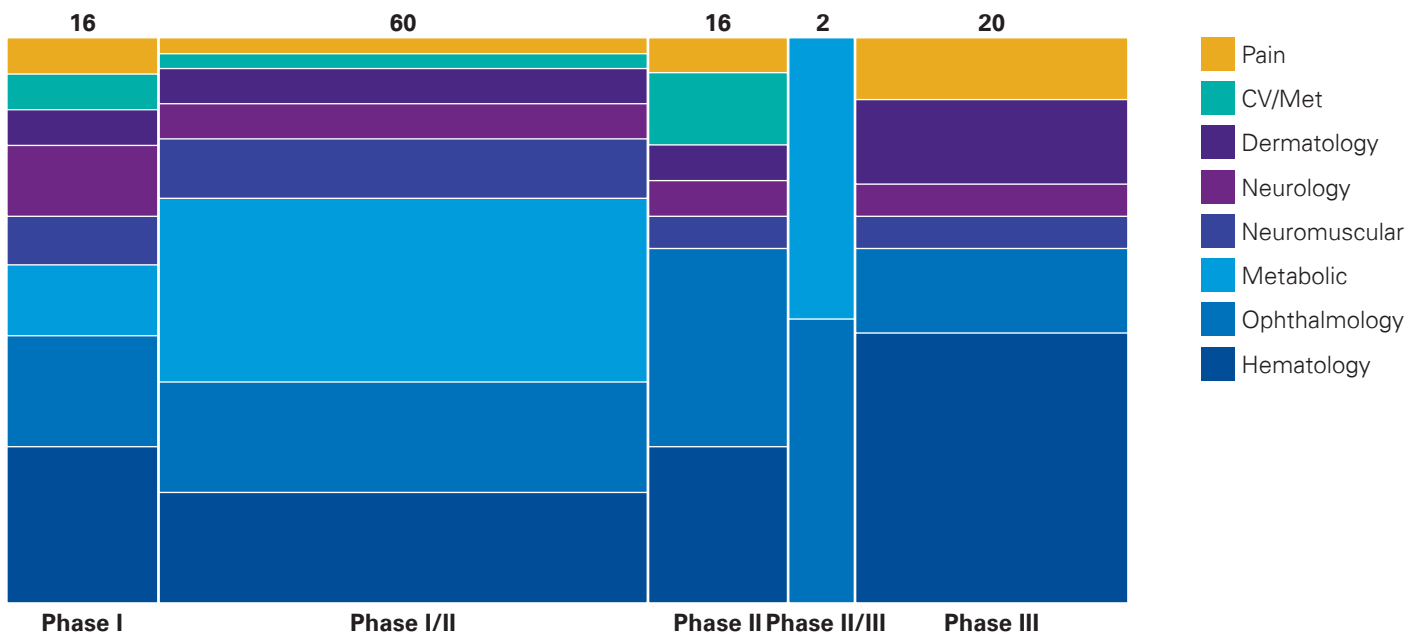
astonishing acceleration in the field in recent years, around 30 percent of these trials were initiated in 2020. Unsurprisingly the field remains in early stages of development, with approximately 65 percent of the 114 trials in Phase I or Phase I / II (Exhibit 3).

Exhibit 2: New trial starts for “one-and-done” gene therapies by therapy area and year, January 2016-December 2020



Source: Clinicaltrials.gov, Informa and KPMG analysis

Exhibit 3: Number of trials by phase and therapy area for current “one-and-done” gene therapy trials initiated from January 2016 through December 2020



Source: Clinicaltrials.gov, Informa and KPMG analysis

⁵ Clinicaltrials.gov search using the term “gene therapy.” Only industry-sponsored interventional Phase I through Phase III open trials, or those that were active but closed for recruiting were included. Only trials with an efficacy endpoint and with at least one site in the U.S. were included. Date range covers trials from January 2016 through the end of December 2020. Oncology and HIV indications were removed and only those trials that stipulated “single dose” in the protocol were included in order to identify those trials using a potentially curative approach. The data was then cross-referenced with various clinical trials databases using the same methodology to ensure completeness.

Three immediate challenges

1. Delivery is still the main obstacle.

Although there has been an increase in the number of clinical trials, pursuing gene therapy is not all smooth sailing. Manufacturers are still finding it difficult to ensure optimal dosing that delivers a therapeutic effect to the target tissue while minimizing toxicity and immunogenicity issues. Although scientists have developed a range of delivery technologies over the years, viral delivery remains the most popular approach, with recombinant adeno-associated virus (rAAV) the “go-to” vector, at least for *in vivo* administration.

