



FROM LAB TO MARKET-PLACE, SUCCEEDING WITH GENE THERAPIES

By Alexandra Teixeira, John Wu, Meghan Luchi, Brendan Smith, and Michael Choy

FOR BIOPHARMA COMPANIES MOVING into gene therapy, the scientific hurdles are only the beginning. Challenges related to pipeline development, platform selection, manufacturing, and reimbursement will be barriers as big as or bigger than biology. Even the largest and most sophisticated companies should undertake a thorough assessment of the strategies and investments that will be necessary before they enter what promises to be a very different type of health care marketplace. Based on our work with leading pharma and biotech companies, this article offers reflections on navigating the emerging gene therapy landscape.

After early gene therapy setbacks, including the death of Jesse Gelsinger in 1999 from an experimental treatment, recent advances are generating substantial excitement and activity. The reasons are both clinical and commercial. Gene therapy is delivering a step change in patient outcomes and, for some, the difference between life and death. (See the sidebar “Defining Gene Therapy.”) There is also

significant commercial potential for pharma companies, biotech firms, and contract service providers. Recent approvals and new treatment launches, including those of Luxturna for inherited retinal disease (Spark Therapeutics, US approval 2018), Zolgensma for spinal muscular atrophy (Novartis, US approval 2019), and Zynteglo for transfusion-dependent beta-thalassemia (Bluebird Bio, Europe approval 2019), have demonstrated that the theoretical can become actual. With many other treatments in clinical trials, including 75 new trials started in 2018, the FDA says it expects to approve new gene and cell therapy products at a rate of 10 to 20 per year by 2025. (See Exhibit 1 and the sidebar “Many Exciting New Therapies Are in the Home Stretch.”)

Multiple factors combine to distinguish gene therapy from more conventional treatments. One is the nature of the conditions being treated: they are typically rare diseases that are debilitating and often terminal, and many have no other effective treatments. Gene therapies offer the

DEFINING GENE THERAPY

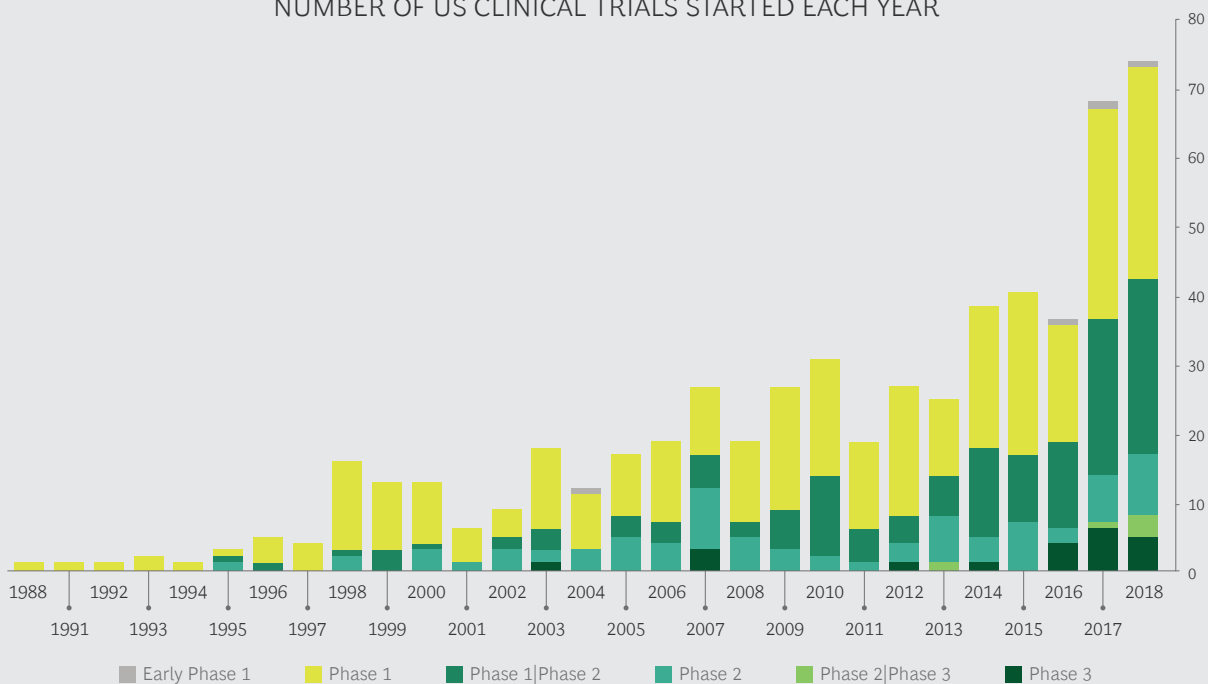
Gene therapy is an umbrella term that encompasses many different treatments that can be subcategorized by type of therapeutic strategy and/or delivery mechanism:

