The Past, Present, and (Near) Future of Gene Therapy and Gene Editing

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Our analysis of a decade of data on clinical trials and venture capital investments suggests that that gene therapy and gene editing will have profound effects on the health-care system—and that these effects are only just beginning.

Julia Pian, MD, MBA
Harvard Business School, Boston, MA
Harvard Medical School, Boston, MA
jpian@mba2020.hbs.edu

Amitabh Chandra, PhD
Harvard Business School, Boston, MA
Harvard Kennedy School, Cambridge, MA
amitabh_chandra@harvard.edu

Ariel Dora Stern, PhD
Harvard Business School, Boston, MA
Harvard-MIT Center for Regulatory Science, Boston, MA
astern@hbs.edu

Summary

Emerging gene therapy and gene-editing technologies will have a growing impact on patient lives and health-care delivery. We analyzed a decade of data on clinical trails and venture capital investments to understand the likely trajectory of genetically focused therapies in the years ahead. The number of clinical trials and venture capital deals increased substantially from 2006-2017. We observed particularly notable growth in both industry-sponsored trials and trials involving specialty fields of drug development, including oncology, neurology, hematology, ophthalmology, and neurology. As the number of gene-therapy and gene-editing technologies continues to grow, we expect that such therapies will have a significant and heterogeneous impact on health-care delivery, including a shifting of resources from chronic disease management to more intense acute episodic care, an increase in the complexity of required intellectual property and manufacturing know-how, and the potential expansion of biopharmaceutical companies into service-based business models.

An Introduction to Gene Therapy and Gene Editing

In recent years, gene therapy and gene editing have gained traction in the scientific, medical, and investing communities. With 181 gene therapies in clinical development in 2017 alone, the global gene-therapy market size is expected to reach $5.55 billion by the year 2026.[1] These technologies—and efforts made to facilitate access for patients in need[2]—have often found their way into media headlines, primarily because of high sticker prices.[3,4,5]

Unlike treatments involving a pill or a simple infusion, gene therapy often requires a complex patient journey. For instance, Zynteglo, a newly approved gene therapy for beta thalassemia, requires at least two hospitalizations for administration and likely many more follow-up encounters with health-care providers.[6] During treatment, patients undergo hematopoietic stem cell mobilization (treatment with factors that stimulate the release of undifferentiated stem cells from the bone marrow into the blood),

myeloablative conditioning with chemotherapy (wiping out the patient's own bone marrow to make room for the edited cells), and infusion of the drug-product-treated stem cells, followed by a monitoring period for the infused stem cells to engraft in order to fully realize the value presented by the therapy.

Like other new biotechnologies, gene therapies are resource-intensive to develop—but, in most cases, they have the added distinction of also being more resource-intensive to deliver. Yet despite the complexities of delivery, such therapies are ushering in possibilities of cures for many patients who were previously destined to be chronically ill and intensive users of health-care resources. For example, in the absence of gene therapy, patients with beta thalassemia typically receive lifelong blood transfusions and iron chelation therapy (given to decrease the overload of iron in the blood resulting from blood transfusions).

To understand trends in the development of new genetically focused therapies as well as how they are likely to impact health-care delivery in different medical specialties, we investigated the pipeline of clinical research on gene therapies in recent years. The trends observed in the number and phases of clinical trials are predictors of the number of new therapies coming to market in the near future; these trends have implications for clinicians (who are curious about what types of new products will be coming to market), health-care systems (which will need to prepare to deliver new therapies as they are approved and launched), and payers (who will have to absorb the cost of these therapies or devise ways to slow their adoption).

As this new era of therapeutics dawns, a clear understanding of the health-care-delivery implications of these therapies and a more complete sense of how they might be paid for will help shape their future.

Clinical Trial and Venture Capital Data

Clinical trial data were extracted from ClinicalTrials.gov.[7] Recent data from ClinicalTrials.gov are expected to be largely comprehensive because, since 2007, all responsible parties investigating new therapeutics have been required to register their clinical trials in order to pursue regulatory approval from the FDA[8]. Venture capital (VC) data were extracted from Preqin, a detailed database for investors and researchers (see Appendix).