This trend is supported by our analysis, which shows that ~70 percent of current clinical trials for “one-and-done” gene

therapies are using rAAV. rAAV is the preferred approach due to its ability to transduce dividing and non-dividing cells, long transgene expression, low immunogenic profile, and broad but distinct tropisms from the various serotypes, as well as the nonpathogenic nature of the wild-type virus (Exhibit 4). In addition, increasing knowledge of capsid structure-function has helped companies engineer proprietary rAAVs that improve both transduction efficiency and tissue specificity while lowering immune recognition. These characteristics are increasingly important as gene therapies move from local (e.g., eye) to systemic (e.g., liver) delivery.

Exhibit 4: Comparison of viral-gene delivery technologies

Virus	Capacity	Integration Into Host Genome?	Duration of Transgene Expression	Adverse Effects	Germline Transmission?
Retrovirus	~9kb	Yes	Long	Insertional mutagenesis	May occur
Lentivirus	~10kb	Yes	Long	Insertional mutagenesis	Yes
Herpes virus	>30kb	Yes	Transient	Inflammatory response	No
Adenovirus	>30kb	No	Transient	Inflammatory response	No
Adenoassociated virus (AAV)	~4.6kb	Rare	Long in post-mitotic cells	Mild inflammatory response	May occur

Source: Goncalves, G. A. R., and Paiva, R. M. A., 2017, Gene therapy: advances, challenges and perspectives, *Einstein (Sao Paulo)*, v. 15(3), p. 369-375.

There have also been efforts by scientists to enhance the rAAV genome, which suffers from slow onset of gene expression and limited cargo capacity. Investments in this area include AskBio’s 2019 acquisition of Synpromics to access its synthetic promoter technology, which claims to “drive gene expression at an uncompromised level of selectivity in any cell type, tissue, environmental, or biological condition.”⁶

In recent years, key research studies have also focused on rAAV packaging limitations, currently ~5kb. For certain diseases, delivery of a full-length therapeutic protein exceeds this packaging size. Therefore, researchers are investigating different strategies to overcome this limitation, including a dual-vector approach

where the transgene is split into two separate vectors. Despite these advances, many diseases require very high doses of systemic rAAV in order to get enough of the functioning gene into the tissue. These high doses can cause toxicity issues and even death in both pre-clinical non-human primate models and, tragically, in recent clinical trials.⁷

To surmount the myriad challenges related to rAAVs, companies are turning to new approaches such as artificial intelligence (AI). For example, Boston-based start-up Dyno Therapeutics has developed a CapsidMap platform that uses AI to optimize its rAAV capsids. The company hopes that these vectors can improve on payload capacity, targeting ability and immune evasion.

⁶ “AskBio Acquires Synpromics Ltd. and Expands its Gene Therapy Technology Portfolio,” AskBio press release, August 13, 2019.

⁷ Mark Terry, Two Patient Deaths Halt Audentes’ Gene Therapy Trial, Biospace, June 29, 2020.

2. Manufacturing and supply chain are major headwinds.

Gene therapy manufacturing remains a highly complex, manual and, therefore, costly exercise, particularly for *ex vivo* approaches. It is also difficult to scale from small clinical trials with just a handful of patients to far larger commercial populations. Serving larger populations is mainly hindered by the increasing demands on raw-input-material suppliers to meet the needs of a growing number of biopharma companies. In some cases, sponsors have had to wait 18-24 months for a manufacturing slot from their CDMO.⁸ There are also issues around the purification of rAAV, large amounts of empty vectors that don't carry the transgene, and inherent batch-to-batch variations, all of which add to manufacturing costs and complexity.

To minimize inconsistency, some companies are taking more control over their supply chains by investing capital in their own manufacturing facilities and bringing capabilities in-house. However, since this strategy is only open to larger biopharma companies with deeper pockets, the smaller biotechs that dominate the cell and gene therapy landscape remain highly dependent on external vendors. The problem is, as long as manufacturing cost of goods sold (COGS) remain high, particularly for *ex vivo* gene therapies, prices will also be high, which could potentially impact commercial uptake.

3. It may not be possible to offer a "cure."

One of the attractions of gene therapy is the idea that a single dose could potentially be curative. The reality is that scientists are still grappling with challenges related to the persistence of gene therapy, raising questions about whether it is really possible to guarantee a "cure." This is especially true in pediatric diseases such as Duchenne's where cellular turnover as children age means there could be loss of efficacy in certain tissues like muscle. Further, some studies suggest that 40-80 percent of the human population is seropositive for antibodies against AAV,⁹ which may reduce the efficacy of therapies. This is a particular concern for systemic gene therapy due to humoral immunity and, although companies have used steroids to deal with this issue in their clinical trials, in many cases the immune response can result in vector clearance and loss of transgene expression.

However, it should be highlighted that other data suggests that levels of neutralizing antibodies in children are low and then increase with age.¹⁰ This has important implications for when gene therapy should be considered as, logically, it would make most sense to intervene in very young children when the risk of complications from neutralizing antibodies is lowest. This then raises the question of whether to expand the newborn screening

Spotlight on non-viral alternatives.

