GENE THERAPY'S FIELD OF DREAMS: IF YOU BUILD IT, WILL WE PAY?*

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Long overpromised and underdelivered, gene therapy has at last achieved clinical validation and, with the advent of improved gene-editing technologies such as CRISPR, seems poised to play a rapidly expanding role in medical care. However, some of the intrinsic qualities of gene therapy pose a unique challenge to our health insurance model. Gene therapy is costly for a number of reasons. It is "personalized medicine," which means that treatments are individualized and not for a broad audience. Additionally, the goal of gene therapy is to provide a one-time cure, so the cost is upfront and not spread over time as it would be with conventional drugs or therapeutics. As our experience to date illustrates, these issues of cost may adversely affect access. In this Article, we argue that a lack of broad access to gene therapy will deepen existing health inequities and may create a society of genetic haves and have-nots, where certain genetic diseases become something that happens only to those who cannot afford treatment. This in turn may increase stigma and decrease resources for affected individuals. For these reasons, the success of gene therapy must be considered as inextricable from issues of cost and coverage.

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INTRODUCTION

It's amazing how many think [looming payment problems are] in the future . . . . This is right now.[1]

The future is already here—it's just not very evenly distributed.[2]

Gene-editing technologies bring the possibility of revolutionary advancements in clinical care through gene therapy and the possibility of realizing the long-imagined futuristic era of genomic medicine. Gene-therapy and gene-editing treatments carry not just a therapeutic goal but a curative goal—where patients' symptoms are effectively cured through genetic changes. Yet a major concern with the introduction of gene editing into clinical care is whether access to these treatments will be evenly distributed in a health-care system that is by no means equitable. Lack of equitable access may result in a society where some are able to cure their genetic conditions before symptoms arise while others are "stuck" with curable genetic diseases—leading to disparities, lack of resources, and stigmatization.

1. Gina Kolata, *New Gene-Therapy Treatments Will Carry Whopping Price Tags*, N.Y. TIMES (Sept. 11, 2017), https://www.nytimes.com/2017/09/11/health/cost-gene-therapy-drugs.html [https://perma.cc/NPR6-WBHB (dark archive)].

2. *The Future Has Arrived—It's Just Not Evenly Distributed Yet*, QUOTE INVESTIGATOR (Jan. 24, 2012), https://quoteinvestigator.com/2012/01/24/future-has-arrived/ [https://perma.cc/VMF7-BRLF].

High costs and inequities of access are hardly unique to gene therapy, but these new treatment models, wildly expensive and resistant to economies of scale, threaten to bring the problem to a new level with profound societal implications. As several recent gene-therapy treatments entering the market illustrate, these procedures have high price tags that challenge our current insurance system, especially as more gene-editing treatments become available for use and the number of patients seeking reimbursement grows.[3] Although high-cost treatments are not uncommon in our health-care system, they are typically associated with treatments spread across months or years. Gene-editing treatments are often posited as a one-time event and as potential cures—meaning that companies providing these treatments must seek to recoup all of their investment in one fell swoop.[4]

The questions are (1) whether and how the U.S. health insurance system will absorb the cost of these treatments, and (2) whether access will be available to many in society.[5] Alternative payment structures have the potential to fulfill one or both of these goals—lowering cost and increasing access. These goals are intertwined: lowering cost is likely to increase access and increasing access may lower cost. This Article argues that it is imperative that equitable access remain a cornerstone consideration in any discussion of gene therapy to avoid increased chasms between the haves and the have-nots, the cured and those left without the ability to pay.

Providing access to gene therapy may well require innovative approaches to pricing and reimbursement and may fundamentally alter the practice of insuring health care. Various alternative payment structures focus on different goals: some attempt to lower the overall cost of the treatments, whereas others spread the cost of gene therapy across time or broader risk pools.[6] However, even if alternative payment structures can be developed to successfully provide reimbursement for gene-editing treatments, there is still no guarantee this will equate to widespread access. Payment issues, such as high co-pays and other out-of-pocket costs, may be prohibitive for a significant portion of society even when insurers provide coverage for

3. *See infra* Part II.

4. *See infra* Section II.B.

5. *See* Bradley J. Fikes, *Wave of Effective—and Expensive—Cell and Gene Therapies Challenges Health Insurers*, SAN DIEGO UNION TRIB. (Oct. 4, 2018, 12:00 PM), https://www.sandiegouniontribune.com/business/biotech/sd-me-effective-expensive-cell-therapies-20181004-story.html [https://perma.cc/ASC5-HSSV].