Upward Trends in Trials and Deals

We analyzed a total of 266 clinical trials along with 53 VC investment deals related to genetically focused therapies and therapeutics companies. The total number of gene therapy trials and the subset of those with industry sponsors grew over time; this growth was mirrored by growth in the number of related VC deals (Fig. 1).

Fig. 1
Graph illustrating the numbers of clinical trials and VC deals from 2008-2017 by year of trial launch and deal close. The numbers of clinical trials are broken down according to industry involvement or no industry involvement; trials were categorized as having industry involvement if they included the tag "industry" among the list of possible sponsors in the "funded by" category on ClinicalTrials.gov.
Source: The Authors.

We also noted that innovation in gene therapy has to a large extent blossomed in the same specialty fields as general therapeutic development, with most new product development occurring in areas such

as oncology, neurology, hematology, and neurology. However, a large number of ophthalmology trials have also launched, likely because of the ease of therapeutic delivery to the eye and relative immune privilege of ophthalmic interventions (Fig. 2).

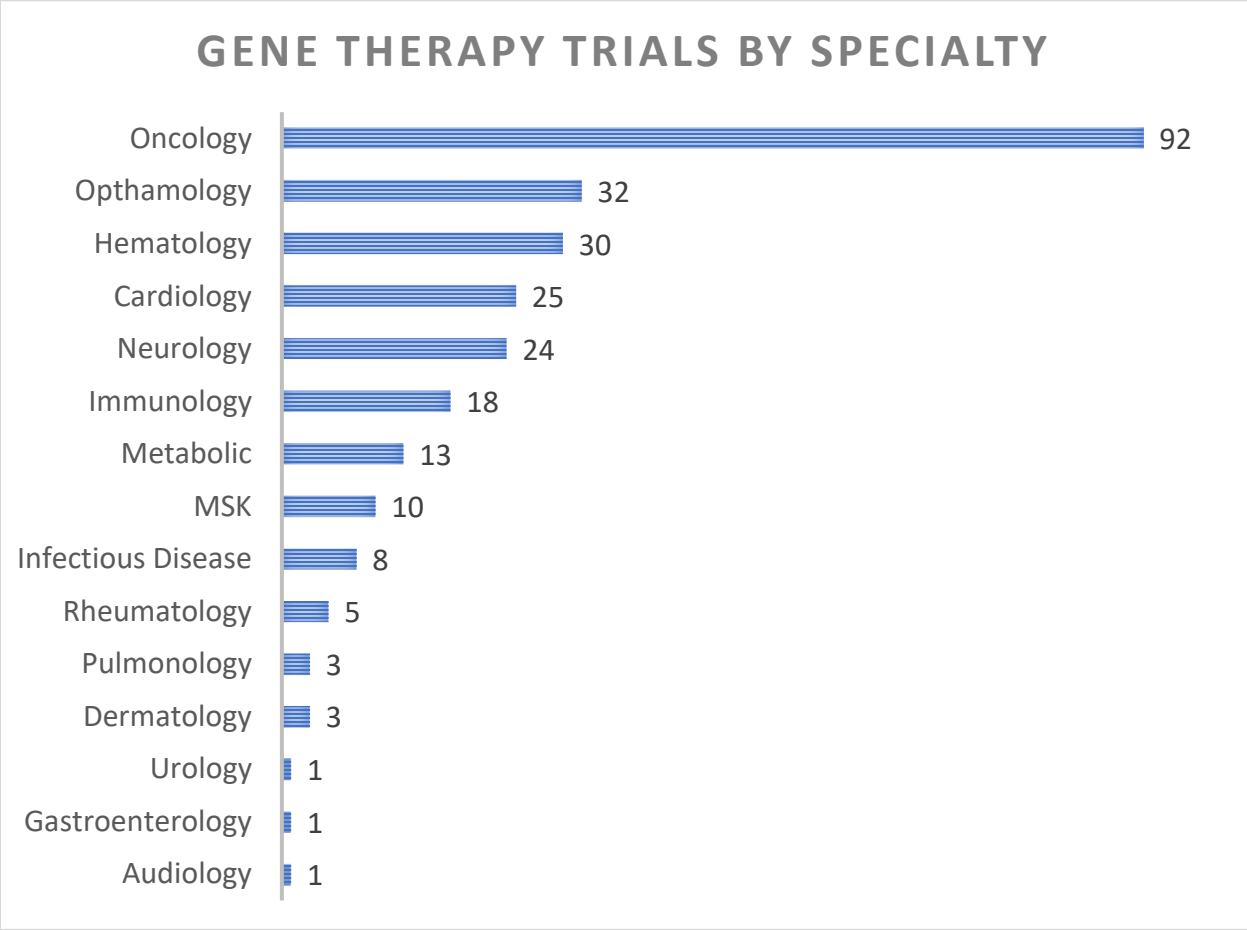

Fig. 2
Distribution of active gene therapy trials by medical specialty; medical specialty was manually coded. MSK = musculoskeletal.
Source: The Authors.

Over our decade of observation, the vast majority of the total activity in gene therapy trials (77% of the sample) was seen in early Phase-1 or Phase-1/2 trials. Later-stage (Phase2/3 or Phase-3) trial sponsorship (8%) was dominated by industry (Fig. 3).

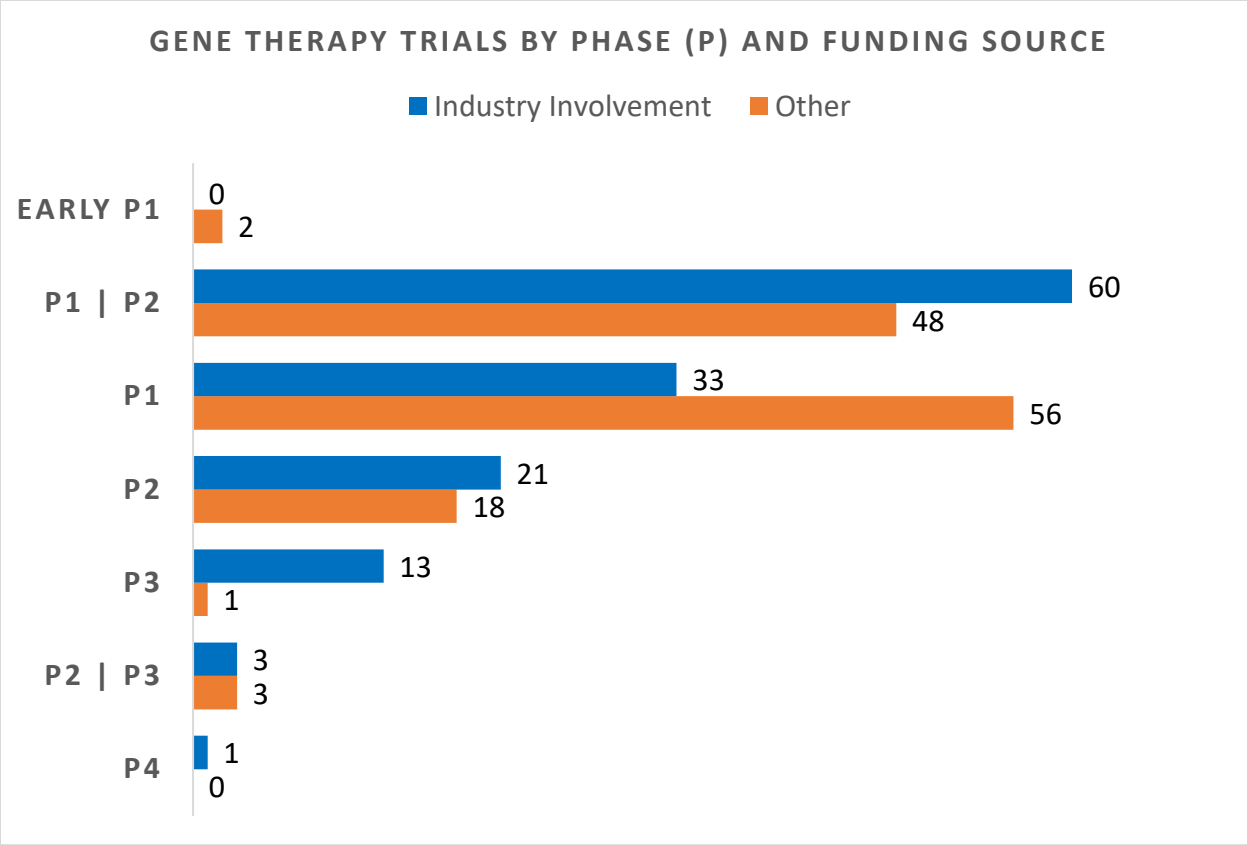

Fig. 3
Distribution of clinical trials by phase and funding source. Seven sample trials were not included in this figure as they were designated "N/A" in the "Phase" category and could therefore not be classified. *Source: The Authors.*