Given the challenges with viral vectors, companies continue to invest in the development of non-viral delivery technologies. Although several years away (only seven of the 114 ongoing "one-and-done" trials we identified are using non-viral delivery methods), non-viral delivery vectors could offer larger packaging capacity, be less cumbersome to manufacture, and possibly allow for re-dosing. Some examples of non-viral development already underway include:

- Vesigen Therapeutics is using its proprietary ARRDC1-mediated microvesicles (ARMMs) to deliver technologies such as gene editing, RNAi, and mRNA in neurological, ocular, and oncology indications. The company launched in July 2020 with a \$28.5M Series A, led by Leaps by Bayer and Morningside Ventures.
- Codiak Biosciences is developing an exosome-based delivery technology, which it claims can avoid the adaptive immune response that plagues rAAV approaches. In June 2020 Codiak partnered with Sarepta, one of the leaders in gene therapy, to apply its technology to delivery of Sarepta's broad range of nucleic-acid therapies for rare monogenic diseases.
- Carmine Therapeutics is developing its Red Cell EV Gene Therapy (REGENT) technology, which is non-immunogenic and can be obtained in large quantities from blood. In June 2020, the company signed an R&D collaboration with Takeda for two undisclosed rare diseases.

program to cover a much wider number of inherited diseases so that newborns can receive appropriate intervention.

Previous efforts by various stakeholders such as patient advocacy groups and the biopharma industry have resulted in a number of diseases being added to newborn screening in the U.S. in recent years, including SMA and severe combined immunodeficiency (SCID). However, much remains to be done and it is critical to remember that the earlier a genetic disease is diagnosed and treated the better the outcome for the patient, whether they receive gene therapy or some other modality.

If therapy persistence does fade with gene therapy, question marks remain around whether patients could even be dosed a second time due to immunogenicity concerns. The question

⁸ Maingi, S., 2020, Visualizing the Future of Contract Development and Manufacturing for Cell and Gene Therapies, *Pharma's Almanac*, v. 6(1), p. 148-151.

⁹ Wang, D., Tai, P.W. L., and Gao, G., 2019, Adeno-associated virus vector as a platform for gene therapy delivery, *Nature Reviews Drug Discovery*, v. 18(5), p. 358-378.

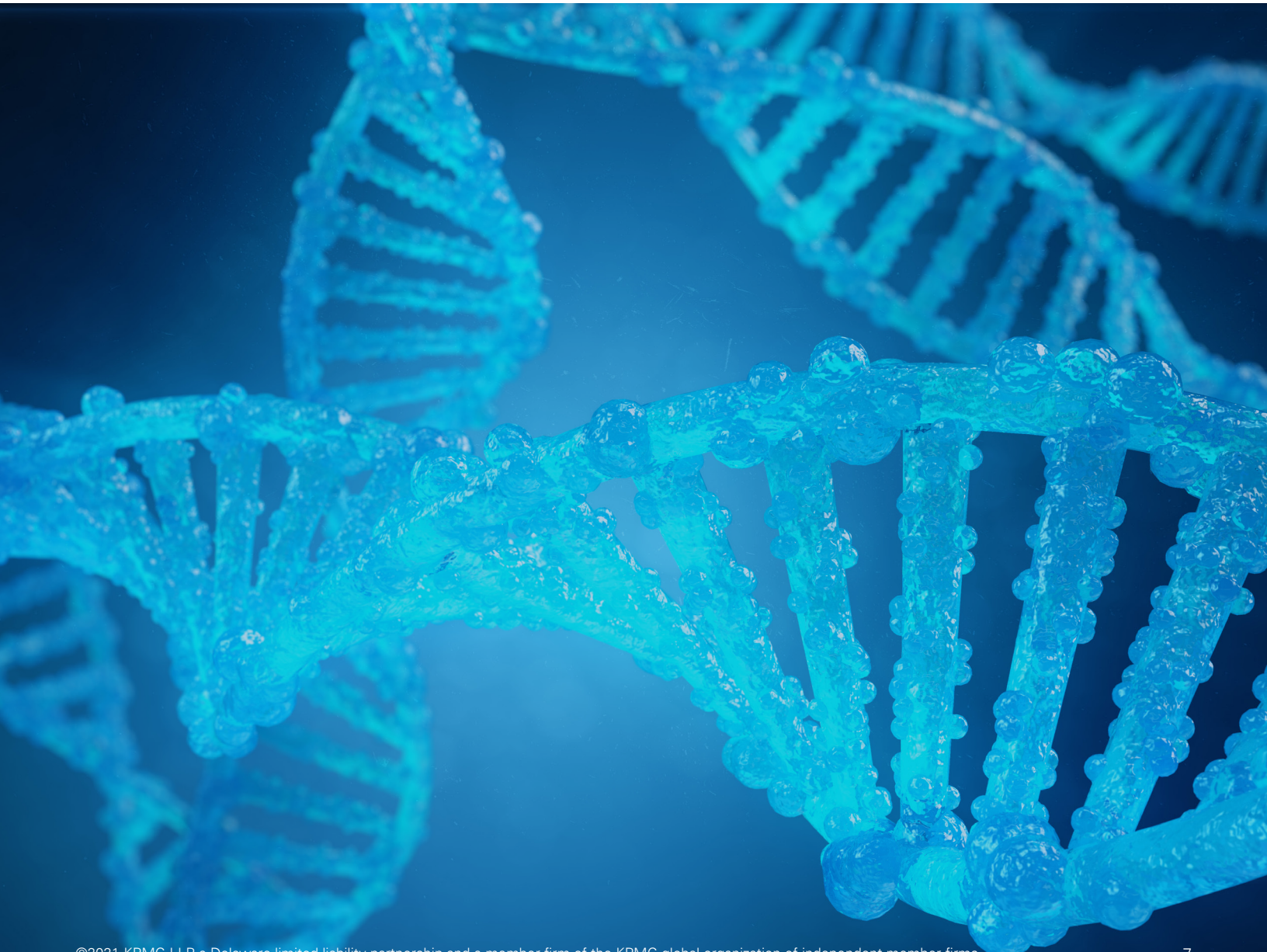
¹⁰ Calcedo, R., Morizono, H., Wang, L., McCarter, R., He, J., Jones, D., Batshaw, M. L., and Wilson, J. W., 2011, Adeno-associated virus antibody profiles in newborns, children, and adolescents, *Clinical and Vaccine Immunology*, v. 18(9), p. 1586-1588