6. *See infra* Section III.B.

the technology.[7] Given the promise of cures for diseases, this prospect paints a worrisome picture of rising inequality of care.

Our U.S. system of health care is rife with inequities of access. While high costs and the inability to pay for treatment are hardly problems unique to gene therapy, the promise of gene therapy to cure genetic diseases threatens to widen the breadth of our society's health disparities and has the potential to decrease resources and social support for those left behind. We argue that a variety of alternative payment structures should be considered for gene-therapy treatments, focusing particularly on increasing equitable access to treatment both by increasing insurance coverage and by decreasing costs.

It has not escaped our notice that this argument drives in the direction of a single-payer system.[8] A single-payer health-care system would increase access to health care and therefore to approved gene therapy treatments across the board, thus making access to these technologies more equitable. It would also provide for greater bargaining power with treatment developers to employ various alternative payment structures.[9] Indeed, the more we understand about the genetic causes of disease, the more a universal health-care system seems to make sense.[10] The single-payer system, however, is by no means the "panacea" to the problems of cost identified here.[11] A focus on access that ignores the overall heightened cost of gene-therapy treatments will threaten to bankrupt the system or drastically overspend limited government resources. Access, however, should not be forgotten as gene therapy is introduced into the market.

This Article proceeds as follows: Part I provides an overview of how gene-editing treatments have been introduced into clinical care, including gene-editing treatments that use older technologies, as well

7. *See infra* Section III.C.

8. *See, e.g.*, Grace Hampson et al., *Gene Therapy: Evidence, Value and Affordability in the US Health Care System*, 7 J. COMP. EFFECTIVENESS RES. 15, 18 (2018) (noting the difficulty of implementing alternative payment structures in a fragmented health-care system).

9. *See, e.g.*, Fikes, *supra* note 5 (noting that single-payer systems are able to consider long-term benefits).

10. James P. Evans, *Health Care in the Age of Genetic Medicine*, 298 JAMA 2670, 2670–72 (2007) ("The potential success of genomic medicine provides a series of additional compelling arguments to embrace a system of care that provides universal coverage and broadly pools risk. It is no small irony that the emergence of individualized medicine ultimately mandates a shared approach to health care delivery.").

11. *Id.* at 2672.

as the prospect of similar treatments utilizing CRISPR.[12] Part II discusses the primary cost drivers of gene-editing treatments—namely, the limited market size of patients, the one-time nature of the treatment, and the patent system. Each of these factors helps to raise the cost of the treatments as companies must recoup their research and development costs among a small number of patients likely only paying for the procedure one time.

Given the potential strain on the insurance system, Part III considers several alternative payment models that have been proposed for reimbursement of gene-editing treatments. While some of these may help ensure reimbursement for treatment, examples illustrate that the implementation of the payment structures can greatly affect both the success of the scheme and whether reimbursement will be accessible across populations. Finally, Part IV discusses how various elements of the U.S. health insurance system may lead to inequitable access to reimbursement for gene-editing treatments and, indeed, possibly to insurance itself.

I. GENE-EDITING TREATMENT AND EXPECTATIONS FOR CLINICAL USE

Prospects for gene therapy have rebounded[13] after a series of high-profile disasters dashed the great hopes associated with the field in the 1990s.[14] Revitalized by improved viral and nonviral DNA delivery systems,[15] gene therapy has expanded in the twenty-first

12. This Article focuses on cost and access to gene-editing treatments. The two common distinctions that arise when discussing gene editing are (1) whether changes will affect only the patient (i.e., only their somatic cells) or whether changes will alter the germline and may be passed down to potential future generations; and (2) whether the editing is occurring for treatment or enhancement. While there are ethical concerns, including issues of equitable access, to potential germline or enhancement gene editing, the Article has a narrower focus on somatic treatment. Given scientific complexities and ethical concerns, implementation of germline gene editing or enhancement in a clinical setting is unlikely to emerge as quickly as somatic gene editing—which is already being used in human clinical trials.

13. Samantha L. Ginn et al., *Gene Therapy Clinical Trials Worldwide to 2017: An Update*, J. GENE MED., Mar. 9, 2018, at 1, 3.