- Gene addition:** The treatment vector enables a cell to express a new gene. Transduction can be in vivo or ex vivo. Examples include adeno-associated virus (AAV) and lentivirus. Spark Therapeutics' Luxturna, the first in vivo gene therapy approved by the FDA, falls into this category.
- Gene editing:** Cellular DNA is modified to repair or delete a gene. The CRISPR/Cas9 sequence is an example. Treatments being developed by Sangamo, Editas Medicine, and Beam Therapeutics are in this category.
- Gene-modified immune cell therapy:** Genetic manipulation changes immune cell function. Examples include CAR-T cell therapy (such as Gilead's Yescarta and Novartis's Kymriah) and tumor-infiltrating lymphocytes.
- Gene expression control:** Manipulation of the translation of genes—through use of small interfering RNA, for example, as Alnylam is doing with Onpatro.

Gene therapy can be delivered via viral or nonviral delivery methods. The most common viral methods are AAVs and lentivirus. Nonviral methods include lipid nanoparticles, gene gun, and exosomes.

EXHIBIT 1 | Gene Therapy Development Is Exploding

NUMBER OF US CLINICAL TRIALS STARTED EACH YEAR



Source: Data from clinicaltrials.gov (10/14/2019).

MANY EXCITING NEW THERAPIES ARE IN THE HOME STRETCH

The pace of gene therapy development is accelerating. Among the many companies with new treatments that are already approved or in late-stage clinical trials are the following:

- **AveXis/Novartis**—Spinal muscular atrophy (approved 2019)
- **Biomarin**—Hemophilia A
- **Bluebird Bio**—CALD, TDT (approved 2019)
- **GenSight**—Leber hereditary optic neuropathy
- **Helixmith**—Foot ulcer, diabetic neuropathy
- **Idorsia**—Fabry disease
- **Lysogene/Sarepta**—Mucopolysaccharidosis type IIIA
- **Nightstar/Biogen**—Choroideremia
- **Pfizer**—Hemophilia B
- **Sarepta**—Duchenne muscular dystrophy
- **Spark Therapeutics**—Retinal dystrophy (approved 2018)
- **UniQure**—Hemophilia B

potential for cures by delivering a functional gene to a cell, overcoming the underlying genetic defect. A second key difference is an accelerated product life cycle. Once the initial universe of patients suffering from a particular condition is treated, the market can shrink quickly, putting a high premium on speed and creativity in clinical and regulatory approaches and on replenishment of the pipeline. (See Exhibit 2.) Third, manufacturing technologies are immature. Developers of new therapies must build manufacturing capabilities and establish a robust supply chain before coming to market. Fourth, sustainable reimbursement models are challenging to establish for treatments with very high upfront costs when life-saving or life-changing long-term benefits have yet to be proven. (As the \$2.1 million price tag of Zolgensma shows, upfront costs can run well into the millions of dollars.)

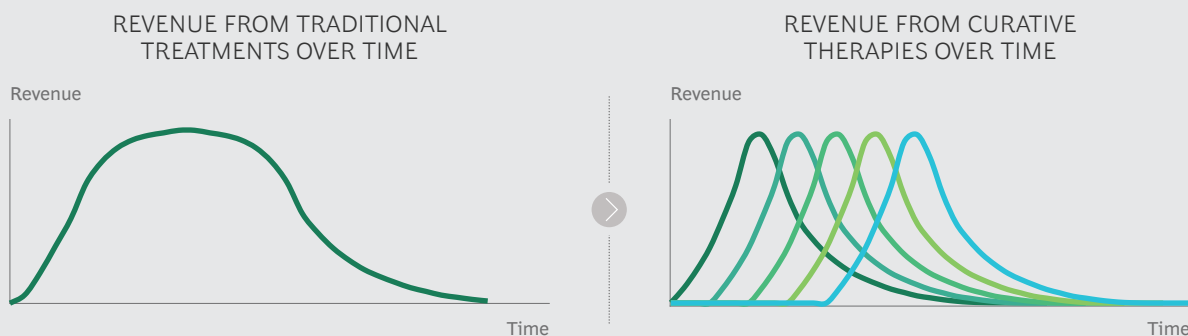
Companies that want to play in the first wave of gene therapies must move decisively in four areas, which we explore in the balance of this article. (See Exhibit 3.)