of “cure” also has profound implications for pricing of gene therapies. Currently, payers are mostly willing to reimburse upfront for these ultra-high-priced therapies due to the small patient populations and limited budget impact. However, what if therapy persistence fades and they are asked to reimburse for a second gene therapy or some other high-priced therapy in order to control the patient’s disease?

To offset payer pushback and spread risk, companies have been striking outcomes-based payment models, where payers receive reimbursement for part of the payment if efficacy wanes at some point over a pre-determined period. But, will they be willing to pay upfront again or will they expect a lower price with a second therapy? These are complex questions that will become more important to address as more and more gene therapies launch in the coming years and payer budgets start to be materially impacted.

Regulators also appear to be looking at durability. The fact that the FDA has requested additional clinical data from some manufacturers following BLA review suggests that the agency will take a closer look at durability as part of future decision making, with important implications for current gene therapy developers.

If curative is not really curative, this has important implications for how companies develop and price their gene therapies and think through their competitive positioning in the market. Other nucleic acid therapies are now entering the market and battling it out for share with gene therapies, e.g., RNA modulation approaches such as anti-sense oligonucleotides. Therefore, it will be critical for gene therapies to prove the “one-and-done” value proposition in order to gain and sustain a competitive advantage.



Pursuing monogenic vs. polygenic diseases

Monogenic diseases:

Over the last five years in the U.S., a number of nucleic-acid-based therapies for monogenic diseases have been approved that significantly lessen the severity of the diseases they target (Exhibit 5). Of those, only Luxturna and Zolgensma are single dose and can, therefore, be called potentially “curative.” However,

both therapies target very small populations with a defined genetic driver of disease. Analysis of the “one-and-done” clinical trials reveals this to be the case for most of the diseases, with 35 of the 38 monogenic diseases companies are developing therapies for either rare or ultra-rare (Exhibit 6).

Exhibit 5: Nucleic-acid therapies approved by the FDA since 2016 for monogenic diseases