14. *See* Jennifer Couzin & Jocelyn Kaiser, *As Gelsinger Case Ends, Gene Therapy Suffers Another Blow*, 307 SCIENCE 1028, 1028 (2005); Tom Hollon, *Researchers and Regulators Reflect on First Gene Therapy Death*, 6 NATURE MED. 6, 6 (2000); Jian Qiao, Rosa Maria Diaz & Richard G. Vile, *Success for Gene Therapy: Render unto Caesar That Which Is Caesar's*, 5 GENOME BIOLOGY 237.1, 237.1 (2004); Barbara Sibbald, *Death but One Unintended Consequence of Gene-Therapy Trial*, 164 CANADIAN MED. ASS'N J. 1612, 1612 (2001).

15. *See* Pieter R. Cullis & Michael J. Hope, *Lipid Nanoparticle Systems for Enabling Gene Therapies*, 25 MOLECULAR THERAPY 1467, 1467 (2017) (discussing nonviral

century to include work on five continents, although as of 2017, the United States remains a driving force with over sixty-three percent of all gene-therapy trials.[16] Gene therapy hit a series of milestones in 2017, when treatments received Federal Food and Drug Administration ("FDA") approval for use in the United States for the first time: Kymriah by Novartis in August to treat acute lymphoblastic leukemia,[17] Yescarta by Kite Pharmaceuticals in October to treat B-cell lymphoma,[18] and Luxturna by Spark Therapeutics in December to treat a recessive form of retinal dystrophy stemming from the loss of both copies of a single gene.[19] There are significant technical differences between the first two products and the last. The first two are so-called CAR-T cell therapies that involve removing, isolating, and manipulating the patient's own T cells to provoke a specific immune response and then returning these cells through an infusion.[20] Luxturna, on the other hand, is delivered directly into the eye to alter retinal cells in vivo.[21] All three treatments fit the current FDA definition of gene therapy as "a technique that modifies a person's genes to treat or cure disease."[22] All of these early entrants into the

delivery systems); Kenneth Lundstrom, *Viral Vectors in Gene Therapy*, DISEASES, May 21, 2018, at 1, 1 (discussing viral delivery systems).

16. Ginn et al., *supra* note 13, at 6.

17. Press Release, FDA, FDA Approval Brings First Gene Therapy to the United States (Aug. 30, 2017) [hereinafter FDA Kymriah Press Release], https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm [https://perma.cc/3JGZ-2MLY].

18. *See generally* Letter from Mary A. Malarkey, Dir., Ctr. for Biologics Evaluation & Research, & Wilson W. Bryan, Dir., Ctr. for Biologics Evaluation & Research, to Rizwana F. Sproule, Vice President of Regulatory Affairs, Kite Pharma, Inc. (Oct. 18, 2017), https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581259.pdf [https://perma.cc/8KSN-Q6XE] (discussing the approval of a license for Yescarta by Kite Pharmaceuticals).

19. Press Release, FDA, FDA Approves Novel Gene Therapy to Treat Patients with a Rare Form of Inherited Vision Loss (Dec. 19, 2017) [hereinafter FDA Luxturna Press Release], https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm [https://perma.cc/TMZ3-5FW2].

20. William F. Kaemmerer, *How Will the Field of Gene Therapy Survive Its Success?*, 3 BIOENGINEERING & TRANSLATIONAL MED. 166, 166 (2018).

21. *Id.*

22. *What Is Gene Therapy?*, FDA, https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm573960.htm [https://perma.cc/X3JG-PLVR]. Others have argued for a new definition of gene therapy that is broad enough to include CAR-T treatment and applies to both in vivo and ex vivo treatments. *See* Jacob S. Sherkow, Patricia J. Zettler & Henry T. Greely, *Is It 'Gene Therapy'?*, J.L. & BIOSCIENCES, Aug. 23, 2018, at 1, 4. Kymriah, Yescarta and Luxturna utilize zinc-finger nucleases ("ZFNs"), as do the treatments for MPS I and II for which Sangamo Therapeutics was recently granted approval to begin human trials in Great Britain. ZFNs are enzymes that can be modified and utilized to target specific genetic sequences and were the most commonly used gene-editing technique prior to the development of CRISPR. In August 2018, Vertex

gene-therapy marketplace were developed using older gene-editing systems and not the revolutionary CRISPR technology.[23]

Improvements in the ease and efficiency with which we can edit DNA using CRISPR have generated sky-high expectations for breakthroughs in clinical care,[24] expectations that have manifested themselves materially as a thriving new market sector. According to *Forbes*, there are now three publicly traded "CRISPR companies" with a combined market capitalization of more than three billion dollars.[25] Each of the three tripled their stock price in the twelve-month period leading up to June 2018[26]—this to fund translational research using the gene-editing technique that did not exist prior to 2012.

