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Gene therapy coming of age: Opportunities and challenges to getting ahead

Amid breakthroughs in gene editing, the pharma industry must recalibrate its development and reimbursement model for therapies that go beyond the traditional approach to disease treatment.

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The completion of the first draft of the human genome in 2001 was supposed to kick off an era of personalized medicine and curative gene therapies.[1] Only in the past few years has that promise started to become reality: several RNA- and DNA-based therapies are now on market, and the first curative gene therapy, Luxturna, was approved in 2018. These successes were largely due to a better clinical and scientific understanding of safety profiles as well as a refined manufacturing process that met the consistency and quality standards required for clinical scale. The bevy of new gene therapies in the development pipeline has the potential to transform care across several therapeutic areas. However, it also creates new challenges for key stakeholders—including pharma companies, regulatory agencies, providers and payers—in how to recalibrate the pharma development and reimbursement model for therapies that go beyond our traditional approach to treating disease.

Overview of the market

The first set of promising gene therapies were brought to a halt after the 1999 death of Jesse Gelsinger from an immune reaction to the vector transporting a gene therapy for his metabolic disorder, and the development of leukemia by multiple patients—including one who died—in trials that ran between 1999 and 2002 for X-linked severe combined immunodeficiency (SCID-X).[2] In the years since, better clinical and scientific understanding of the safety risks have enabled the first wave of clinical success. This has included a better understanding of immunogenicity and integration patterns of viral vectors as well as improved technology and modified delivery mechanisms. Manufacturing improvements have included new chemistry, manufacturing, and controls regulations and improved accuracy of oligo synthesis.

More than 150 investigational new drugs applications were filed for gene therapy in 2018 alone.[3] With this in mind, we expect this market to grow significantly, with ten to 20 cell and gene therapy approvals per year over the next five years.[4] This growth is set to come from a wide range of modalities (Exhibit 1), from ASOs and RNAi[5]—Spinraza and Onpattro being the first two therapies approved using this modality to potentially curative modalities deploying AAV[6] and lentivirus therapies, such as Luxturna and Zynteglo. CRISPR (clustered regularly interspaced short palindromic repeats) gene editing–based therapeutics present a long-term growth opportunity, generating significant excitement and investment in the technology (more than $600 million invested in CRISPR start-ups by 2017 and the first in human trials expected to kick off in 2019),[7] however they are unlikely to have significant clinical impact before 2025.