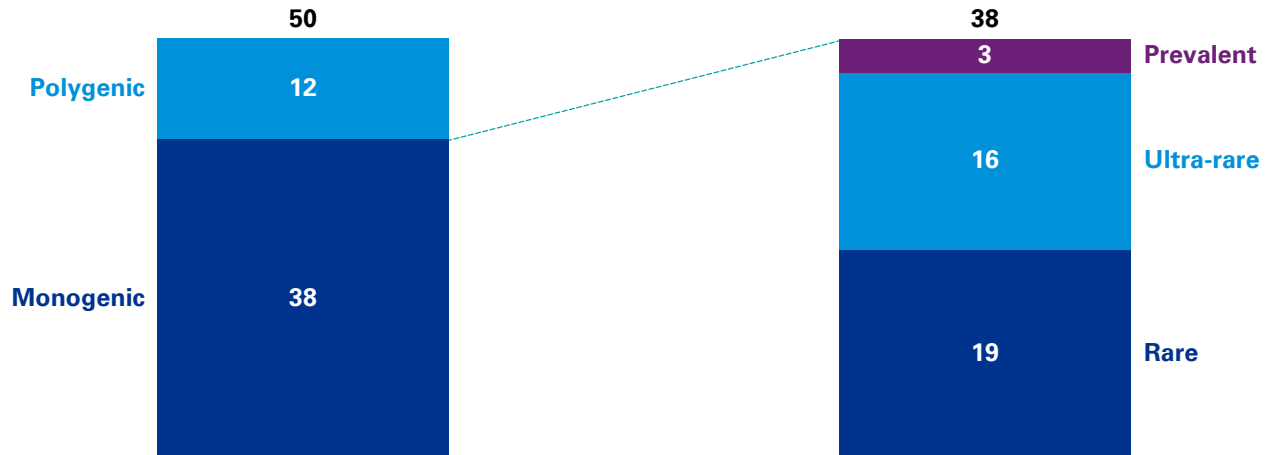
Therapy	Originator	Technology	Disease	FDA Approval Year	Single Dose?
Amondys 45	Sarepta	Antisense oligonucleotide	Duchenne Muscular Dystrophy	2021	
Oxlumo	Alnylam	RNAi	Primary hyperoxaluria type 1	2020	
Viltepso	Nippon Shinyaku	Antisense oligonucleotide	Duchenne Muscular Dystrophy	2020	
Vyondys 53	Sarepta	Antisense oligonucleotide	Duchenne Muscular Dystrophy	2019	
Givlaari	Alnylam	RNAi	Adult patients with acute hepatic porphyria	2019	
Zolgensma	Avexis*	Gene Replacement	Spinal Muscular Atrophy	2019	✓
Tegsedi	Ionis	Antisense oligonucleotide	Polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults	2018	
Onpattro	Alnylam	RNAi		2018	
Luxturna	Spark**	Gene Replacement	Biallelic RPE65 mutation-associated retinal dystrophy	2017	✓
Spinraza	Ionis	Antisense oligonucleotide	Spinal Muscular Atrophy	2016	
Exondys 51	Sarepta	Antisense oligonucleotide	Duchenne Muscular Dystrophy	2016	

Source: Informa

*Acquired by Novartis

**Acquired by Roche

Exhibit 6: Single-dose gene therapy pipeline categorization



Number of monogenic vs. polygenic diseases for single-dose gene therapies

Prevalence categorization for monogenic diseases being targeted by "one-and-done" gene therapies

Source: Clinicaltrials.gov, Informa and KPMG analysis

From a scientific standpoint, focusing on monogenic diseases makes perfect sense. Companies have a clear understanding of disease drivers and can decide on the best approach to target the gene in question (e.g. knockdown, replace, edit), knowing in all likelihood that it will have an impact on the disease, or even offer a cure. There are estimated to be between 5,000 and 8,000 monogenic diseases,¹¹ many with high unmet medical needs and no treatment options. These tend to be rare or ultra-rare diseases that often affect newborns, meaning they have well-informed and vocal patient groups that can help companies understand the natural history and burden of disease, provide valuable insights

throughout the drug development process, and act as advocates for therapies in regulator and payer conversations. Indeed, many patient groups are among the most sophisticated stakeholders in the gene-therapy ecosystem. Further, they are often involved in cutting-edge innovation in their respective diseases, for example setting up bio-banks for researchers and funding new biotech start-ups. That being said, companies must be aware that many rare genetic diseases don't have a patient voice, and so they must be willing to spend time and money to help build out advocacy organizations to represent patients and their caregivers.

Polygenic diseases:

By contrast, polygenic diseases often have multiple genetic drivers, as well as environmental, lifestyle, and other compounding factors. Although polygenic conditions such as heart disease, hypertension, and type II diabetes have large patient populations, we believe they represent a scientific mountain to climb for current gene therapy technologies. In addition to the delivery issues highlighted previously, and the difficulty meeting the needs of hundreds of thousands of patients due to already constrained manufacturing capacity, the question of how to deliver multiple genes at the same time remains a challenge. We would argue this will be the case for many years to come. In addition, unlike monogenic diseases, many polygenic diseases have well-established (albeit often imperfect) standards-of-care, some of which are inexpensive generics.

This adds to the commercial headwinds gene therapies would face if competing in polygenic diseases. As highlighted above, unless COGS for gene therapies can be brought down substantially, list prices will remain high, which could mean a huge budget impact for payers that are trying to cover therapies for highly prevalent diseases.

As such, we believe that major scientific, technical and manufacturing advances will be needed before gene therapy breaks out into large polygenic diseases, and the potential depends upon whether "cure" proves to be a reality. Therefore, we believe that "one-and-done" gene therapies will remain mostly confined to small, monogenic diseases for the foreseeable future.

