L.E.K.

Special Report

Gene Therapy: Competitive Dynamics and Commercial Implications

Contents

Executive summary

After more than 25 years of investment, commercialization of gene therapies (GTs) has reached a pivotal point. Four GTs have launched in the U.S. and Europe, and biopharma companies are following up this success with ~140 additional GTs in clinical development with the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in indications outside oncology. These therapies have the potential to benefit patients by providing what in many cases could be a one-time, curative treatment.

As GTs mature, biopharma companies continue to develop strategies that optimize their ability to improve patients' lives and drive commercial opportunity. Two key dimensions influence commercialization — the level of competition and patient epidemiology — and together these dimensions can be used to segment GTs into four archetypes:

- **Archetype 1: Competitive, prevalence-driven opportunities,** where initial patient populations diminish due to treatment and rapid launch is key
- **Archetype 2: Competitive, incidence-driven opportunities,** with a competitive focus on treating the incident population, as the prevalent populations typically are relatively small due to high mortality
- **Archetype 3: Noncompetitive, prevalence-driven opportunities,** where a large population of untreated patients exists, typically because it is hard to treat a condition or there is lower unmet need
- **Archetype 4: Noncompetitive, incidence-driven opportunities,** where incidence is large compared with prevalence, with few competitors present

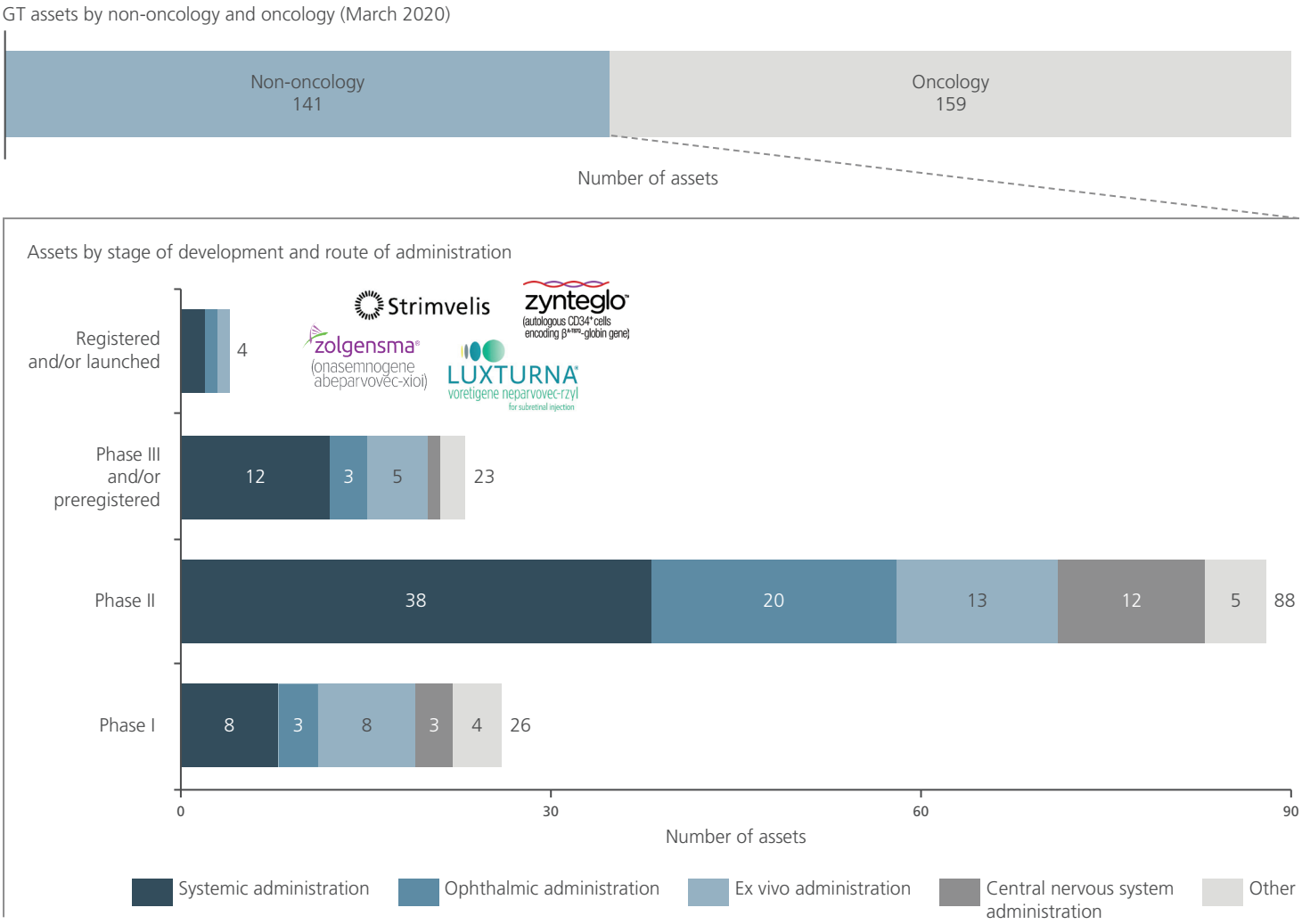
Depending on which archetype best represents a development-stage GT, biopharma companies must consider several factors to improve their positioning in a competitive market, including, for instance, unmet patient need by subpopulation, where their therapy best aligns with treatment goals, creative/novel pricing models, flexible commercial infrastructure, value-added services on top of treatment, and additional studies to demonstrate value (e.g., additional health economics and outcomes research studies, head-to-head comparisons). Furthermore, based on market entry timing, companies in each archetype must evaluate their position and define solutions to derive benefits from these assets for both patients and company stakeholders.

In this Special Report on the emerging non-oncology GT market, L.E.K. Consulting presents key success factors and strategic considerations by archetype that a biopharma company should assess when faced with competition to its GT. Successfully addressing these considerations can support biopharma companies' efforts to effectively position themselves to deliver patient benefits and generate value in the GT field.

Gene therapy background and landscape

The GT development race started on Sept. 14, 1990, when a clinical trial began treating its first adenosine deaminase severe combined immunodeficiency (ADA-SCID) patient. Today, 300 GTs have been launched or are in development with the FDA and EMA that involve some form of persistent, protein-encoding DNA transfer, utilizing a variety of in vivo and ex vivo techniques (see Figure 1).[1] It is becoming clear that GT launches are poised to take off and that GTs will become part of the therapeutic armamentarium, along with small molecules and other biologics. Based on standard probabilities of success for orphan disease assets, analysis of the current pipeline of GT assets indicates that approximately 20 therapies may be approved in the next five years. A recent report from the Massachusetts Institute of Technology also estimates 10-20 genetically modified therapies launching over the same time frame.[2] GT approvals may accelerate over time, and

Figure 1
GT assets in development



Note: Phase I to marketed therapies by latest FDA or EMA status. An additional 11 non-oncology and 114 oncology assets are in development in other geographies
Source: L.E.K. research; L.E.K. analysis of Informa Pharmaprojects

former commissioner of the FDA Scott Gottlieb predicted 10-20 genetically modified products will be approved each year by 2025.[3]

Of the 300 GTs launched or in development, approximately 100 are for non-oncology indications and aim to directly provide a functional copy of a missing or deficient gene (RPE65, SMN1, HBB, F8, etc.), including some of the first key non-oncology therapies to market: Spark Therapeutics' (Roche's) Luxturna and Novartis' Zolgensma. These therapies typically seek to treat rare diseases via direct replacement, substitution or supplementation of a defective gene. Early results have been promising, with many therapies, including the two mentioned above, showing life-altering, durable results. Sales likewise have shown potential, with Zolgensma achieving greater than $150 million in sales in Q3 2019,[4] $180 million in Q4 2019[5] and $170 million in Q1 2020,[6] and Luxturna now selling over $100 million annually.