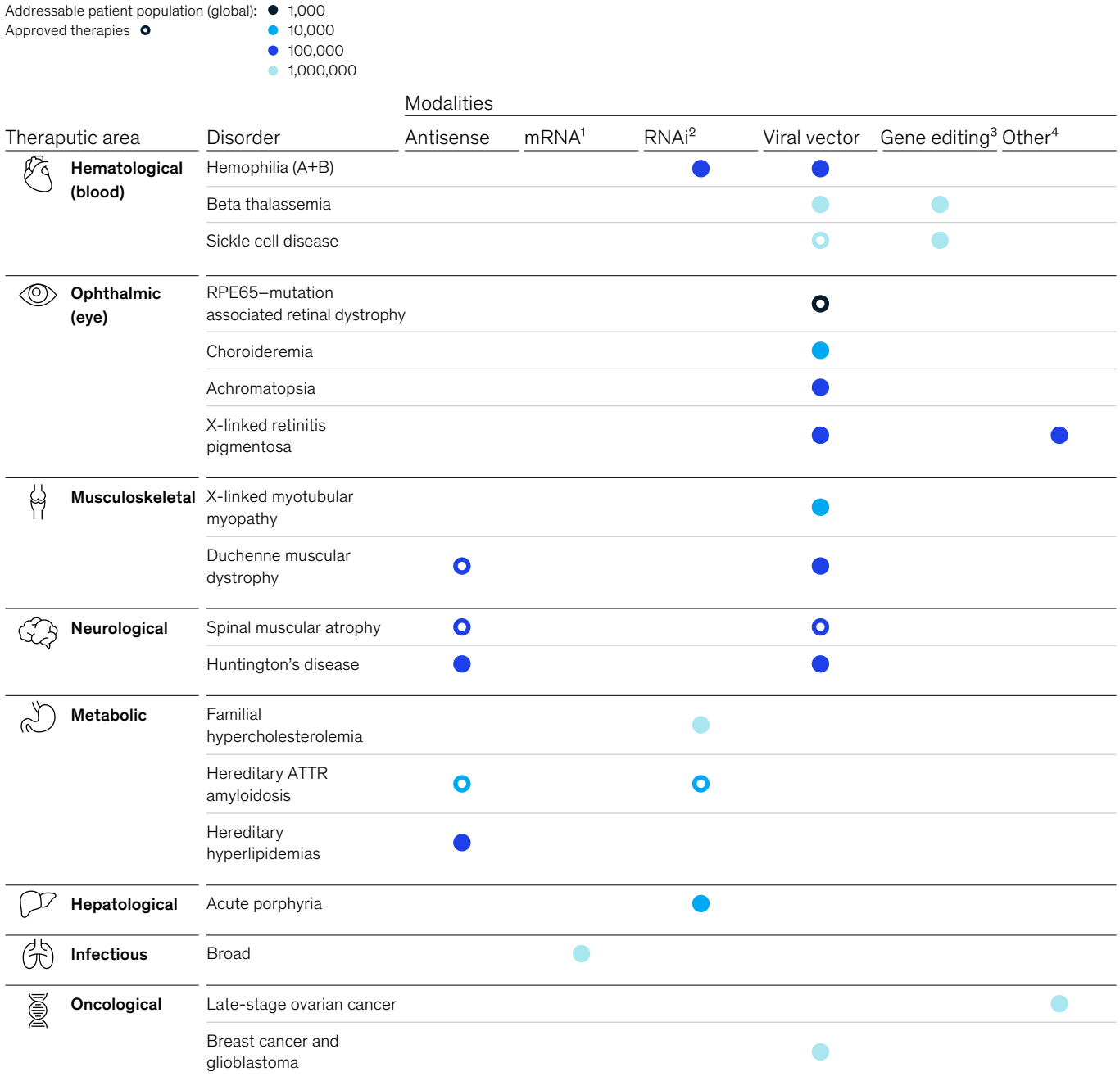
As of 2019, much of the focus in development has been on monogenic rare diseases; all currently approved therapeutics fall into this category (Exhibit 2). Rare diseases tend to have clear genomic targets as well as high unmet need in small patient populations. These patients have generally been underserved by other, more traditional, therapeutic modalities (including monoclonal antibodies)—making them ideal targets for gene therapies.

Furthermore, this focus on high unmet need in smaller, underserved populations has enabled faster approval by regulatory authorities than diseases that impact larger patient populations. Most gene therapies have come to market under an accelerated regulatory review pathway (for example, a regenerative medicine advanced therapy or breakthrough designation by the FDA), which expedites the approval process. The importance of this accelerated process was emphasized in a May 2018 speech by then–FDA

[1] International Human Genome Consortium, "Initial sequencing and analysis of the human genome," *Nature*, February 2001, Volume 409, pp. 860–921.
[2] For more, see Barbara Sibbald, "Death but one unintended consequence of gene-therapy trial," *Canadian Medical Association journal*, May 2001, Volume 164, Number 11, p. 1612, ncbi.nlm.nih.gov.
[3] Zachary Brennan, "Two gene therapy approvals headline CBER's FY 2018 report," *Endpoints News*, April 18, 2019, endpts.com.
[4] Scott Gottlieb, "Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies," Food and Drug Administration, press release, January 15, 2019, fda.gov.
[5] Antisense oligonucleotides; RNA (ribonucleic acid) interference.
[6] Adeno-associated virus.
[7] For more, see Katelyn Brinegar et al., "The commercialization of genome-editing technologies," *Critical Reviews in Biotechnology*, January 2017, Volume 37, Number 7, pp. 924–32, dx.doi.org/10.1080/07388551.2016.1271768.

Exhibit 1

The gene therapy market is set to expand across modalities and theraputic areas.



[1] Messenger RNA.
[2] RNA interference.
[3] Eg, CRISPR, ZFN.
[4] Eg, plasmids.

Exhibit 2

The current industry-wide gene therapy pipeline can be organized by stage and therapeutic area.