¹¹Prakash, V., Moore, M., and Yanez-Munoz, R. J., 2016, Current Progress in Therapeutics Gene editing for Monogenic Diseases, *Molecular Therapy*, v. 24(3), p. 465-474

Competing in rare monogenic diseases

Despite the scientific attractiveness of developing therapies for monogenic diseases, they tend to be rare diseases and some are ultra-rare, impacting only a few people born each year. To be commercially successful in this arena, and bring potentially transformative therapies to patients, we believe companies need to address a number of critical considerations.

Decide where to play: As highlighted above, there are between 5,000 and 8,000 monogenic diseases, but companies must carefully choose “where to play.” Companies must understand the underlying etiology, biological complexity and natural history of the diseases they are targeting in order to design the appropriate basic research and clinical programs.

In addition to the usual considerations around competitive dynamics, unmet need and strength of standard-of-care, companies must also decide whether the market size is large enough for them to achieve a return on investment.

Companies in the monogenic markets will also have the same headwinds that have historically faced developers of other modalities in the rare disease market – how to find patients. Developers in rare diseases often underestimate how hard it can be to identify and recruit patients for clinical trials or start them on therapy.

Recognizing these headwinds, some biopharma companies are moving away from ultra-rare populations towards larger (albeit still rare) genetic diseases. For example, in May 2020, Orchard Therapeutics, which is developing an autologous *ex vivo* gene therapy using hematopoietic stem cells, announced that it was pivoting away from some of its ultra-rare disease treatments to “accelerate research in less rare indications, including two new programs in genetic subsets of frontotemporal dementia (FTD) and Crohn’s disease.”¹²

Importantly though, when companies decide “where to play” in rare genetic diseases, they should not do so based on the prevalence of manifest disease, i.e. those patients who are symptomatic. Often the prevalence of pre-manifest (non-symptomatic) patients is far higher as identified through genetic analysis or other methods. Therefore, early identification of these pre-manifest patients could significantly expand the addressable

patient population. For example, in the U.S. it is thought that around 30,000 people have Huntington’s Disease, but another 200,000 are at risk of developing the disease.¹³

Be first or a fast follower: One of the primary considerations for “one-and-done” gene therapies is being first-to-market, or at least a fast follower. As most monogenic diseases have small patient populations, being first could mean the difference between commercial success and failure. Given the potential for a cure, other “one-and-done” companies that enter late will be left with the treatable incident population.

Despite this significant challenge, in some rare monogenic diseases there are multiple “one-and-done” competitors jostling for position. For example, we estimate that there are 5 companies developing 5 separate AAV-based gene therapies for Pompe disease, with 3 of these programs now in the clinic (2 in Phase I / II and 1 in Phase I) and the rest in pre-clinical development.¹⁴ With a U.S. prevalence of only around 8,000-9,000 patients and approximately 100 new cases each year, companies with therapies in pre-clinical development should assess whether it makes strategic sense to continue with their programs given the competitors that are ahead of them.

Stack your indications: An ability to “stack” future indications so that top-line revenues are sustainable in the long-term will also be crucial. Similar to the hepatitis C market back in the 2013-2018 timeframe, “cure” can mean an inverted “V-shaped” revenue line that can impact a company’s ability to predict future margins and cash flow. This can be particularly detrimental for small biotech companies. Given the shortened clinical development and regulatory timelines associated with many rare monogenic diseases, companies in this position will require tight co-ordination between R&D, regulatory and commercial teams in order to successfully execute the launch of successive therapies. Companies should pursue and “stack” diseases where there is clinical and pathological overlap. For example, in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), both diseases have a reported association through pathogenic GGGGCC hexanucleotide repeat expansions in the C9orf72 gene, which is present in ~35% and ~25% of ALS and FTD, respectively.

¹² Orchard Therapeutics Unveils New Strategic Plan and Reports First Quarter 2020 Financial Results, Orchard Therapeutics press release, May 7, 2020.

¹³ [National Organization for Rare Disorders](#).

¹⁴ Informa, KPMG analysis.



Engage key stakeholders early:

Engaging key stakeholders early, from patient groups to healthcare providers (HCPs) and payers, will be critical given how complex and technically advanced the field is. Many physicians are unfamiliar with the underlying science or are unsure of the benefits of gene therapy, so peer-to-peer conversations with company medical science liaisons (MSLs) are critical. In some diseases, there may be skepticism from patients and their families around the safety profile of gene therapies. These concerns must be recognized and addressed if gene therapy is to be successful, particularly in diseases where there may be an existing standard-of-care.

Not engaging early with influential stakeholders like patient advocacy groups often puts companies at a disadvantage when they begin discussions with payers and regulators, as rare disease patient groups can be vocal supporters of certain therapies, as previously highlighted. Companies should also build early relationships with non-traditional stakeholders such as the non-profit Institute for Clinical and Economic Review (ICER) in the U.S., which is increasingly influencing payer decision making through its cost-effectiveness models.