Many of the bold-faced names credited with the discovery of CRISPR and the development of techniques for its use in organisms more complicated than a bacterial cell, including human cells, have become partners in commercial ventures to develop and bring to market clinical applications of the technology. George Church and Feng Zhang are scientific advisors and co-founders of Editas, which received FDA approval in late 2018 for human trials of a treatment for Leber congenital amaurosis, a genetic disorder that primarily affects the eye.[27] This would be the first in vivo use of a CRISPR-derived medication.[28] Editas also reports that it is conducting preclinical studies of treatments for Duchenne muscular dystrophy, cystic fibrosis, β-thalassemia and alpha-1 antitrypsin deficiency.[29]

Pharmaceuticals and CRISPR Therapeutics opened enrollment in Germany in a study combining phase 1 and phase 2 clinical trials for β-thalassemia; this will be the first-ever human trial of a CRISPR-based gene therapy. Catherine Offord, *US Companies Launch CRISPR Clinical Trial*, SCIENTIST (Sept. 3, 2018), https://www.the-scientist.com/news-opinion/us-companies-launch-crispr-clinical-trial-64746 [https://perma.cc/594F-MMJ4].

23. In-Young Jung & Jungmin Lee, *Unleashing the Therapeutic Potential of CAR-T Cell Therapy Using Gene-Editing Technologies*, 41 MOLECULES & CELLS 717, 717, 721 (2018); Morgan L. Maeder et al., *Development of a Gene-Editing Approach to Restore Vision Loss in Leber Congenital Amaurosis Type 10*, 25 NATURE MED. 229, 229 (2019).

24. Kaemmerer, *supra* note 20, at 166–67.

25. Robert Glatter, *How CRISPR Gene Editing Is Revolutionizing Medicine and the Companies Who Invest in It*, FORBES (June 25, 2018, 6:30 AM), https://www.forbes.com/sites/robertglatter/2018/06/25/how-crispr-gene-editing-is-revolutionizing-medicine-and-the-companies-who-invest-in-it/#2a73f7b06f46 [https://perma.cc/MWF2-WZKQ].

26. *Id.*

27. *See Editas Medicine, Inc.*, IPO BOUTIQUE, https://www.ipoboutique.com/0605Advisories/EDIT.htm [https://perma.cc/QYB5-BC4Y].

28. Press Release, Editas Med. Inc., Editas Medicine Announces FDA Acceptance of IND Application for EDIT-101 (Nov. 30, 2018), http://ir.editasmedicine.com/news-releases/news-release-details/editas-medicine-announces-fda-acceptance-ind-application-edit [https://perma.cc/BKP8-FXZF].

29. *See Editas Medicine, Inc.*, *supra* note 27.

Jennifer Doudna and Rodolphe Barrangou are co-founders and scientific advisors at Intellia Therapeutics,[30] which has touted its late-stage preclinical work on gene therapy for sickle cell disease[31] and has a partnership with Regeneron aimed at developing a treatment for transthyretin amyloidosis.[32] Emmanuelle Charpentier is a founder and Scientific Advisory Board member of CRISPR Therapeutics,[33] which has been granted "Fast Track Designation" from the FDA for human application of its sickle cell therapy.[34] Like the β-thalassemia study in Germany, these therapies will modify and return isolated blood stem cells to the blood stream in an attempt to provide the cells with a functioning hemoglobin gene that will compensate for the defective version associated with both diseases.[35]

Overall, these trials illustrate progress in the development of gene therapy, including therapies using CRISPR technologies, which are likely to continue.[36] As the next part discusses, several market

30. *Leadership*, INTELLIA THERAPEUTICS, https://www.intelliatx.com/overview/leadership/ [https://perma.cc/8PSA-UEMS].

31. *See* Press Release, Intellia Therapeutics, Inc., Intellia Therapeutics Announces New, Robust Genome Editing Data for Sickle Cell Disease at the American Society of Hematology Meeting (Dec. 11, 2017), https://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-announces-new-robust-genome-editing-data-0 [https://perma.cc/MQ8S-BLM4].

32. Press Release, Regeneron Pharm., Inc., Regeneron and Intellia Therapeutics Announce Collaboration to Discover and Develop CRISPR/CAS Therapeutics (Apr. 11, 2016, 4:05 PM), https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-and-intellia-therapeutics-announce-collaboration [https://perma.cc/YJD7-C9EB].