In addition to these 100 one-to-one functional gene augmentations, approximately 40 additional non-oncology therapies are in development that provide some form of genetic extension via exogenous protein-encoding nucleic acids.[1] These therapies include VY-AADC,[7] which provides the gene that codes for aromatic L-amino acid decarboxylase to enable Parkinson's patients to create dopamine in the putamen of the brain, and ADVM-022,[8] the aflibercept GT for wet age-related macular degeneration, among many others.

While the mechanisms vary, commercial interest in GT is clear — large biopharma companies are attracted. The myriad display of promising GTs has attracted the interest of these companies, which have begun to invest heavily in GT via acquisitions (e.g., Novartis' acquisition of AveXis,[9] Roche's acquisition of Spark[10] and Astellas' agreement to acquire Audentes[11]) (see Figure 2) and other tie-ups (e.g., Pfizer's GT deals with Bamboo,[12] Sangamo Therapeutics[13] and Spark,[14] and Roche's deal with Sarepta[15]).

As GTs continue to read out further clinical efficacy data, L.E.K. expects this trend will continue to develop, with more partnerships and large acquisitions on the way.

Figure 2
Recent biopharma GT deals and costs

Biopharma/Deal Partner	Value	Year
Roche/Spark	$4.8B	2019
Astellas/Audentes	$3.0B	2019
Roche/Sarepta	$2.9B	2019
Novartis/AveXis	$8.7B	2018
Pfizer/Sangamo	$0.5B	2017
Pfizer/Bamboo	$0.6B	2016
Pfizer/Spark (Hem B)	$0.3B	2014

Source: L.E.K. research and analysis

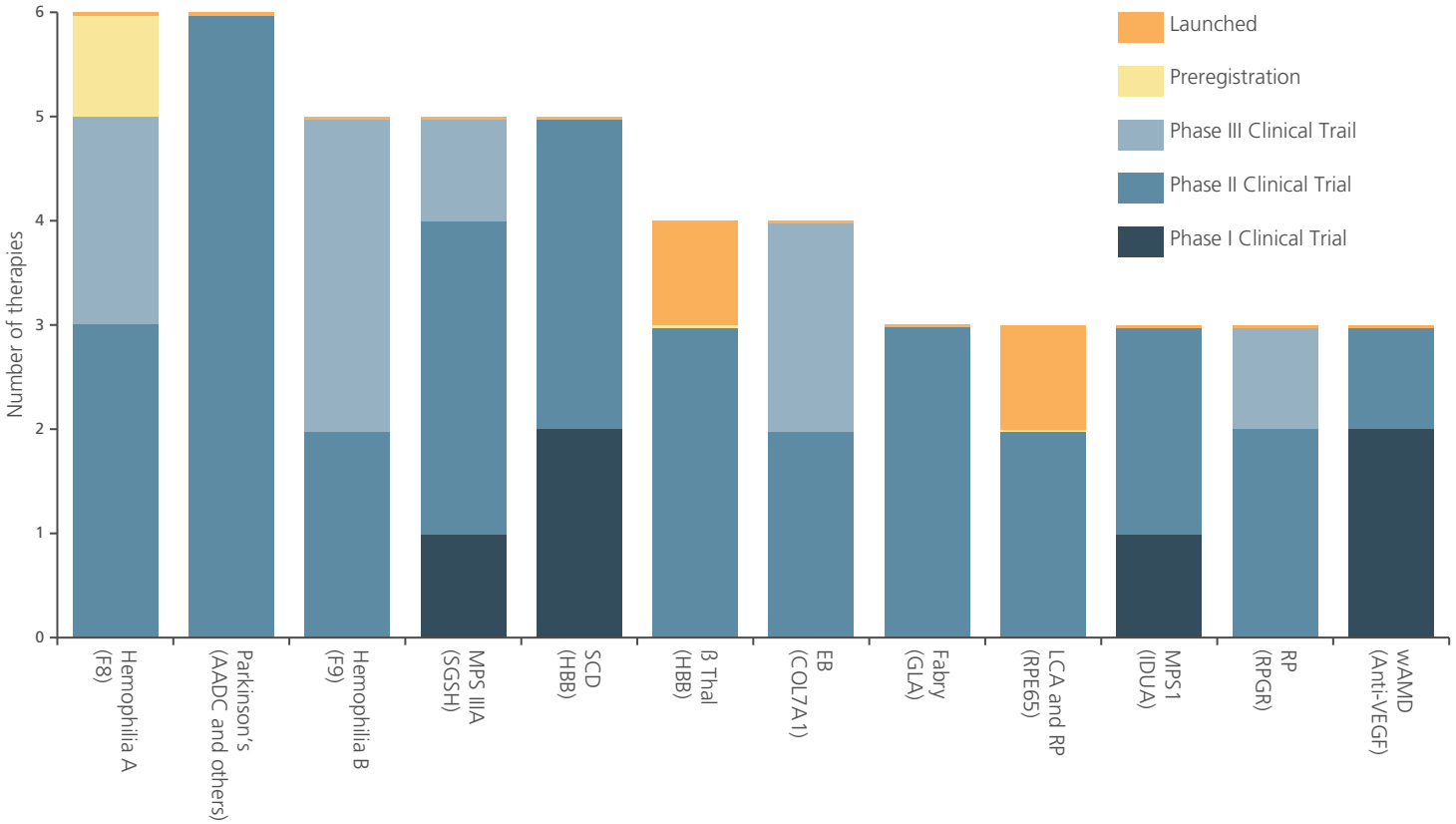
An increasingly crowded arena: Gene therapy competition

Many indications targeted by GTs have approved disease-modifying therapeutic options and robust development pipelines. Emerging GTs will face competition from existing small-molecule and protein-based therapies, various pipeline therapies, and most relevantly, highly similar competitive GTs. Today, there are 54 GTs alone clustered in the 13 most competitive GT-targeted indications (see Figure 3), plus many more non-GT treatments marketed or in development. These competitive indications typically are in hematologic, metabolic or ophthalmologic therapeutic areas, owing to a favorable confluence of factors that have facilitated developing early therapies in these areas.

For example, in highly competitive markets, hemophilia A and B serve as excellent cases. Both of these forms of hemophilia are caused by factor deficiencies and have complex treatment paradigms with a number of alternative branded therapies (see Figure 4). These indications have traditionally been handled via factor replacement therapy, and serious additional non-GT competition exists, especially in hemophilia A, in the form of

Figure 3
Competitive GT markets

Indications (genes) targeted by GTs, by stage of development (March 2020)



Note: Gene replacement therapies approved or in clinical trials, by indication; only indications with three or more assets are included; abbreviations include MPS (mucopolysaccharidosis), SCD (sickle cell disease), ß Thal (b thalassemia), EB (epidermolysis bullosa), LCA (Leber congenital amaurosis), RP (retinitis pigmentosa) and wAMD (wet age-related macular degeneration)
Source: L.E.K. research; L.E.K. analysis of Informa Pharmaprojects

Roche's Hemlibra,[16] Alnylam's late-stage Fitusiran[17] and others. BioMarin, Spark and other GT-advancing biopharma companies will have to determine how to best position their therapies in the context of this existing competition, as well as with other competitive GT entrants.