Build the right team:

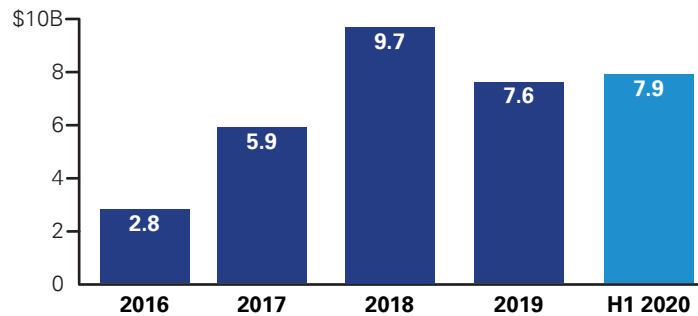
Developing and launching a “one-and-done” gene therapy is fundamentally different from launching traditional small molecules or even biologics, which most biopharma companies are used to. Therefore, building the right team is essential. For example:

- In R&D, employees must be steeped in the science and natural history of genetic disease, and also understand how to design, recruit, and run clinical trials for rare or even ultra-rare patient populations with complex conditions. Every patient matters when some trials have just a handful of participants, and so the clinical operations team must train principal investigators (PIs) to look for potentially complex side-effects and must be on hand at all times to respond to inquiries from PIs.
- Considering the FDA’s focus on the chemistry, manufacturing and control (CMC) package for gene therapies, it is critical to hire regulatory experts who understand gene therapy and can ensure tight coordination with the FDA and development of a robust CMC package.
- In manufacturing, the team must ensure supply can meet demand, especially given the complex and fragmented nature of the raw material supplier ecosystem, and the previously highlighted manufacturing and commercial scaling challenges.
- In supply chain and distribution, the team will be responsible for moving high value, low volume therapies to treatment centers around the world, a model that most biopharma companies are not familiar with.
- Given the highly technical nature of therapies and complexity of genetic diseases, companies need to hire MSLs with gene therapy experience who can have peer-to-peer conversations with key opinion leaders, help educate payers on the disease burden, and connect with patient groups in order to understand the patient journey.
- Scientific communications experts must ensure that key data is released incrementally and at the right moments to prime the market and put the company in an optimal competitive position.
- Pricing and market access experts must understand the complexities of various payment models, such as outcomes-based models, and engage with various stakeholders to educate them on the value that a therapy brings to patients and the healthcare system.
- HEOR specialists will support payer conversations, as well as provide input on how to design the lengthy post-marketing trials that regulators and payers expect in order to understand the long-term safety and efficacy of therapies.
- Depending on the disease, genetic counselors may be needed who understand the diagnostics landscape and can help support the Medical Affairs team in educating payers and KOLs, while also working with patient advocacy groups.

Acquire or partner?

Despite these challenges, the gene therapy field continues to see significant investment from investors and biopharma (Exhibit 7), although the way companies are deploying capital varies.

Exhibit 7: Gene and gene-modified cell therapy global financing, 2016-H1 2020



Source: Alliance for Regenerative Medicine

Note: Financing across all therapy areas, including oncology; figures do not include M&A transactions

Acquire for long-term value? Some large biopharma companies are going “all in” by spending billions of dollars on M&A targets. This strategy is based on the ascribed value of the platform and what it provides from a long-term R&D technology perspective rather than any near-term revenue opportunities.

For example, in the latest example of large scale M&A in the gene therapy space, Bayer announced a deal worth up to \$4.0B for AskBio in October 2020 in which it gains access to its rAAV platform as well as the company’s rAAV CDMO capabilities.¹⁵ Although these rich valuations are out of reach for all but the largest biopharma companies, they reflect the excitement in the field and the limited number of targets with late-stage assets and a proven scientific platform from which to build.

However, post-acquisition, large biopharma companies have not always executed well when integrating innovative targets. Companies must strike a delicate balance between managing and controlling risks associated with the acquisition and not stifling innovation.¹⁶ Given the esoteric nature of the gene therapy field, losing intellectual capital by smothering the entrepreneurial spirit of the target can be extremely detrimental to the long-term prospects of the acquirer.

Above all, large biopharma companies must be patient and willing to invest in improvements to their acquired technologies.

Intriguingly, major biopharma companies that have previously made large acquisitions in the gene therapy space have struck recent deals with small biotech companies that are focused on improving current rAAV capsids in the areas of payload capacity, tissue targeting, immune evasion and manufacturing. This would suggest that these biopharma companies are looking to build on their acquisitions by investing in technologies that could address some of the limitations with their current vector platforms, and give them a long-term competitive advantage.