33. *Leadership: Dr. Emmanuelle Charpentier*, CRISPR THERAPEUTICS, http://www.crisprtx.com/about-us/leadership/dr-emmanuelle-charpentier [https://perma.cc/VFR8-NMB6].

34. Press Release, CRISPR Therapeutics, CRISPR Therapeutics and Vertex Announce FDA Fast Track Designation for CTX001 for the Treatment of Sickle Cell Disease (Jan. 4, 2019), http://ir.crisprtx.com/node/8556/pdf [https://perma.cc/KQG5-PBH3].

35. Offord, *supra* note 22.

36. Notwithstanding all this rapid progress, technical challenges persist that may complicate the in vivo use of CRISPR technologies. *See* Carsten T. Charlesworth et al., *Identification of Pre-Existing Adaptive Immunity to Cas9 Proteins in Humans*, 25 NATURE MED. 249, 249 (2019) (suggesting that a majority of people may harbor preexisting antibodies to Cas9, an enzyme that plays an integral role in the most common version of the CRISPR gene-editing system); Michael Kosicki, Kärt Tomberg & Allan Bradley, *Repair of Double-Strand Breaks Induced by CRISPR–Cas9 Leads to Large Deletions and Complex Rearrangements*, 36 NATURE BIOTECHNOLOGY 765, 765 (2018) (reporting an unexpectedly high number of problematic genetic changes, such as large deletions and structural rearrangements, following the use of CRISPR-Cas9 gene editing in mouse cell lines). Such challenges have reanimated concerns about gene therapy, causing malignancies which have troubled the field from its earliest days. *See* Sam Sherratt, *DNA Damage from CRISPR 'Seriously Underestimated'*, BIONEWS (July 23, 2018), https://www.bionews.org.uk/page_137304 [https://perma.cc/TA29-E5Y9]. For example, in 2002, an apparently successful trial of gene therapy for immunodeficiency was shut down

forces drive costs of these treatments upwards. While increasing utilization of gene-therapy treatments could be beneficial to targeted patient populations, how the health-care system will absorb the cost of the growing number of treatments is currently unclear.

II. GENE EDITING AND COST DRIVERS

As gene-editing treatments continue to rapidly gain regulatory approval and be introduced into the clinical market, greater focus must be given to the impact this will have on insurance and the downstream implications for access to the treatments.[37] The cost of gene-editing therapies is likely to be a major barrier for many patients in need of treatment and will create challenges for pharmaceutical companies, payers, and patients. While most gene-editing treatments are still in development or available only through clinical trials, the handful of gene-therapy products that have received approval for commercial use are illustrative of the ways in which gene therapy is inherently an awkward fit for our current model of health-care reimbursement. As discussed above, none of these approved therapies use CRISPR, but while the gene-editing system may change, the issues remain the same.[38] Each of the therapies introduced to date highlight specific challenges for gene-editing treatments to come. An overarching theme is that high costs of the treatments are likely to stretch the existing insurance reimbursement

when two of the eleven children treated became ill with leukemia. Donald B. Kohn, Michel Sadelain & Joseph C. Glorioso, *Occurrence of Leukemia Following Gene Therapy of X-Linked SCID*, 3 NATURE REVIEWS CANCER 477, 477 (2003); Charles Marwick, *FDA Halts Gene Therapy Trials After Leukaemia Case in France*, 326 BRIT. MED. J. 181, 181 (2003). However, prevailing sentiment is that these are obstacles rather than roadblocks and that workarounds or alternate strategies will emerge. *See Expert Reaction to Study Looking at Deletions and Rearrangements Due to the CRISPR/Cas9 Genome Editing Technique*, SCI. MEDIA CTR. (July 16, 2018), http://www.sciencemediacentre.org/expert-reaction-to-study-looking-at-deletions-and-rearrangements-due-to-the-crispr-cas9-genome-editing-technique/ [https://perma.cc/LEZ8-E3PX]; Julianna LeMieux, *Another "CRISPR Calamity"? U.K. Team Reports CRISPR-Induced Gene Rearrangements*, GEN (July 16, 2018), https://www.genengnews.com/gen-exclusives/another-crispr-calamity-uk-team-reports-crispr-induced-gene-rearrangements/77901116 [https://perma.cc/627F-SECF].

37. Incentives and the cost of research and development of preclinical care also greatly impact the cost of gene-therapy treatments. Changes to innovation and regulatory approval could have the potential to lower costs for society. For example, either changes to how research is funded or a more streamlined regulatory process could potentially lower research and development costs to companies—thus lowering costs to patients. However, such policy recommendations are beyond the scope of this Article, which focuses on how payers will address costs once introduced to market given that near-term treatments are likely to continue to be expensive unless and until innovation policy changes.