Less competitive markets exist as well, especially in ophthalmologic indications, where prior treatments via other modalities were often ineffective. Some of the more common gene mutations do feature multiple players, but others are currently targeted by only one or two therapies.

Depending on the level of competition in a given market, GT companies will have to make choices regarding their optimal commercial strategy. More competitive markets may require faster launches in some cases or more efficacious treatments in others, and hence, understanding where a specific asset lies along this competitive spectrum will be critical. Various other decisions regarding pricing, market access and patient engagement will also be affected and should be considered separately in each unique situation.

Figure 4
Other modality therapies in competitive GT markets

	Indication	Non-GT competition (standard of care and emerging)
Highly competitive	Hemophilia A	• Factor FVIII replacement, Hemlibra and others
	Sickle cell disease	• Standard of care (SOC) includes roxadustat (improved erythropoiesis-stimulating agent), Oxbryta, blood transfusion, bone marrow transplant and erythropoiesis-stimulating agents (ESAs)
Competitive	Parkinson's disease	• SOC includes levodopa, dopamine agonists and deep brain stimulation (DBS)
	wAMD	• Vascular endothelial growth factor (VEGF) inhibitors, photodynamic therapy, laser surgery • Several stem cell therapies are under development
	Hemophilia B	• Factor IX replacement
	Fabry's disease	• Fabrazyme
	Mucopolysaccharidosis I	• Aldurazyme and hematopoietic stem cell transplant
Noncompetitive	Beta thalassemia	• Deferiprone and deferasirox (iron chelators)
	Duchenne muscular dystrophy	• Exondys 51 (antisense RNA), Translarna (protein restoration therapy), Emfalza (glucocorticoid agonist)
	Epidermolysis bullosa	• Skin grafts and medication for pain, itching and infection
	Leber congenital amaurosis/retinitis pigmentosa	• One gene therapy approved (voretigene neparvovec)
	Mucopolysaccharidosis IIIA	• There are no approved therapies

Note: Examples of competitive biopharma archetypes with non-GT competition in which some GTs are in development or approved
Source: L.E.K. research and analysis

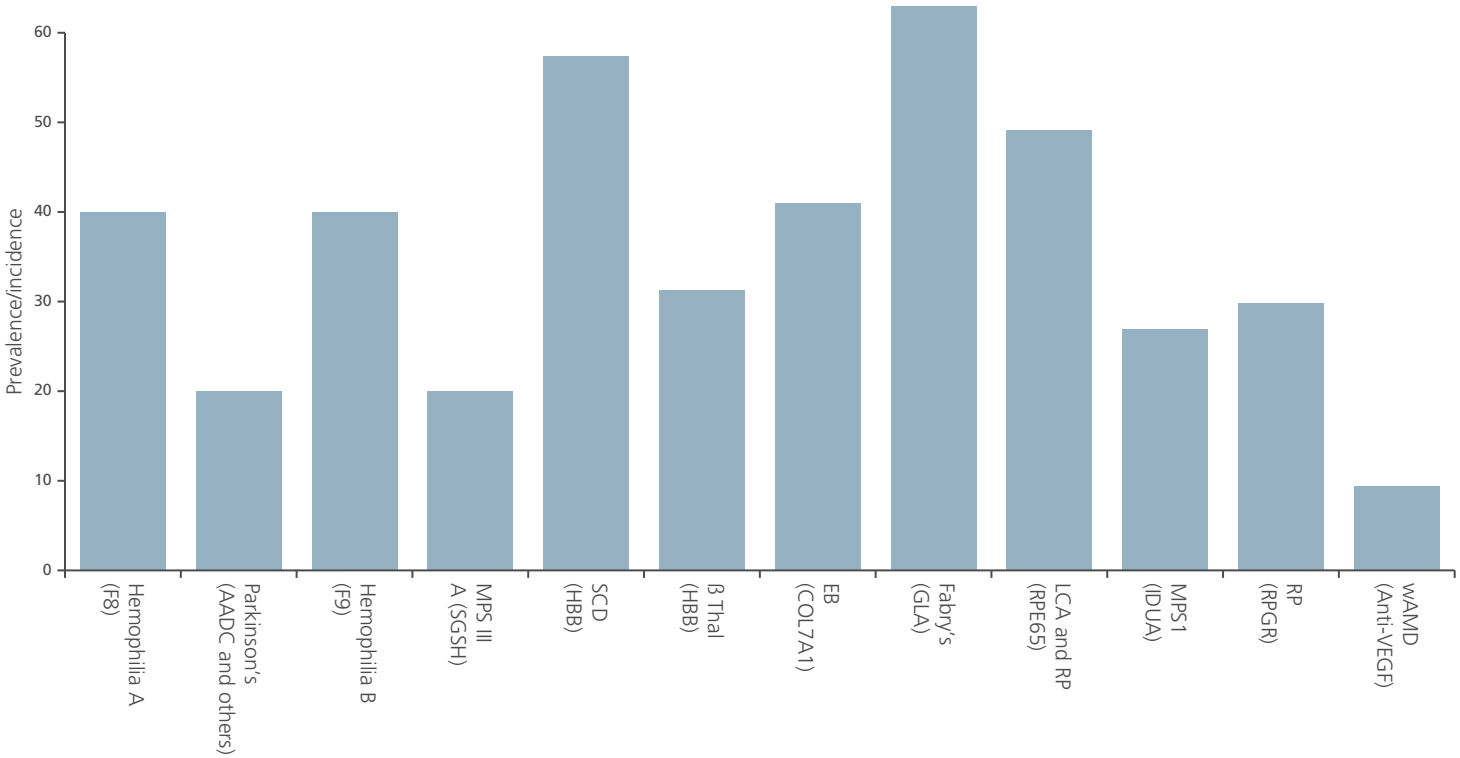
Patient dynamics in diseases with curative therapies

Non-oncology GTs target a variety of diseases, though predominately their goal is to help patient populations with germline-based monogenetic etiologies. These targeted genetic diseases cause significant morbidity and mortality. However, in order for the populations to be viable in the first place, most of these monogenetic mutations are broadly compatible with life. Mutations that cause significant mortality early in life, such as spinal muscular atrophy (SMA) type I, are more rare, as the mutations that cause the disease are precariously balanced on being nonviable in the first place.

From a commercial perspective, the implication of this dynamic is that diseases typically feature large prevalent populations in need of treatment as opposed to a prominent incident population (see Figure 5). Prevalent populations are existing patients suffering from disease and typically in need of treatments to alleviate their disease burden. Incident populations do exist, including in the cases of monogenetic diseases like SMA, myotubular myopathy (MM) and ADA-SCID, as well as in more complex polygenetic pathologies, though they are rarer. These incident opportunities often come with different challenges, such as the need to drive early diagnosis, and should be approached differently from prevalent opportunities.