Act Fast and Develop a Sustainable Pipeline

The combination of the small number of patients with any of these conditions and the potentially curative impact of gene therapies creates a winner-take-all dynamic in many therapeutic areas (TAs). This has several ramifications. Companies that want to capture value will need to develop a sustainable gene therapy business model and the ability to move fast to market in their target TAs. They need to have assets, R&D, and manufacturing and commercial processes ready to support the speedy development and approval of new therapies, which they will very likely want to launch in rapid succession to ensure sustained revenues.

Companies need to invest in delivery platforms that have the potential to supply a stream of assets that require only minimal modification. They cannot rely on internal product development alone; they will need to draw on work underway in academia, biotech, and other areas. Notably, 58 of 120 registered gene therapy Phase 1 trials have an academic sponsor.

EXHIBIT 2 | Curative Therapies Have Short Life Cycles and Require Continuous Business Development



Source: BCG analysis.

The field will be competitive, and recent business development and licensing trends indicate that companies will likely need to be prepared to spend big for innovative assets. Gene therapy has become a hot business area as companies scramble to access IP across a broad range of therapies and enabling technologies. For example, Novartis acquired AveXis for \$8.7 billion in 2018, Roche is in the process of acquiring Spark Therapeutics for \$4.3 billion, and Pfizer paid \$645 million for Bamboo in 2016. Buyers are also looking to invest earlier, which means taking on higher risk and building the business development muscle necessary to support early-stage evaluations and explore alternative partnership models. Maintaining a consistent revenue stream will require a sustainable pipeline of new treatments.

Focus on Building Talent, Expertise, and Experience

Because the gene therapy field is still an emerging area, acquiring talent, expertise, and experience quickly is essential. Early leaders will achieve scale value by focusing their efforts on building a platform that will support a portfolio of treatments, as opposed to spreading R&D across a broad range of vector (delivery) technologies. Each vector requires significant investment in infrastructure and the capabilities needed to bring new therapies to market—advantages in one vector do not necessarily transfer to another. To enable speedy entry into clinical testing, companies should in-

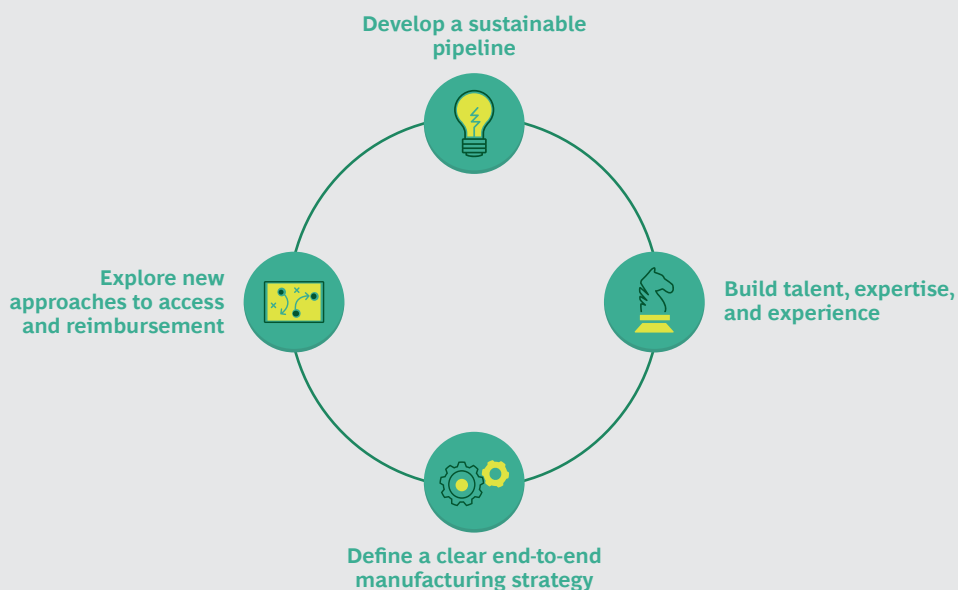
vest in foundational capabilities in genetics, translational medicine, and immunology to support rapid characterization of the immunogenic, mutagenic, pharmacokinetic, and pharmacodynamic properties of their therapy candidates.