Gene therapy (in vivo),
number of assets

		RNA-directed therapies	DNA-directed therapies	mAbs[3]	**Total by stage**
Phase 1	Hematology	3	6	7	574
	Oncology	17	8	338	
	Sensory organs	0	8	12	
	Internal medicine[1]	10	5	26	
	Others[2]	12	15	107	
Phase 2	Hematology	3	11	13	520
	Oncology	13	23	187	
	Sensory organs	3	21	8	
	Internal medicine	15	13	25	
	Others	29	41	115	
Phase 3	Hematology	1	4	5	205
	Oncology	2	4	75	
	Sensory organs	4	3	7	
	Internal medicine	6	4	10	
	Others	11	9	60	
Filed/ approved/ marketed	Hematology	0	1	13	237
	Oncology	0	1	104	
	Sensory organs	1	2	4	
	Internal medicine	2	2	8	
	Others	9	5	85	
Total number of assets by therapy type		141	186	1,209	1,536

[1] Includes respiratory, endocrine, gastro-instestinal and cardiovascular.
[2] Includes dermatology, systemic anti-infectives, genito-urinary, CNS, immunomodulators, musculoskeletal, and other.
[3] Monoclonal antibodies.

Source: Evaluate Pharma, September 2019, McKinsey analysis

Commissioner Scott Gottlieb: "These products are initially being aimed at devastating diseases, many of which are fatal and lack available therapy. In these settings, we've traditionally been willing to accept more uncertainty to facilitate timely access to promising therapies."[8]

These accelerated pathways are shifting the paradigm of clinical trials by consolidating the Phase I, II, III process into Phase I, Phase II/III, and confirmatory Phase III trials after approval (similar to the trend in oncology research). The small patient populations also make it possible for companies to experiment with innovative trials designs (with regulatory involvement and approval), including single-arm and novel or surrogate endpoints. However, these trials may also require a different approach to decision-making within biopharma operations.

Although rare disease remains a focus in gene therapy, much of the early-stage gene therapy pipeline is in oncology. As of September 2019, roughly 25 percent of the overall gene therapy Phase I and II pipeline is oncology focused, including 17 Phase I RNA based and 8 Phase I DNA-based therapies. These oncology-directed therapies will compete with more traditional modalities (many of which will soon have biosimilar competition), and thus will need to demonstrate increased cost-effectiveness.

Much of the innovation and development in gene therapy have been driven by smaller biotech companies or research universities, sometimes in partnership with a large pharma company or an entity specialized in the targeted therapy. In fact, 90 percent of gene therapy development to date is from companies with fewer than 500 employees.[9] Many of these biotechs are platform companies who have optimized the manufacturing and delivery of their technology. When combined with the current funding climate, this has enabled many of them to quickly scale to multiple clinical programs across multiple therapeutic areas. As the technology underlying gene therapy matures, large

[8] Scott Gottlieb, "Remarks to the alliance for Regenerative Medicine's annual board meeting," Food and Drug Administration, May 2018, fda.gov.
[9] EvaluatePharma World Preview 2018.

Exhibit 3

Challenges across sectors stand in the way of realizing potential of gene therapy.

Degree of difficulty
● Low
●● Medium
●●● High

	Description	Difficulty to overcome
Market access	Therapies are costly, and health systems— especially in the US—are not set up for one-time large payments	●●● Requires significant changes to the healthcare ecosystem; multiple stakeholders involved
Clinical	Long-term safety and efficacy have yet to be established	●●● Requires time and further research to ensure long-term safety and efficacy; common issue in new modalities
Manufacturing	COGS remain high partially due to low and variable yields, with limited manufacturing capacity	● Significant investment required to expand capacity; yields will increase as more therapies reach clinical scale
Customer journey	Finding patients is challenging, especially for rare diseases that were previously untreatable	● Challenge expected to expand beyond rare diseases
Provider and hospital economic disruption	One-time therapies disrupt current healthcare economics (buy-and-bill)	●● Can be mitigated by selectively choosing providers but challenging to implement more broadly

Making the case for hemophilia A

The estimated total cost for the current standard of care in the United States for a patient with hemophilia A is $500,000 per year on average.[1] If a gene-therapy product for hemophilia were priced at $2 million, for example, it would have to demonstrate four years of efficacy. However, many payers in the United States would not automatically consider the gene therapy to be cost effective, as the likelihood of patient movement before that four-year benchmark would prevent them from realizing the full cost savings.