Figure 5
Patient characteristics in indications with competitive GT development

Indications and genes targeted by gene replacement therapies

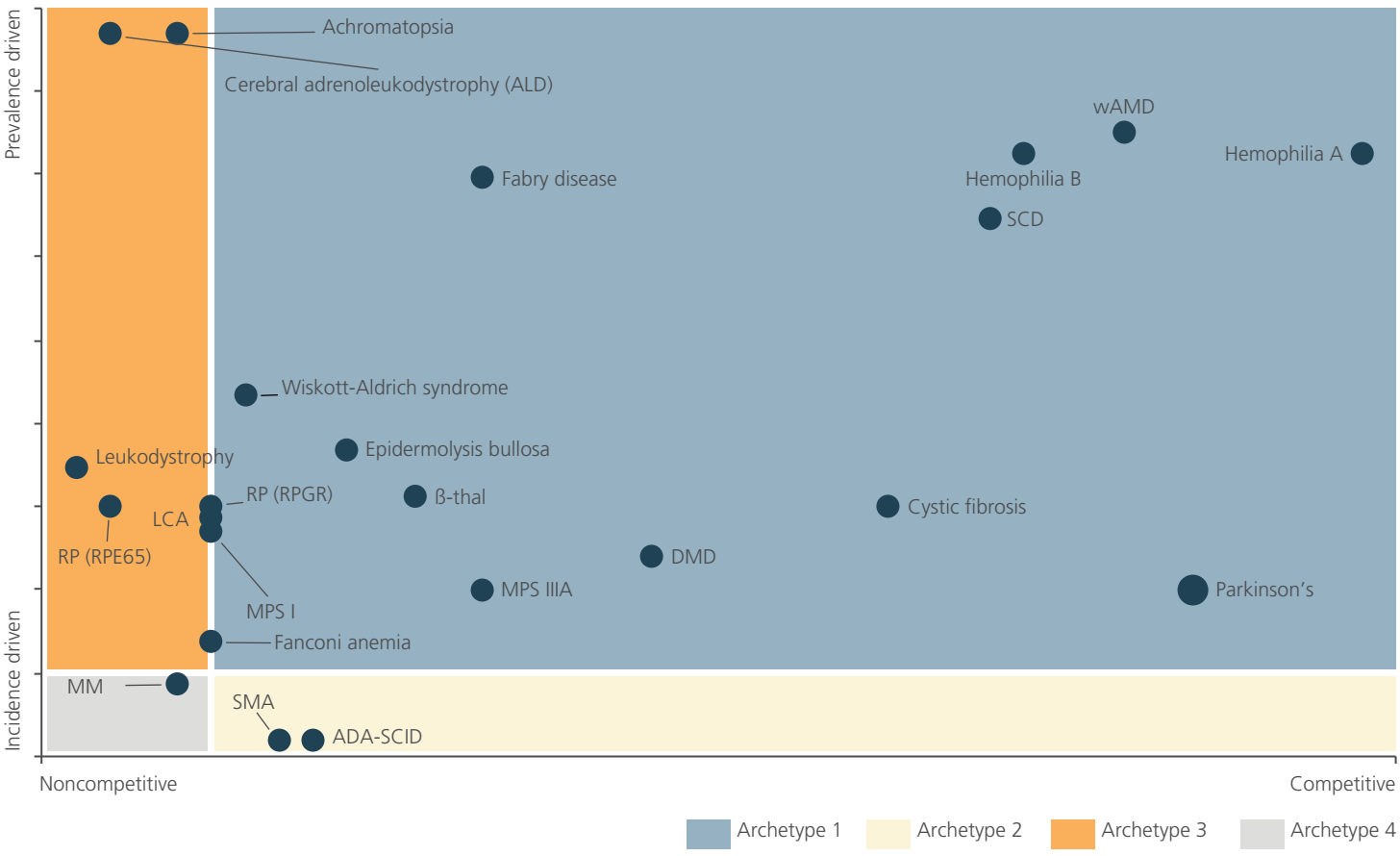


Note: The prevalence of indications targeted by GTs divided by their incidence provides an estimate of the size of the upfront bolus of patients expected versus ongoing new diagnoses; a reasonable assumption for exclusivity of 10 years after launch highlights nearly all competitive indications will primarily benefit patients alive at launch; abbreviations include MPS (mucopolysaccharidosis), SCD (sickle cell disease), ß Thal (beta thalassemia), EB (epidermolysis bullosa), LCA (Leber congenital amaurosis), RP (retinitis pigmentosa) and wAMD (wet age-related macular degeneration)[37-42]
Source: L.E.K. research and analysis

No clear delineation exists for what diseases are primarily prevalent versus incident, but we believe that indications with prevalent populations greater than 10 times the incident population can be classified as "prevalence driven" and those with prevalence below 10 times incidence can be classified as "incidence driven" (see Figure 6). This assumption is based on the fact that 10 years of exclusivity is a reasonable estimate for a new therapy and that any diseases that already have more than 10 years of warehoused patients will likely focus on those patients first.

When the previously discussed competitive dynamics of GT markets are coupled with this view on prevalent versus incident populations, four archetypes of opportunities emerge that each present different commercial needs (see Figure 6). Understanding where a GT exists along both of these axes can be important in understanding the ideal commercial strategy for each.

Figure 6
Market competition and patient characteristics in select GT markets



Note: Select GTs, including all competitive indications, by level of competition and prevalence/incidence; abbreviations include MPS (ucopolysaccharidosis), SCD (sickle cell disease), DMD (Duchenne muscular dystrophy), LCA (Leber congenital amaurosis), RP (retinitis pigmentosa), wAMD (wet age-related macular degeneration), SMA (spinal muscular atrophy), MM (myotubular myopathy) and SCID (severe combined immunodeficiency)
Source: L.E.K. research and analysis

Gene therapy opportunity archetypes

Archetype 1: Competitive, prevalence-driven opportunities

The majority of GTs target indications where large prevalent populations present the bulk of opportunity and the existing addressable population is greater than 10 times the incident population. L.E.K. considers these types of indications prevalence driven (see Figure 6), as the number of warehoused patients exceeds incident patients over a 10-year horizon, which is a reasonable estimate for exclusivity. The large number of patients creates greater space in the market for increased competition, and there may be many treatments seeking to target these indications. At the same time, these indications will rapidly deplete patients and commercial success will be highly dependent on the near term.

In competitive, prevalence-driven populations, a winner-cures-most scenario may develop for the more competitive spaces. In the case of curative first-to-market therapies, or those very closely behind with significantly differentiated performance, rivalry may arise as the key treatments compete for parts of an ever-shrinking patient pool (see Figure 7). Timing and initial advantage play a large role in these competitive markets as the one-time and possibly curative nature of treatment rapidly diminishes the prevalent patient population. In these prevalent populations, if a given program is not first to launch, or is launched within a year or two of the first competitor, a significant portion of the opportunity may vanish prior to launch. Thus, a potential advantage can be held by the first-to-market GT players.

Fast followers and subsequent second-generation offerings will need to evaluate the remaining market as to whether a possibly greatly diminished population post-first-mover launch would present an attractive option for entry. These later entrants will

Figure 7
Archetype 1: Competitive, prevalence-driven opportunities

Market characteristics	Large patient populations that may benefit from a curative therapy, with many biopharmas racing to be the first to treat a rapidly depleting patient population	
Expected revenue curve	Large initial bolus with modest long-term potential	
Example indication	Hemophilia A	
Example success factors, by function		
	Development	Launching first, or within one to two years of the first curative treatment, is critical
	Patient services and medical	Identifying patients and driving quick adoption to deliver the maximal benefit to patients while preempting competition will enable commercial success
	Operations	Supporting a launch into large populations requires adequate supply planning
Key strategic considerations		
	First movers	What key subpopulations are not reached, and what life cycle management opportunities can be developed to better serve unreached patient communities?
	Fast followers	How can fast followers differentiate from first movers (e.g., alternative pricing, new patient subpopulations, re-dosing opportunities)?
	Second generation	Given depletion of warehoused patients, is the incident population large enough to support another product on the market?