The Impact of Gene Therapy and Gene Editing Is Only Beginning

The collected data paint an early but clear picture of how the gene therapy and gene editing field is evolving and growing, with ascendancy seen among a subset of medical specialties. The number of trials emerging from academic centers and hospitals seems to be remaining steady, even as industry's role in clinical research expands. In addition, the preponderance of early Phase-1 or Phase-1/2 trials suggests that many genetically focused therapies are still nascent. Furthermore, because therapeutic development has focused on many rare diseases, relatively rapid regulatory approval may be possible despite testing in a relatively small number of patients because of high unmet medical need and the presence of predictive biomarkers (often genomic) that permit trials to be enriched. These features are also likely to facilitate the use of expedited regulatory review programs such as the FDA's *Accelerated Approval* pathway and the *Breakthrough Therapy* and *Priority Review* designations.

Importantly, the implications of recent developments in genetically focused therapy for different fields of medicine will be heterogenous. While dozens of trials have been launched in oncology, hematology, and ophthalmology, a negligible amount of clinical research has been seen in other large areas of medicine such as rheumatology and pulmonology. The different pace of development (and, thus, anticipated product launch) across specialties will lead to large differences in the intensity of genetically

focused care. For example, as close-to-curative options emerge in hematology, ophthalmology, and immunology, these specialties will see decreases in the medium and long-term frequency of acute hospitalizations, clinic visits, and administrative resources required in those areas. These therapies could have profound effects on the utilization and allocation of hospital departmental resources, including physicians and staff as well as equipment and other physical capital.

How Do We Pay for Life-Changing Therapies?

Prices are likely to remain a headline issue in the years ahead. Some of the newest therapies have garnered attention in the press because of sticker shock.[3] While a nuanced discussion of therapeutic pricing is beyond the scope of this article, it is important to recognize that therapies for medicines that target smaller diseases, like many of the gene therapies studied here, command high prices for three reasons. First, the presence of genetic biomarkers means that manufactures can engage in price-discrimination by using "indication based pricing."[19] Second, the smaller the market, the higher the ex ante prices required to induce innovation.[20] Finally, high prices are a result of a high willingness to pay for therapies for some diseases, such as cancers and rare genetic diseases.

Critics argue that high prices are unfair and unethical, given that, in many cases, taxpayer money has funded the basic science and some of the clinical research that led to these novel gene therapies (as seen in Figs. 1 and 3). Absent a contract whereby the public sector requires a price concession as a result of these subsidies, it is not likely that prices for taxpayer-subsidized drugs will be lower. Moreover, these price concessions will lower the financial incentives for private entities to make investments. As more data emerge on both the prices and the effectiveness of gene therapies, health economists will increasingly be able to identify where such therapies create value over the life-cycle of the disease.

Regardless of cost effectiveness, high prices drive innovation in areas in which the willingness to pay is high and in which payers have a hard time refusing coverage.[9] Even if prices are high, the set of patients who currently benefit from early gene therapies focused on rare disease is expected to be extremely small, so the budget impact of these therapies will be small. As the therapeutic targets of gene therapies expand beyond rare disease, prices may drop with manufacturing efficiencies, more competition, and lower willingness to pay. In these cases, the impact of each individual therapy on medium-term health-care spending will be smaller. However, some genetic therapies require complementary health-care spending. One notable example is the cost associated with hospitalization for cytokine release syndrome, a side-effect associated with chimeric antigen receptor T-cells (CAR-Ts). Uncertainty about these complementary costs spill over onto payers, so a bundled-payment model that accounts for the total cost of care (including probability-weighted cost of care for side effects) could be well suited for such a context. Another option is for manufacturers to develop companion diagnostics and/or therapies that do not require complementary inputs, which would allow them to capture more of the value of their innovations.