38. *See infra* Part II.

system.[39] These high costs are driven by: (1) market challenges for pharmaceutical companies due to limited patient populations,[40] (2) one-time treatments,[41] and (3) a patent system that purposefully imposes monopolies into the market in order to allow pharmaceutical companies to recoup their research and development costs.[42]

A. Restricted Market Size

Developing a drug for a small patient population requires a higher price tag per treatment to recoup the cost and return value to investors.[43] As the prices are pushed upwards, the financial burden may become prohibitive, leaving patients without recourse to treatment. The small patient populations also make it difficult to develop the clinical evidence necessary to fully understand and document effectiveness[44]—an important consideration for payers deciding what to reimburse.

For example, Glybera, developed by uniQure to treat the ultrarare disease lipoprotein lipase ("LPL") deficiency, was the first gene therapy granted regulatory approval for the European market and debuted in 2012 with a price tag of approximately one million dollars per patient.[45] The company argued that the high price tag was justified by a limited patient population, but it also served to restrict use of a drug already limited by a small potential audience. In fact, the clinical trials sponsored by the company treated over ten percent

39. *See, e.g.*, Kolata, *supra* note 1.

40. *See infra* Section II.A.

41. *See infra* Section II.B.

42. *See infra* Section II.C.

43. *See* GRACE MARSDEN ET AL., INST. FOR CLINICAL & ECON. REVIEW & OFFICE OF HEALTH ECON., GENE THERAPY: UNDERSTANDING THE SCIENCE, ASSESSING THE EVIDENCE, AND PAYING FOR VALUE 26 (2017) [hereinafter ICER REPORT], https://icer-review.org/wp-content/uploads/2017/03/ICER-Gene-Therapy-White-Paper-030317.pdf [https://perma.cc/8QZQ-ZT77]; Stuart H. Orkin & Philip Reilly, *Paying for Future Success in Gene Therapy*, 352 SCIENCE 1059, 1060 (2016). Of course, a treatment's price is not only based on the past research costs but also on willingness to pay and other economic assessments. *See* David R. Carr & Steven E. Bradshaw, *Gene Therapies: The Challenge of Super-High-Cost Treatments and How to Pay for Them*, 11 REGENERATIVE MED. 381, 383 (2016).

44. ICER REPORT, *supra* note 43, at 18; Carr & Bradshaw, *supra* note 43, at 383.

45. Chris Morrison, *$1-Million Price Tag Set for Glybera Gene Therapy*, 33 NATURE BIOTECHNOLOGY 217, 217 (2015).

of the entire potential European patient population.[46] Of the rest, only a single patient went on to receive treatment.[47]

Having spent over 100 million dollars bringing the drug to market, uniQure hoped to recoup its investment by expanding to the United States, but when the FDA demanded further trials as well as long-term follow-up, the company decided to cut its losses and withdraw from FDA review.[48] UniQure also allowed its European approval to lapse in 2017.[49] Though Glybera provided proof that gene therapy could work and that regulators were open to approving its use, the drug was a commercial failure.[50]

The problems that beset Glybera are not specific to LPL deficiency. Cancer immunotherapy aside, the principal targets for gene therapy to date have been Mendelian diseases—diseases where a single gene is the target.[51] Genetic diseases are individually rare if collectively common, offering many potential targets for gene therapy but few with blockbuster potential. Small audiences are the inherent flip side of individualized treatment because the whole premise of "individualizing" treatment is to make a smaller, more targeted market. This obviously applies to rare and ultrarare diseases, but even in the case of more common diseases, genetic medicine often targets specific genetic changes that make up a subset of the disease or specific disease mechanisms, limiting its effectiveness to a slice of the affected population. Some recent targeted therapies from the drug-development world illustrate this pattern. Ivacaftor, a breakthrough medication for cystic fibrosis ("CF"), is an effective cure but only for three to four percent of the CF population.[52] The FDA approved Eteplirsen for Duchenne muscular dystrophy in 2016 but only for those with a specific genetic mutation, an estimated thirteen to

46. *See* Antonio Regalado, *The World's Most Expensive Medicine Is a Bust*, MIT TECH. REV. (May 4, 2016), https://www.technologyreview.com/s/601165/the-worlds-most-expensive-medicine-is-a-bust [https://perma.cc/S8CC-VSD3].