Source: L.E.K. research and analysis

need to evaluate their own GTs in order to determine whether they present a sufficiently differentiated offering from the first mover to warrant a launch. The possibility of targeting a subpopulation unreached by the first mover might be a worthy consideration, as could a possibly novel commercial factor, in terms of either price or creative reimbursement options.

The combination of larger patient populations and higher competitive factors leaves the prevalence-driven disease areas in significant need of strategic action. In these indications where high levels of competition arise, it will be critical for biopharma companies to quickly recognize what role they occupy and to strategically plan appropriately.

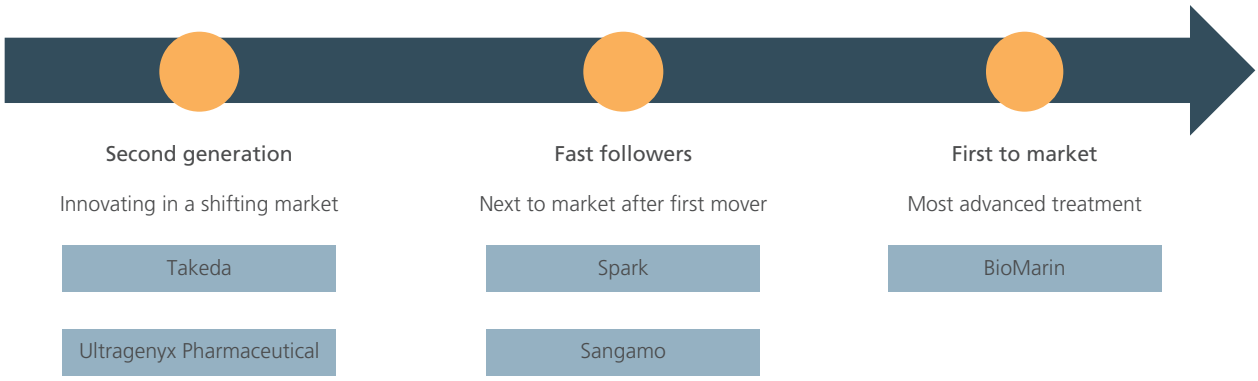
Case study: Hemophilia A

One competitive, prevalence-driven market that presents several archetypical examples of companies competing in the GT space is for hemophilia A. The various competitors in the space are facing crucial strategic choices regarding development and commercialization of GT treatments.

The most advanced hemophilia A GT candidate is valoctocogene roxaparvovec (Valrox) from BioMarin, despite a recent complete response letter from the FDA that has delayed its launch by two years[18] (see Figure 8). In spite of this delay Valrox still has the potential to be first to market, benefit many patients, and develop a strong market position prior to competition launching. As the likely first-to-market player, BioMarin will want to ensure it is answering questions necessary to rapidly reach and treat patients, including providing the new data on durability the FDA has requested. BioMarin would also need to factor in life cycle management of Valrox, potentially to patients who are initially ineligible, to maximize asset productivity. As the most easily identifiable or severe patients are treated, the company may require development of other strategies to continue to identify and help patients with unmet need.

Behind BioMarin are a few key assets, which present their own set of unique considerations. Roche's Spark is undergoing pivotal trials for its lead asset, SPK-8011.[19] Pfizer and Sangamo have also shown

Figure 8
Archetype 1 case study: Clinical-stage hemophilia A GTs



Note: Six therapies are in development for hemophilia A across five competitors, with various timing and clinical data; groupings regarding timing are estimates and may change based on trial results, on changes in strategic decisions or for any other reasons
Source: Company websites and press releases; ClinicalTrials.gov; L.E.K. research and analysis

compelling data for SB-525.[20] These companies have different considerations as fast followers than does BioMarin as the potential first to launch. They must actively seek to determine where exactly they fit in the treatment paradigm. Assessment must be made regarding remaining unmet need (e.g., for better durability) and of the remaining untreated population, particularly relating to the size, severity and neutralizing antibody status of each patient segment. These fast-follower companies will need to understand how their own products can differentiate from that of the first-to-market player in order to provide enough value for patients to choose alternative treatment.

Following the lead competitors, two additional clinical-stage competitors exist in the form of DTX-201 from Bayer/Ultragenyx[21] and TAK-754 from Takeda.[22] Each of these represents a likely second-generation product with potentially promising early safety and efficacy data. These second-generation therapies face the prospects of launching in a hemophilia A market largely treated by the first mover and fast followers, leaving the market dependent on a small number of newly incident patients. The second-generation therapies must address whether they are differentiated enough from the other offerings to encourage use.

Archetype 2: Competitive, incidence-driven opportunities

The smaller prevalent population and subsequent dependence on newly incident patients define the dynamics of incidence-driven indications (see Figure 9). Competition may be limited by the nature of the small available prevalent population and is primarily dependent on newly incident patients. The market may have space for only a few treatments, and entering GTs may struggle to gain a foothold if comparable incumbent GT or non-GT options exist. GT developers in competitive, incidence-driven opportunities will need to focus on therapy efficacy, safety and durability in order to provide patients with the best treatment available in the replenishing incidence-driven indication.

Figure 9
Archetype 2: Competitive, incidence-driven opportunities

Market characteristics	A larger incident population relative to a smaller prevalent population drives a recurrent opportunity and a focus on treatment of newly incident patients	
Expected revenue curve	Smaller initial bolus followed by more consistent steady-state revenues	
Example indication	SMA, type 1 primarily	
Example success factors, by function		
	Development	Treatment efficacy will be vital to differentiate, as indications may have difficulty supporting multiple treatments
	Patient services and medical	Rapid patient identification and accelerated treatment initiation will be critical, given limited therapeutic window
	Commercial	Innovative payment mechanisms/revenue streams are important for sustainable, long-term success
Key strategic considerations		
	Differentiation	What are some strategies to differentiate from existing and pipeline treatments (e.g., treatment durability of effect, efficacy or safety)?
	Patient reach	How quickly can patients be reached and treated? What subpopulations are not reached? What life cycle management opportunities can be developed to better serve unreached patient communities?

Source: L.E.K. research and analysis

In incident populations, being the first to launch may not be as critical, as the most successful treatment will be able to gain appreciable market share over time regardless of launch order. Instead, GT developers should focus on ensuring that their treatment is differentiated and best in class when it launches. Such an approach will offer patients the best possible treatment and ensure that developing biopharmas can obtain a preferred position in treating physicians' and reimbursing payers' repertoires.

Beyond optimizing each GT's profile, patient identification and outreach may be important considerations, since these indications typically feature higher mortality rates, which may limit the window of therapeutic action. Education of patients, caretakers, providers and advocacy groups will be key to effectively generate treatment volume early enough to assist the maximum number of patients.

Many incidence-driven populations may be too small to support multiple competitors, and follow-up therapies should be developed only if there is a real belief they can differentiate and displace earlier launches (see Figure 9). Fast followers and subsequent second-generation offerings of GTs may find difficulty entering the field, although the replenishment by incident population may provide opportunity. Companies with these types of assets would need to consider the altered treatment landscape and ascertain whether the opportunity exists to generate a viable market presence. These potential next-in-class treatments would need to show enough differentiation from previous products to encourage patient uptake, whether in terms of efficacy, untreated subpopulation targeting or pricing advantage.

Case study: Spinal muscular atrophy

There are few indications that pose a current example for the competitive, incidence-driven archetype, but SMA presents some instructive dynamics. Novartis' performance while launching Zolgensma for SMA may provide an illustrative instance of managing GT development and launches in competitive, incidence-driven indications.