In the long term, the price trajectory of genetically focused therapies will depend on how much competition emerges for these treatments and the extent to which manufacturing processes can be streamlined. These processes also rely on intellectual property, so such streamlining may not easily diffuse across manufacturers, thereby creating strong economies of scale for larger companies to enter. Unlike a single small-molecule patent, developing a gene therapy typically requires access to many pieces of intellectual property through ownership or licensing. For example, uniQure, a company that is developing adeno-associated virus (AAV) gene therapy for hemophilia and Huntington disease, provides a partial list of the patents associated with their development programs, including those associated with

the modified protein they aim to express, specifically designed sequences, AAV vectors, manufacturing methods, and purification optimization procedures, among others.[10,11]

Gene Therapy's Mark on Industry

As companies take gene therapies through the FDA approval process, they will accumulate valuable regulatory experience, which may lead to a competitive advantage in expanding to new products and indications compared with less-experienced start-ups. In addition, because of the complexity of both the drug approval process and manufacturing, larger biopharmaceutical firms have invested in their own gene therapy units—both through internal investment in research and development as well as through acquisitions of smaller companies.[12,13,14] As a result, the average size of companies that are developing gene therapy assets may grow over time to help absorb the cost and complexity of intellectual property and operational inputs. As larger biotech and pharmaceutical firms move into the space, we may see an evolution in disease areas targeted by gene therapy (for example, through less focus on rare diseases and more focus on larger therapeutic markets)[15,16] and parallel increases in manufacturing and commercialization capacity.

Finally, biopharmaceutical manufacturers may look to develop new service-based business models or delivery mechanisms for "high-touch" treatments such as genetically focused therapies whose manufacturing facilities may be extremely localized. For example, a recent ruling by the United States Department of Health and Human Services Office of the Inspector General would allow pharmaceutical manufacturers to cover treatment-related travel costs for patients receiving personalized medicines under certain conditions.[17] These advancements not only will require rethinking payment models but also will fundamentally change the role that biotech and pharmaceutical companies play in care delivery and reimbursement.[18]

Gene therapy will transform care delivery

Gene therapy continues to have an increasing footprint on both clinical trials and venture capital investment in biotechnology. However, the impacts of gene therapy on the world are just beginning, from changing the landscape of health-care spending in various specialties to remodeling the way in which care for chronic illnesses is received. Ultimately, gene therapy and gene editing will be an incredible force for bettering patient's and family's lives.

Disclosures
None of the authors have any disclosures related to this manuscript.

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Appendix: Data Collection

ClinicalTrails.gov Data

We studied clinical trial data extracted from ClinicalTrials.gov by searching the intervention/treatment field for *gene therapy*, *gene transfer*, and *gene editing* with the following filters: first, we limited *Trial Status* to those trials that were "Recruiting; Active, Not Recruiting; Completed; Enrolling by invitation; Suspended; Terminated" in order to capture only the set of trials that had actually begun. Second, we limited the *Study Type* to only "Interventional" trials. "Observational" trials were not included because we did not want to include follow-up studies after trial participants had received treatment. We dropped duplicate trials—those that came up more than once in the 3 intervention search terms. On the basis of manual inspection, we then removed trials that were not gene therapy trials and trials that began prior to 2008 and after 2017, allowing us to focus on trials for which clinical trial registration is likely to have been both comprehensive and completed by the time of data collection (February 6, 2020). Appendix Figure 1 presents detail on how these steps were applied to arrive at a final sample of 266 relevant trials.

Appendix Fig 1.
Clinical trial flow.
Source: The Authors.

Venture Capital Data

Venture capital (VC) data were extracted from Preqin, a detailed database for investors and researchers. These data are collected through relationships with industry professionals, detailed monitoring of public regulatory filings, and other news sources such as press releases. We screened the database for all VC investments within the "healthcare" category over the decade 2008-2017 (inclusive). Within the Preqin database, "Genetics and Gene Therapy" is included as a predefined subcategory of "healthcare" investments. We collected data for all VC investments within this subcategory and private equity transactions with a "gene therapy" flag. This search identified a total of 53 investment deals in relevant companies over our period of study.