Take a more cautious approach? Given the challenges around the development, manufacturing and commercialization of gene therapies, it is understandable that many other companies are taking a more cautious approach to playing in the market, at least in the near-term. Most major biopharma companies are executing smaller acquisitions while also entering multiple partnerships or options to acquire.

Smaller companies with less financial muscle have also been entering the field. They realize that they need to “play to defend” themselves from the competitive threat that gene therapy poses to their portfolio, or that they need to diversify away from older franchises that could be facing pricing and/or generic headwinds and embrace new innovative technologies. However, given their limited financial capacity compared to big pharma and the tremendous cultural, scientific and logistical leaps they need to take to enter such an innovative field, partnering will likely make more sense than outright M&A.

¹⁵ Bayer Acquires AskBio to Broaden Innovation Base in Cell and Gene Therapy, AskBio press release, October 26, 2020.

¹⁶ [Getting integration right in biotech acquisitions, KPMG, April 2021](#)

Conclusion: Spread your bets and stay the course

For now, we believe that the more cautious approach to playing in the gene therapy market makes sense for most companies because it remains to be seen which modalities and delivery technologies, if any, will win. The field continues to see the emergence of new modalities and delivery technologies, and companies are continually working to improve existing technologies. Although not covered in this paper, there are myriad other nucleic-acid technologies evolving, such as anti-sense oligonucleotides, mRNA, RNAi and other modalities, all of which will compete with “one-and-done” gene therapies.

In this rapidly changing space, spreading your bets from a modality and delivery standpoint makes strategic sense, especially if there are minimal upfront costs and lower risk exposure. Some companies are building a multi-faceted approach, deploying gene therapy, gene editing, and RNA technologies across a number of monogenic diseases. Companies taking this path exemplify both the promise and the limitations of gene therapy. We clearly have the tools now to add, edit, and replace genetic material to potentially cure certain diseases. And yet, our ability to manufacture at scale and deliver in a targeted, safe, and effective way that results in a durable response remains elusive.

This is why we believe companies must stay the course. In the past, we have seen companies lose interest when results don't meet expectations. In fact, delivery issues drove many big pharma players to exit the RNAi field completely around 2010. In contrast, the launch of the first FDA-approved RNAi therapy in 2018, Alnylam's Onpatro for hereditary transthyretin-mediated amyloidosis (hATTR) in adults, was only possible because the players that remained in the field were patient and continued to work on delivery issues. This example emphasizes the importance of exercising a measured, long-term strategic approach to building out a presence in gene therapy.

We are undoubtedly entering a new era in medicine. However, we would argue that the next 5-10 years will be mostly focused on clearly defined monogenic diseases with small patient populations. Despite holding immense promise long-term, we believe “one-and-done” gene therapies will likely be a near-term niche. As such, companies will need to be hyper-focused on where and how they play in order to build long-term success.

How KPMG can help

At KPMG, we assist clients working at the forefront of the next-generation of therapies - cell and gene technologies. While these technologies are transforming patient care for certain diseases, they also bring their own unique complexities. We support clients, from small biotechs to large biopharma, contract research organizations, contract development and manufacturing organizations, and private investors, to help them successfully negotiate these challenges and seize the opportunities that cell and gene therapies present. We engage clients across functions that include R&D, manufacturing/supply chain, medical affairs, business development, pricing/market access, and sales/marketing. Our services include:

Strategy

- Assess modalities/delivery technologies to support R&D and business development strategies
- Evaluate the size of market opportunities to support investment decisions
- Design innovative pricing models to support market access
- Support the go-to-market strategy of the organization, from the design of the end-to-end distribution and value chain, through to the optimal structure of organizational functions such as sales and marketing, medical, and market access
- Develop financial and tax operating models

Technical Operations

- Design cross-functional operating models/detailed road maps for “make-to-order” cell therapies
- Analyze supply chain processes, systems, organization, and metrics to reduce lead times
- Develop manufacturing strategies that align with product characteristics and patient needs

Deals

- Identify inorganic growth opportunities for corporate clients and execute full diligence on targets
- Support corporate clients as they look to develop strategic partnerships with raw material suppliers
- For private investors, conduct market landscape assessments and full diligence on targets
- Support optimal organizational design and functional integration following acquisition of cell and gene targets

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The author would like to thank the following contributors:

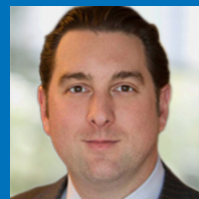
Special thanks to Brian Tam, Saurabh Sancheti, Priyanka Sinha and Amandeep Singh for their invaluable contributions

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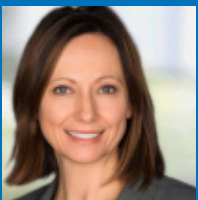
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DASD-2021-3793