SMA is caused by loss of or mutation to the SMN1 gene, and severity is determined by the copy number of the SMN2 gene. SMA patients face significant challenges, with untreated type I patients as most severe and frequently not living beyond the age of 2, and types II and III patients also facing extreme levels of mortality and motor function-related complications. While an incidence rate of ~400 patients per year in the U.S. may appear to signal a limited market for competition, prices have been high enough to allow a number of competitors to exist.

The first disease-modifying treatment, Spinraza,[23] launched in 2016 and, as the only option to slow progression, quickly generated significant market share. Zolgensma launched into this market and faced a number of commercial challenges. First, at launch, Zolgensma had to displace Spinraza. Owing to its durable nature as a GT, Zolgensma may offer curative potential, differentiating it from Spinraza immediately on the basis of its development.

While its durability offers adoption upside, Zolgensma has had to contend with the fact that its one-time treatment approach requires it to recoup its value all in one purchase versus over a patient's lifetime for a chronic therapy. As such, Zolgensma is considerably more expensive than Spinraza up front, with a $2.1 million list price versus Spinraza's $750,000 price in the first year. The one-time administration and upfront cost of Zolgensma present possible barriers to payers for reimbursement, despite potentially being more cost-effective in the long run.[24]

In order to provide additional options, Novartis offers alternative arrangements for Zolgensma, including both those related to risk sharing and options where reimbursement can occur over the time frame of up to five years.[25] Together, these commercial innovations may provide additional adoption upside, helping ease the burden on payers.

Zolgensma has thus far presented a viable entry into the SMA market, with Novartis reporting over $360 million in sales during 2019,[5] and is poised to continue to penetrate its addressable market in 2020. This success is likely due in part to Zolgensma's differentiation, its pricing mechanics, and other strategic choices Novartis made considering the patient and competitive dynamics of the SMA market.

Any fast followers or second-generation GT offerings will have to consider Zolgensma, Spinraza and potentially Risdiplam.[26] The crowded nature of the market will require discernment as to whether the market can bear any additional GT competitors and what sort of differentiation might allow a commercially successful entry. Exploration into subpopulation treatment or novel pricing may be necessary before considering a launch in this space.

Archetype 3: Noncompetitive, prevalence-driven opportunities

Noncompetitive, prevalence-driven indications present another dynamic situation (see Figure 10). Although the prevalent populations are much larger than the incident populations, there are fewer competitors in these markets and they may present attractive opportunities for GT solutions. The low competitor number may result either from small absolute patient population sizes or from efficacy or administration challenges that non-GT treatments have in treating these populations. The higher prevalence versus incidence may also indicate a possibly less-severe patient population that may be managed fairly well by the current standard of care.

A first-to-market GT will likely have fewer competitors in the field, so the search for patients will often be more important than the race to treatment. As these patients may be either rare or in less need of immediate treatment, patient outreach and collaboration with advocacy groups may be important to identify addressable patients. The costs of these therapies may also require consideration, since if patients exhibit less-severe symptoms, payers may be unwilling to reimburse for potentially expensive treatments. Innovation in pricing and patient outreach will be primary considerations for any first-to-market GT within the noncompetitive prevalent space.

Potential fast followers and second-generation products will need to consider the prospect of searching for rare patients and whether the market landscape could support multiple GT competitors. Differentiation and diligent patient outreach would also be important issues to take into account.

Case study: Cerebral adrenoleukodystrophy

As the GT market is still emerging, there are few examples of what could potentially be noncompetitive, prevalence-driven indications. One that may prove instructive is cerebral adrenoleukodystrophy (ALD), a rare X-linked neurodegenerative disease in children. Bluebird Bio's Lenti-D is the only clinical GT candidate for ALD, and

Figure 10
Archetype 3: Noncompetitive, prevalence-driven opportunities

Market characteristics	Reasonable-size prevalent populations with less competition, typically in diseases that were difficult to treat	
Expected revenue curve	Larger initial bolus with more modest long-term potential	
Example indication	ALD, a rare neurodegenerative disease	
Example success factors, by function		
	Development	First launch may be critical, as indication may have a smaller patient population
	Patient services and medical	Identifying patients and driving adoption to deliver the maximal patient benefit, possibly with support or input from advocacy groups
	Commercial	Innovative payment mechanisms are important for sustainable, long-term success
Key strategic considerations		
	Patient reach	How quickly can patients be found? What are the unaddressed subpopulations? What life cycle management opportunities can be developed to better serve these subpopulations?
	Pricing	What pricing innovations are needed to increase commercial feasibility?

Source: L.E.K. research and analysis

non-GT development is limited to early experimental treatments. Lenti-D stands as the likely first to market with potential approval by 2021-22. Bluebird Bio will need to consider several factors as it advances Lenti-D. The decision to launch into this market has to be strategically considered, as the relatively small number of patients might be difficult to find. Stakeholder outreach may be important, particularly with respect to offering patients and caregivers education on ALD and treatment options. Bluebird Bio's patient advocacy team will also be an important factor in leading outreach efforts to drive penetration.[27]

The company also acknowledges challenges with pricing and reimbursement for a one-time, potentially curative treatment.[28] Focus on value-based pricing is being considered, as well as potentially pioneering risk-sharing models. Several approaches are under consideration, including the option to spread payments across up to five years, and payments may be required only if the treatment is effective. While the final price for the therapy is yet to be determined, Bluebird Bio will be assessing many factors to optimize the therapy's value for all stakeholders.

Archetype 4: Noncompetitive, incidence-driven opportunities

A final competitive situation exists in noncompetitive, incidence-driven indications (see Figure 11). These diseases may have high mortality rates that result in relatively low prevalent populations compared with incident populations, which can limit the size of any potential opportunity. Many biopharma companies may not consider opportunities in these segments, but those that seek GT launches here have several factors to evaluate. First, being first to launch may be a lower priority than treatment success, as the market is replenished by the larger incident population, which may allow trailing launches to still attain viable market share. Rapid patient identification will also be necessary due to untreated population life span. As the treatment may be lifesaving, the price might subsequently be high, which would necessitate pricing

Figure 11
Archetype 4: Noncompetitive, incidence-driven opportunities

Market characteristics	Smaller prevalent populations with high-need incident patients	
Expected revenue curve	Smaller initial bolus followed by more consistent revenues	
Example indication	MM, a rare X-linked neuromuscular disorder	
Example success factors, by function		
	Development	Treatment efficacy may be critical to differentiate from any incumbent treatments or to hinder new entrants
	Patient services and medical	Rapid patient identification and treatment will be important, as mortality may diminish treatable populations
	Commercial	Innovative payment mechanisms may be required to offset the potential challenge of high therapy costs
Key strategic considerations		
	Patient reach	What are the unaddressed subpopulations? What life cycle management opportunities can be developed to better serve these subpopulations?
	Pricing	What pricing innovations are needed to increase commercial feasibility?

Source: L.E.K. research and analysis

innovation, although the potential for being the sole most effective treatment might allow for a pricing premium. Differentiation with regard to efficacy and patient outreach might be among the primary considerations of a company working to offer a GT solution within the space.

Case study: Myotubular myopathy

There are few examples of such unique opportunities for GT, but MM, an X-linked neuromuscular disorder, may serve as an instance. Although few treatment options are available beyond symptom management or ventilation,[29] one GT is in clinical development.[30] Astellas/Audentes' AT-132 is in phase 2 trial investigation and would potentially be the first to launch in the market if its clinical hold is lifted and it progresses. The high level of unmet need with MM makes it an attractive indication, though likely large enough only for a sole competitor. Rapid treatment initiation will be an important consideration, as MM has a mortality rate of nearly 50% at 18 months of age. It may also be important to increase patient education around the potential for GT to treat the disease — to both improve adoption after launch and support clinical trial recruitment.