Focusing in this way could enable companies to use a plug-and-play approach for their pipeline. Such platforms allow for better management of costs, consistency in processes, and timeline efficiency. For example, Pfizer has built out an adeno-associated virus (AAV) platform with a combination of acquisitions (Bamboo and Vivet) and strategic licensing partnerships (with Spark Therapeutics and Sangamo), while making substantial internal investments (more than \$500 million in manufacturing). Sarepta has built its pipeline by licensing a series of assets from academic institutions and smaller biotech firms (including Nationwide Children's Hospital, Myonex, Lysogene, and Lacerta), while developing an external network for manufacturing with companies such as Brammer, Paragon, and Aldevron.

Define a Clear End-to-End Manufacturing Strategy

It's not enough to be first to approval. Companies must be able to produce new therapies and deliver them to patients, and some have already experienced challenges. For example, Bluebird Bio secured approval of its beta-thalassemia therapy in Europe, but manufacturing issues are delaying its

EXHIBIT 3 | Four Actions for Success in Gene Therapy



Source: BCG analysis.

launch. Adding pressure are the often short development timelines for rare-disease treatments. The FDA has provided guidance that simplifies several aspects of gene therapy development for rare diseases, and many companies are exploring innovative clinical designs and regulatory strategies. But the shortened timelines mean companies have even less time to line up manufacturing capacity.

The immature manufacturing sector for gene therapy will force companies to make some bets to circumvent current capacity constraints and meet demanding timelines. The average time to secure capacity for plasmid DNA production, for example, is 6 to 9 months. It can take 18 to 24 months to build up internal capabilities. In addition, the manufacturing processes are still developing and can involve technology that has not been commercially proven. In this regard, gene therapy currently bears some similarities to the early days of biologics, when the tensions between capacity and yield ultimately resulted in a glut of physical infrastructure. Leading-edge companies walk a tricky line between making major investments and risking write-offs if manufacturing yields dramati-

cally improve or their anticipated pipelines do not materialize.

Explore New Approaches to Access and Reimbursement

The high cost of these transformative therapies puts new pressure on payers, and as more treatments come to market, the financial burden will increase exponentially. The current reimbursement model—paying for treatments as they are administered—breaks down when the treatments themselves are few or of limited duration but the benefits last a lifetime. There are also significant implications for dosing, packaging, and distribution depending on the reimbursement model(s) chosen, and there needs to be close coordination among the commercial, regulatory, manufacturing, and supply chain functions beginning early in the development process.

The pharma industry needs to present a clear new value proposition to payers, and that requires new data and new reimbursement models.

Data. In this nascent field, collecting robust data on such factors as outcomes,

efficacy, and durability will be critical to all participants. Pharma companies need to integrate data generation and collection into both their early clinical development activities and their postmarketing and real-world evidence strategies. The latter become increasingly important as clinical development timelines shorten. Pharma companies and payers need clarity and alignment on the definitions of outcomes, especially for outcomes-based contracts. Profitability will depend in part on the ability to identify the full universe of people with a particular condition and on supporting the case for a therapy's transformative benefits for patients, payers, and policymakers.

Reimbursement Models. Several alternative coverage and payment models have been proposed to address the high price of specialized treatments such as gene therapies. These include population coverage (as opposed to individual coverage) and outcomes-based contracts. Cigna recently announced a per-member, per-month, "cost recovery" model for two gene therapies, Zolgensma and Luxturna.

The need for new models is clear, but implementation faces high hurdles in systems that were built for very different types of coverage and reimbursement. Portability of coverage, for example, is a big issue in markets where private coverage dominates. Pharma needs to lead the search for new ways to pay for these treatments, and it needs to be flexible in how it derives its revenue and profit streams.

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Organizing for Success

The recommendations presented here are imperatives for the gene therapy market. How each company implements them will depend on its circumstances and on the decisions it makes in the pipeline, expertise, manufacturing, and access and reimbursement areas. Given the technical complexity of gene therapy, the need for speed, and the differences between gene therapy and traditional treatments with respect to development and manufacturing, we believe that most large companies will want to run gene therapy as a separate business unit that brings together all the capabilities needed. Containing specialized regulatory, commercial, manufacturing, and clinical expertise, the unit would handle everything from preclinical phase through commercialization. It will likely need its own KPIs, metrics for success, and incentive programs. A separate organization may be the only way for large pharma companies to achieve the focus and the concentration of expertise necessary to bring gene therapies to profitable business fruition.

THERE IS LITTLE doubt that gene therapy is a clinical and commercial reality. This is an enormous scientific accomplishment and a commercial starting point. Companies that want to bring these once theoretical treatments to market must approach the task with creativity, flexibility, and an appetite for uncharted territory. The scientific foundation is in place, but there is still much to do to deliver the full benefit of gene therapy to patients.

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