[1] Cost estimated based on costs of drugs, hospitalization, and other associated expenses. See *Express Scripts 2015: drug trend report*, Express Scripts Lab, March 2016, lab.express-scripts.com; and D.R. Globe, R.G. Curtis, M.A. Koerper, HUGS Steering Committee, "Utilization of care in haemophilia: a resource-based method for cost analysis from the Haemophilia Utilization Group Study (HUGS)," Haemophilia, March 2004, Volume 10, Number 1, pp. 63–70.

pharma companies are becoming more excited about owning the technology versus partnering, as shown by the recent large acquisitions of Avexis by Novartis (for $8.7 billion) and Spark by Roche (currently in negotiation for $4.3 billion).[10]

Current challenges of on-market drugs

Although the first gene therapies have been approved and offer significant clinical benefit, they have run into challenges that require rethinking the drug development and delivery system across key stakeholders. These challenges fall into one of five general areas (Exhibit 3).

Market access

Especially in the United States, where willingness to pay for innovative therapies has generally been the highest, the healthcare system is not set up to handle large, one-time payments that may be cost-effective over the long term (see sidebar, "Making the case for hemophilia A"). Insurance companies in the United States expect customers to frequently change health insurance (every three to five years, on average)—and are thus unwilling to pay for treatments that may only become cost effective in a time frame of at least ten years. Legal and regulatory reforms to enable multiyear payment models may be required for these therapies to become broadly accessible.

This issue may become particularly acute when insurance companies have the choice of either a one-time therapy at a high cost versus a more frequent therapy at a still high, but significantly lower cost. In addition, depending on delivery mechanism, the cost of the gene therapy can be nearly completely decoupled from the expected cost savings. Most gene therapies also have limited long-term efficacy data, which can make the long-term cost effectiveness argument challenging from a clinical perspective. Finally, while in certain US and ex-US systems (such as integrated delivery networks), incentives are more closely aligned for payers to consider total cost-effectiveness in decision making, the insurers or governments have not budgeted for large upfront payments for a recently approved drug. This is especially true as gene therapies move from rare diseases with small patient populations to broader populations and thus bigger system-wide price tags. As an analog, new therapies for hepatitis C, which are curative and have significantly lower price tags than current gene therapies, have seen significant payer-pushback. As a result, the therapies now require significant rebates and alternate models, such as authorized generics, to compete.

Clinical

Although the innovative clinical trial designs enabled by (or required due to) small patient populations and high unmet need allow therapies to get to market faster, there are often clinical questions that are left unresolved because of the accelerated pathway—a situation that is less likely to occur in standard randomized controlled trials. For example, novel or surrogate endpoints that include changes to gene or protein expression and are accepted by the regulatory authorities for accelerated approval may, over time, actually fail in providing long-term efficacy. Long-term follow-up is essential to ensure the durability of response or long-term safety—including the potential for liver toxicity due to viral load (observed across multiple modalities including RNAi and ASOs) and

[10] "Novartis enters agreement to acquire AveXis Inc. for USD 8.7 billion to transform care in SMA and expand position as a gene therapy and neuroscience leader," Novartis, April 09, 2018, Novartis.com; "Roche enters into definitive merger agreement to acquire Spark Therapeutics," Roche, February 25, 2019, roche.com.

immunogenicity (which has led to clinical holds for several trials). AAV–based therapies are particularly sensitive to durability of response, as antibodies against AAV can prevent additional dosing and may lead to waning response.

Preexisting immune reactivity is also an important factor as it can limit the potential patient population. In one instance, BioMarin needed to exclude 10 percent (2 out of 21) of patients in the initial trial for Valoctocogene Roxaparvovec due to preexisting antibodies (although they are now running a new study to understand efficacy within this population.)[11] In the CRISPR therapy field, preclinical data suggest that a high percentage of people already have antibodies to Cas9[12] which could impact efficacy of CRISPR–based therapies.[13]

Finally, there are ongoing concerns about genomic integration and off-target effects, which could prove to be long-term safety risks, particularly for in vivo systemic gene-editing approaches.