There are as of yet no apparent fast-follower or second-generation GTs in development in this indication, although should any emerge, differentiation will be a key initiative to consider. There may be improvements that other companies make on the efficacy of AT-132 or the treatment of MM subpopulations. That said, any of these companies will need to consider the position of the MM market after a potential AT-132 launch and whether the market would be able to sustain an additional competitor.

Although there are no disease-modifying therapies treating MM, companies seeking development in this or similar spaces will likely need to evaluate treatment efficacy, patient outreach and pricing as key considerations. Any companies considering launching after a first-to-market GT will also need to evaluate the updated standard of care, as the possibility of a small or greatly diminished market may not present an attractive entry point.

Implications for gene therapy companies

The GT market is still relatively undeveloped, with only four approved therapies. However, the stage is set for rapid growth over the next several years. GT biopharma companies have an unprecedented opportunity to provide value to patients. To do so, companies will need to evaluate key strategic factors at all stages of GT development, especially with regard to their timing of entry and market position, to develop an optimal go-to-market strategy. The four archetypes presented in this Special Report present a robust framework for GT companies to understand their competitive positioning within GT markets by indication and to provide a structured approach to address strategic development and commercial planning. At this critical juncture in the development of curative GTs, GT companies should consider these questions:

1. Which archetype are you?
2. What is your competitive positioning within that archetype (e.g., are you first, second, disease modifying)?
3. What are the key factors of success and challenges that need to be addressed?
4. What key strategic developmental, clinical, commercial and/or patient outreach considerations and solutions (e.g., innovative pricing and reimbursement models, targeted patient outreach, more durable treatment efficacy) are needed in order to overcome key challenges?

One key challenge is pricing. Significant pricing considerations will arise based on competition, and these will be set against a complicated backdrop of GT manufacturer/payer negotiations.

Currently, the pricing of GTs is a contentious topic, with arguments for both higher and lower pricing versus existing therapies. Companies may need to identify new pricing strategies for these GT treatments, possibly relying on third-party analyses to guide pricing, such as those done by the Institute for Clinical and Economic Review (ICER), and taking into account their curative nature. The aforementioned Zolgensma costs more than $2 million, within the value-based range estimated by ICER.[24,31] Additionally, the likely price of Valrox is forecasted to fall between $2 million and $3 million.[32] A one-time and potentially curative treatment such as this has advantage over repeatedly administered, noncurative therapies and may save money over time, but a large upfront payment is difficult for payers to consider.

There are other potential reimbursement models under examination. Payment may be reimbursed over an extended time period, as long as the treatment is effective. Spark and Harvard Pilgrim negotiated a system where payment for Luxturna would be delivered based on measured improvements at 30 and 90 days, as well as at 30 months.[33] Were the therapy to perform inadequately, Spark would provide a rebate to Harvard Pilgrim. Other patients may turn to cure "futures,"[34] paying a small premium payment to drug developers to support the development of a treatment that, if approved, would be sold to the owner of the cure future at a reasonable price covered by insurance. Companies may even decide to provide these therapies under outreach programs. Novartis has made Zolgensma available under its Managed Access Program, which works to support patients seeking treatment in countries where the therapy may not yet be approved.[35] Novartis is also planning to offer 100 doses of Zolgensma free of charge to eligible patients where Zolgensma is not yet approved.[36] However, this program may present challenges with how to fairly prioritize which patients will receive the limited doses, whether by disease severity, length of time before the patient's country approves the drug or other factors. Possible solutions to pricing and reimbursement challenges will require some innovation from biopharma companies or payers in order to optimally position companies to sustainably provide GT treatment.

And if this situation is not complicated enough, competition can create various alternative strategies. For example, should a biopharma player believe its therapy is more durable than the competition's, improved reimbursement-over-time options, if legally possible, may provide a benefit to stand out via lower upfront pricing. More efficacious therapies may similarly be able to negotiate for risk-sharing agreements based on the cost of future supportive care.

It is key for companies developing GTs to understand their likely market positioning, based on both the level of competition and likely patient dynamics in each applicable market. Each of these situations requires unique considerations, from strategic decisions surrounding pricing, as highlighted, to treatment launches and sequencing, life cycle management, and other considerations. Although the GT market is set to undergo numerous changes, we believe that companies can evolve to address the specific concerns of gene therapy development, ultimately producing innovative treatments that can provide cures for previously untreatable patients.

Endnotes

[1]Pharmaprojects. (April 1, 2020). Citeline Informa. Retrieved from the Citeline Informa Pharma Intelligence website: https://citeline.informa.com.

[2]Quinn, C., Young, C., Thomas, J., Trusheim, M. & Group, M. N. (2019). "Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System." *Value in Health*, 621-626.

[3]Gottlieb, S. (Jan. 15, 2019). Statement from FDA Commissioner Scott Gottlieb, M.D.

[4]Novartis. (Oct. 22, 2019). Media. Retrieved from the Novartis corporate website: https://www.novartis.com/sites/www.novartis.com/files/q3-2019-media-release-en.pdf.

[5]Novartis. (Jan. 29, 2020). Q4 2019 media release. Retrieved from the Novartis corporate website: https://www.novartis.com/sites/www.novartis.com/files/q4-2019-media-release-en.pdf.

[6]Novartis. (April 28, 2020). Media. Retrieved from the Novartis corporate website: https://www.novartis.com/sites/www.novartis.com/files/q1-2020-media-release-en.pdf.

[7]Neurocrine Biosciences. (Jan. 21, 2020). Media. Retrieved from the Neurocrine corporate website: https://www.neurocrine.com/pipeline/opicapone/parkinsons-disease/vy-aadc/.

[8]Adverum Biotechnologies. (Jan. 21, 2020). Science. Retrieved from the Adverum corporate website: https://adverum.com/pipeline/#wet-AMD.

[9]Novartis. (April 9, 2018). Media Relations. Retrieved from the Novartis corporate website: https://www.novartis.com/news/media-releases/novartis-enters-agreement-acquire-avexis-inc-usd-87-bn-transform-care-sma-and-expand-position-gene-therapy-and-neuroscience-leader.

[10]Roche. (Feb. 25, 2019). Media Relations. Retrieved from the Roche corporate website: https://www.roche.com/media/releases/med-cor-2019-02-25.htm.

[11]Astellas. (Dec. 3, 2019). Media Relations. Retrieved from the Astellas corporate website: https://www.astellas.com/jp/en/news/21636.

[12]Pfizer. (Aug. 1, 2016). Media Relations. Retrieved from the Pfizer corporate website: https://www.pfizer.com/news/press-release/press-release-detail/pfizer_aims_to_become_industry_leader_in_gene_therapy_with_aquisition_of_bamboo_therapeutics_inc.

[13]Pfizer. (May 10, 2017). Media Relations. Retrieved from the Pfizer corporate website: https://www.pfizer.com/news/press-release/press-release-detail/sangamo_therapeutics_and_pfizer_announce_collaboration_for_hemophilia_a_gene_therapy.

[14]Pfizer. (Nov. 7, 2017). Media. Retrieved from the Pfizer corporate website: https://www.pfizer.com/news/press-release/press-release-detail/spark_therapeutics_and_pfizer_amend_license_agreement_for_investigational_spk_9001_in_hemophilia_b.