47. ICER REPORT, *supra* note 43, at 20; Ben Hirschler, *Biotech Firm Pulls Pioneering Gene Therapy Due to No Demand*, REUTERS (Apr. 20, 2017, 11:19 AM), https://www.reuters.com/article/us-health-gene-therapy-uniqure/biotech-firm-pulls-pioneering-gene-therapy-due-to-no-demand-idUSKBN17M1WI [https://perma.cc/T2YN-CZZ7].

48. Regalado, *supra* note 46. There were also some questions as to the effectiveness of the treatment, leading to the decision to withdraw. *Id.*

49. Press Release, uniQure, uniQure Announces It Will Not Seek Marketing Authorization Renewal for Glybera in Europe (Apr. 20, 2017), http://www.uniqure.com/GL_PR_Glybera%20withdrawal_FINAL_PDF.pdf [https://perma.cc/SYT8-T749].

50. *Id.*

51. Ginn et al., *supra* note 13, at 7.

52. Lisa B. Feng et al., *Precision Medicine in Action: The Impact of Ivacaftor on Cystic Fibrosis-Related Hospitalizations*, 37 HEALTH AFF. 773, 773 (2018).

fourteen percent of affected boys.[53] These examples of a limited audience are not exceptions but rather are the very nature of personalized medicine.

The potential inability to recoup costs discourages pharmaceutical companies from researching treatments for rare diseases. Legislation has attempted to address some of the issues surrounding rare disease development in the past. For example, federal law incentivizes companies to develop pharmaceuticals for rare diseases when it might not be financially feasible to invest in the research and development costs.[54] Yet this only solves part of the problem, since the newly developed treatments can still be expensive. Therefore, some have argued that a portion of these funds could be diverted towards lowering the cost of the therapies for the patient.[55]

Over time, greater expertise may allow us to simplify the development of therapeutics or the process of obtaining regulatory approval, but for the foreseeable future, the costs involved with bringing a treatment to market will remain formidable relative to the potential audience. This suggests that prices will remain high and, in some cases, prohibitive.

B. One-Time Therapy Versus Lifetime Costs

The initial price tag for Kymriah, the first gene therapy approved by the FDA,[56] was $475,000.[57] Although undeniably expensive, it compares well with the cost of existing therapies in those cases where it is either a cure or a long-term solution. This is, however, only true where the therapy forestalls further treatment. When it does not, it is a significant added expense.

In December 2017, four months after Kymriah was approved, Luxturna became the third gene-therapy treatment approved by the FDA and the first gene therapy approved to be administered directly into a patient.[58] Luxturna was approved as a treatment for an inherited form of vision loss and blindness that affects between 1000 to 2000 patients in the United States.[59] Luxturna is also expensive,

53. FADY SHAWI, CHRISTINE PERRAS & MELISSA SEVERN, CADTH, EMERGING DRUGS FOR DUCHENNE MUSCULAR DYSTROPHY 4 (2017), https://www.ncbi.nlm.nih.gov/books/NBK476440/pdf/Bookshelf_NBK476440.pdf [https://perma.cc/J6CS-2SWX].

54. 21 U.S.C. §§ 360aa–360ee (2012).

55. Orkin & Reilly, *supra* note 43, at 1061.

56. FDA Kymriah Press Release, *supra* note 17.

57. Kolata, *supra* note 1.

58. FDA Luxturna Press Release, *supra* note 19.

59. *Id.*

costing $850,000 per patient.[60] Administered in two phases—one for each eye at $425,000 each—the treatment is a one-time deal. Given the lifetime costs of treatment and lost productivity related to disability, Luxturna may or may not be a good investment; the Institute for Clinical and Economic Review has argued that it is not.[61] But even assuming that it is, the economic analysis necessitates that it works as anticipated. Also, best-case scenario, Luxturna condenses a lifetime of costs into one very expensive month. One-time treatment is a common theme—and, indeed, often the *raison d'etre*—of gene-therapy treatments. Gene-therapy treatments may drastically alter our medical and reimbursement systems because they have the potential to be one-time, curative treatments. However, for the same reason, a pharmaceutical company must recover all of its per-person investment in research, development, and cost of treatment from a single payment rather than spread them over time, as in the typical model of ongoing treatment or lifetime care. This will place a hefty initial burden on all insurers and government payers and create special challenges for most U.S. insurers, who have high rates of turnover as customers change jobs or policies and thus cannot amortize benefits of one-time cures over an extended period of time.[62]