Manufacturing

Certain modalities, especially viral vectors, still suffer from capacity constraints, high cost of goods, long lead times, and significant upfront investment requirements. Despite considerable investment in building additional manufacturing (more than 700,000 square feet over the past two years), there is a shortage of AAV and lentiviral capacity. Viral vector manufacturing is expensive because of low yields (approximately ten doses per batch) due to low transfection efficiency, use of adherent cells limiting volume, and packaging efficiency. The result is an average of only 1:100,000 clinically useful viral particles. Limited capacity of good manufacturing practice–grade commercial manufacturing, especially for AAV and lentivirus, has led to long wait times for clinical trial manufacturing as well as increased prices. The alternative is building in-house capabilities, which is a major investment that can be challenging for an early stage company.

In addition, demonstrating the safety, quality, and potency of the final product is a major manufacturing challenge, given that assembling the different components in a functional manner is a precarious process. Chemistry, manufacturing, and controls and quality have also presented roadblocks; for example, the presence of foreign DNA after purification has led to several clinical trial holds.

Patient journey

Because the early gene therapies have been focused on rare diseases, finding eligible patients is difficult, exacerbated by the fact that gene therapies have been focused largely on the easiest-to-target diseases. For example, Onpattro and Tegsedi were approved within months of each other (hATTR[14] has an estimated prevalence of 30,000–50,000 people worldwide, less than 30 percent of whom have been diagnosed), leading to intense competition for a limited patient pool to treat.[15] In addition, some therapies are only available at a limited number of facilities, requiring patients to travel for diagnosis, treatment, and follow-up.

Provider and hospital economic disruption

In addition to the disruption in payer economics discussed earlier, gene therapy also disrupts provider economics. Many of the current treatments that gene therapies could replace (such as blood transfusions for hemophilia) are "buy and bill" and provide substantial long-term revenue for providers and hospitals. Meanwhile, a single high-priced dose via buy and bill presents risk to the hospital and distribution system—requiring significant negotiations or potentially even a new approach to the traditional pharmaceutical distribution system.

Although these challenges impact all gene therapies to some extent, potentially curative therapies face an additional impediment. Unlike the traditional pharma model, which assumes patients use therapies for extended periods, curative therapies will shift the demand curve from the traditional S-curve to a bell curve with a long tail (to reflect new incidences of the disease),

[11]For more, see Jeremy Arens et al., "Impact of pre-existing immunogenicity to AAV on vector transduction by Bmn 270, an AAV5-based gene therapy treatment for Hemophilia A," *Blood*, December 2017, Volume 130, Number 1, p. 3332, bloodjournal.org.
[12]CRISPR associated protein 9.
[13]Corie Lok, "Pre-existing immunity to CRISPR found in 96% of people in study," *Xconomy*, October 29, 2018, xconomy.com.
[14]Hereditary transthyretin amyloidosis.
[15]Morie A. Gertz, "Hereditary ATTR amyloidosis: Burden of illness and diagnostic challenges," *American Journal of Managed Care*, June 13, 2017, ajmc.com.

Public payers are often more willing to experiment since their incentives are more closely aligned to overall health economics.

as patients are cured and thus are no longer part of the addressable market. This leads to an even greater than usual first-to-market advantage: the first therapy in a given indication has first access to the largest bolus of patients. Once a percentage of these patients are treated and cured by the first-to-market therapy, that leaves a smaller population of untreated patients for those companies whose therapies are not first-to-market.

When treated, these patients also provide the long-term efficacy and safety information that enables market access and gets healthcare professionals comfortable with the therapy. Once the initial set of patients has been treated, the addressable population shrinks to a long tail of the newly diagnosed. Furthermore, increases in premarital, prenatal, and noninvasive prenatal testing are likely to further decrease the accessible patient populations in these monoallelic rare diseases. In the 1970s, after three Mediterranean countries began requiring premarital genetic screening for beta thalassemia, at-risk births all but disappeared.[16]

How to unlock the true potential of gene therapy

Realizing the potential of gene therapy will require working with multiple stakeholders to address the five key areas critical to implementation.