[15]Roche. (Dec. 23, 2019). Media. Retrieved from the Roche corporate website: https://www.roche.com/media/releases/med-cor-2019-12-23.htm.

[16]Roche. (Oct. 4, 2018). Media. Retrieved from the Roche corporate website: https://www.roche.com/media/releases/med-cor-2018-10-04c.htm.

[17]Alnylam. (Jan. 24, 2020). Pipeline. Retrieved from the Alnylam corporate website: https://www.alnylam.com/alnylam-rnai-pipeline/.

[18]BioMarin. (August 19, 2020). Media. Retireved from BioMarin corporate website: https://investors.biomarin.com/2020-08-19-BioMarin-Receives-Complete-Response-Letter-CRL-from-FDA-for-Valoctocogene-Roxaparvovec-Gene-Therapy-for-Severe-Hemophilia-A

[19]Spark. (Jan. 21, 2020). Pipeline. Retrieved from the Spark corporate website: https://sparktx.com/scientific-platform-programs/.

[20]Sangamo. (Dec. 7, 2019). Media. Retrieved from the Sangamo corporate website: https://investor.sangamo.com/news-releases/news-release-details/sangamo-and-pfizer-announce-updated-phase-12-results-showing.

[21]ClinicalTrials.gov. (Jan. 7, 2020). Clinical Trials. Retrieved from ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT03588299.

[22]Takeda. (Oct. 31, 2019). Media. Retrieved from the Takeda corporate website: https://www.takeda.com/siteassets/system/what-we-do/research-and-development-rd-in-takeda/our-pipeline/pipeline_en_2019_q2.pdf.

[23]FDA. (Dec. 23, 2016). Access Data. Retrieved from the FDA website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf.

[24]ICER. (April 3, 2019). ICER Review. Retrieved from the ICER website: https://icer-review.org/wp-content/uploads/2019/04/ICER_SMA_RAAG_040319.pdf.

[25]Novartis. (May 24, 2019). Media. Retrieved from the Novartis corporate website: https://www.novartis.com/news/media-releases/avexis-announces-innovative-zolgensma-gene-therapy-access-programs-us-payers-and-families.

[26]Roche. (Jan. 23, 2020). Media. Retrieved from the Roche corporate website: https://www.roche.com/media/releases/med-cor-2020-01-23.htm.

[27]Bluebird Bio. (Jan. 8, 2020). Media. Retrieved from the Bluebird Bio corporate website: http://investor.bluebirdbio.com/static-files/942436fc-fc3a-4d9e-9429-7df393f6494c.

[28]Bluebird Bio. (Feb. 5, 2020). Patient Advocacy. Retrieved from the Bluebird Bio corporate website: https://www.bluebirdbio.com/patients-and-advocacy/patient-advocacy.

[29]National Organization for Rare Disorders (NORD). (Jan. 30, 2020). X-Linked Myotubular Myopathy. Retrieved from the Rare Disease Database: https://rarediseases.org/rare-diseases/x-linked-myotubular-myopathy/.

[30]Audentes. (Jan. 30, 2020). "Audentes is developing AT132 for the treatment of X-Linked Myotubular Myopathy." Retrieved from the Audentes corporate website: https://www.audentestx.com/x-linked-myotubular-myopathy/.

[31]ICER. (May 24, 2019). ICER Zolgensma Comments. Retrieved from the ICER website: https://icer-review.org/announcements/icer_comment_on_zolgensma_approval/.

[32]Hopkins, J. (Jan. 16, 2020). "BioMarin Explores Pricing Experimental Gene Therapy at $2 Million to $3 Million." Retrieved from the *Wall Street Journal* website: https://www.wsj.com/articles/biomarin-explores-pricing-experimental-gene-therapy-at-2-million-to-3-million-11579190318.

[33]Harvard Pilgrim. (Jan. 3, 2018). Harvard Pilgrim News Page. Retrieved from the Harvard Pilgrim corporate website: https://www.harvardpilgrim.org/public/news-detail?nt=HPH_News_C&nid=1471914707173.

[34]Ferrante-Schepis, M. (Dec. 14, 2018). "Cure 'futures' offer a way to pay for million-dollar medicines." Retrieved from Statnews.com: https://www.statnews.com/2018/12/14/cure-futures-offer-way-to-pay-for-million-dollar-medicines/.

[35]Novartis. (Jan. 28, 2020). Managed Access Program. Retrieved from the Novartis corporate website: https://www.novartis.com/our-focus/healthcare-professionals/managed-access-programs.

[36]Novartis. (Dec. 19, 2019). AVXS-101 Managed Access Program. Retrieved from the Novartis corporate website: https://www.novartis.com/news/avxs-101-managed-access-program.

[37]NORD. (March 12, 2020). Retinitis Pigmentosa. Retrieved from the Rare Disease Database: https://rarediseases.org/rare-diseases/retinitis-pigmentosa/.

[38]NORD. (March 12, 2020). Mucopolysaccharidosis Type III. Retrieved from the Rare Disease Database: https://rarediseases.org/rare-diseases/mucopolysaccharidosis-type-iii/.

[39]Bader et al. (April 2003). "X-Linked Retinitis Pigmentosa: RPGR Mutations in Most Families With Definite X Linkage and Clustering of Mutations in a Short Sequence Stretch of Exon ORF15." Retrieved from *Biochemistry and Molecular Biology*: https://iovs.arvojournals.org/article.aspx?articleid=2124197.

[40]Centers for Disease Control and Prevention (CDC). (March 2020). Hemophilia, Sickle Cell Disease and Muscular Dystrophy Data and Statistics. Retrieved from the CDC.

[41]Genetics Home Reference, U.S. National Library of Medicine. (March 2020). Leber Congenital Amaurosis. Retrieved from the U.S. National Library of Medicine.

[42]Conner et al. (Feb. 18, 2019). "An online survey on burden of illness among families with post-stem cell transplant mucopolysaccharidosis type I children in the United States." Retrieved from the *Orphanet Journal of Rare Diseases*: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6378738/.

Acknowledgments

The authors would like to acknowledge Thomas Pangia, Elizabeth Min, Susan Chen and Katherine Lee for their contributions.

About the Authors

Matt Mancuso

Senior Manager, Boston

Matt Mancuso is a Senior Manager in L.E.K. Consulting's Life Sciences practice. He has a focus on advanced modalities in life sciences and advises clients on a range of critical business issues, including long-term strategic planning, R&D portfolio management, trial planning, biological target identification, commercialization and transaction support, and growth strategy. Matt received a Ph.D. in Biomedical Engineering from Cornell University and a B.E. in Biomedical Engineering from Stony Brook University.

Peter Rosenorn

Managing Director, Boston

Peter Rosenorn is a Managing Director and Partner in L.E.K. Consulting's Life Sciences practice. He has a focus on growth strategy and organization and performance, and he advises clients on a range of critical business issues, including organizational scale-up and development, launch planning and commercialization, transaction support, forecasting and valuation, and post-merger integration. Peter received a Master of Science in International Marketing and Management from Copenhagen Business School.

Ricardo Brau

Managing Director, Boston

Ricardo Brau is a Managing Director and Partner, focusing on the biopharmaceutical and life sciences sector, and has experience across most therapeutic areas and industry segments, in both large and emerging biopharma companies. He advises clients on a range of critical issues, including corporate and business unit strategy, innovation, R&D portfolio management, and commercial planning. Ricardo is a winner of *The M&A Advisor* 2019 Emerging Leaders Award.