Market access

Innovative schemes are required to make large, one-time payments feasible, especially as patient numbers increase. Pharma companies and payers have experimented with outcomes-based pricing; however, these contracts have been limited and not game-changing for access. Significant challenges to implementation remain, mostly due to the fragmentation of the US healthcare system. Broadly, overcoming these challenges will include the following:

— establishing agreement on the standard outcomes to track,

— tracking these outcomes across long time scales in near real-time, and

— being able to follow individual patients using different provider systems and different payers as patients switch insurances or move across borders.

The first two can be addressed through investments in infrastructure. The third is the most demanding, particularly in the United States, as contracts are payer by payer. Public payers are often more willing to experiment since their incentives are more closely aligned to overall health economics, such as Louisiana's new subscription model for hepatitis C treatment.[17] Real innovation will require significant infrastructure investments, the openness to work with third-party data players, and risk-sharing across the healthcare ecosystem. This innovation in market access and pricing will enable gene therapies to become established but will come with larger structural implications in the payment and delivery of care across therapeutic classes.

Manufacturing

Investments in automation are required to reduce manual labor, variability, and cost of goods. Improvements to vectors and cell technology will increase throughput (such as moving from adherent

[16]"The expanding prevalence of Beta-thalassemia," *Celgene*, December 1, 2018, celgene.com.
[17]Melinda Deslatte, Louisiana reaches 'Netflix-model' deal to tackle hepatitis C, *Associated Press*, June 26, 2019, apnews.com.

cells to suspension) and efficiency while also increasing purity of active particles. Optimizing delivery systems will broaden the diseases that can be targeted beyond those affecting blood (and the immune system, more broadly), liver, spine, and eyes while reducing invasive (intrathecal or intraocular) injections. More precise targeting can also reduce safety and potential off-target effects, which can be especially important if the therapy integrates into or edits the genome.

Clinical development

Clinical development organizations will have to adjust to the new paradigm of compressed clinical development timelines and long-term follow-up. This means significant investment in data collection beyond launch, including patient registries, confirmatory trials, and innovative usage of real-world data to monitor safety and efficacy over extended time periods, in addition to continuing to build the value story. Further validation of surrogate endpoints (including digital biomarkers for neurodegenerative diseases, such as Huntington's disease), will further help streamline clinical trials.

Integrated clinical and commercial models

Gene therapies, particularly the one-time or curative versions, are disruptive to the current delivery models for pharmaceuticals in the following ways:

— *The high price* creates risk for distribution and storage.

— *Limited patient populations* mean that most doctors see a declining number of eligible patients per year—usually a single patient, at most.

— *The curative nature* disrupts hospital economics.

One possible solution is to create gene therapy centers of excellence at a limited number of sites. This would allow doctors to see more patients per year (thus building real experience), control quality, better manage risk, and ensure patients receive a better experience overall. These centers can be chosen so that the economic incentives align with gene therapies. Examples include patient-centric integrated delivery networks that control total cost of care and leading research centers that have other revenue streams and rely on delivering cutting-edge care. Identifying sites early in the clinical development process is essential, as building doctors' clinical experience with the therapies is key in a highly competitive and patient-limited market.

Regulation

Regulatory agencies are taking steps to expand regulatory review capacity for gene therapies. For example, the FDA is circumventing capacity issues that could delay timelines by hiring additional reviewers; it has also released draft guidance for cell and gene therapies, which should continue to pave a clearer path to approval for pharma and biotech players. As gene therapy evolves, regulatory challenges will continue. For instance, in the emerging field of personalized gene therapies, targeted oligonucleotides are matched to an individual's genotype, which is particularly applicable for gene silencing and direct gene editing cases. This is a challenge for the current regulatory environment because a single molecule is required for clinical development.

Thanks to clinical, manufacturing, and technological advancements, we are beginning to realize the promise of gene therapy. However, significant hurdles still require a paradigm shift across the drug development and delivery ecosystem, as well as investment and buy-in from multiple stakeholders. Yet-to-be-established regulatory and ethical frameworks will also need to evolve to keep up with the science. And the companies developing these life-changing therapies will have an important role in working with the complex network of stakeholders: empowering the necessary changes and, ultimately, ensuring that their scientific advances are reaching those in need.

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