Justification for the high prices of drugs like Kymriah and Luxturna are often predicated on their value as a one-time treatment, but this may not be a realistic expectation in all cases. Effectiveness over a lifetime cannot be proven in advance since neither the manufacturers nor their patients are willing to wait a generation to test the hypothesis.[63] In addition, approvals may be based on the economics of the best-case scenario, but in reality, the therapies are likely to be used more widely, including "off-label" use for patient populations that are a less perfect match than those considered under the regulatory process.[64] Indeed, off-label uses of gene-therapy treatments utilizing CRISPR have been anticipated. For instance, the

60. Bill Berkrot, *Spark's Price for Luxturna Blindness Gene Therapy Too High: ICER*, REUTERS (Jan. 12, 2018, 12:56 PM), https://www.reuters.com/article/us-spark-icer/sparks-price-for-luxturna-blindness-gene-therapy-too-high-icer-idUSKBN1F1298 [https://perma.cc/2DZM-BUEA].

61. *See id.*

62. *See infra* text accompanying notes 77–79.

63. *See* ICER REPORT, *supra* note 43, at 18.

64. Off-label uses occur when a patient uses an FDA-approved treatment for a use not approved by the Agency. *Understanding Unapproved Use of Approved Drugs "Off Label"*, FDA, https://www.fda.gov/ForPatients/Other/OffLabel/ucm20041767.htm [https://perma.cc/ZSE8-Z2VP]. In this scenario, the gene therapy would be approved for a specific patient population and the off-label use would expand the treatment to a broader segment of society.

National Academy of Sciences report on genome editing gives the example of a treatment approved for adults that is expanded to a pediatric patient population through off-label use, although it notes that the extent of off-label use may be more limited than in the case of pharmaceuticals.[65]

A potential problem with off-label uses from a reimbursement perspective is that it shifts the economic model justifying the cost of treatment. As the treatment is extended to other patient populations, it may be less effective, yet it likely carries the same price tag. An analogous example is the drug Kalydeco, which was developed as a treatment for the five percent of CF patients with a specific mutation in CFTR, the CF gene.[66] The drug was effectively a cure in that population[67] but had limited effectiveness for other CF patients who lacked this specific mutation. Nevertheless, many CF patients with other mutations clamored to use the expensive therapy to obtain whatever improvements in quality of life it afforded.[68] Kalydeco, which costs $311,000 per year, is not a one-time treatment.[69] But, like gene therapies, its high price tag is potentially justified by effectiveness and by the savings it generates by eliminating the need for more expensive ongoing therapy—a savings not seen when the expected therapeutic value falls short of full recovery.

C. Patents

Patents are another aspect of our medical system that can potentially drive up costs. Patents are provided to ensure that the research and development costs of a new treatment can be recouped through a period of market monopolization.[70] With companies controlling patents for the newly developed treatments, there will likely not be market competition to help bring down the cost of gene-editing treatments in the near future. Additionally, lack of market competition alters the motivations of the companies already holding

65. NAT'L ACADS. OF SCIS., ENG'G, & MED., HUMAN GENOME EDITING: SCIENCE, ETHICS, AND GOVERNANCE 105 (2017).

66. *See* Bonnie W. Ramsey et al., *A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation*, 365 NEW ENG. J. MED. 1663, 1664 (2011).

67. *See id.* at 1663.

68. *See* Elie Dolgin, *First 'Breakthrough' Drugs Designated, but Dilution Worries Linger*, 19 NATURE MED. 116, 116–17 (2013).

69. Joe Nocera, Opinion, *The $300,000 Drug*, N.Y. TIMES (July 18, 2014), https://www.nytimes.com/2014/07/19/opinion/joe-nocera-cystic-fibrosis-drug-price.html [https://perma.cc/8YGN-DJWN].

70. Jacob S. Sherkow, *CRISPR, Patents, and the Public Health*, 90 YALE J. BIOLOGY & MED. 667, 667–68 (2017).

these patents, making them less willing to negotiate for the complex alternative payment systems, described below, because these systems will not give them an advantage over their (nonexistent) competitors.[71]

The development costs for these new technologies is nothing to sniff at. One article estimated that it will take eight years and several hundred million dollars to develop a new gene therapy and obtain the necessary regulatory approval.[72] Additionally, the patents provide a buffer for companies that can invest in a variety of potential treatments in case some do not thrive, like Glybera.[73] There are ongoing patent fights over CRISPR technologies, but overall, the potential therapeutic market is controlled by a couple of players that have broad patents and are issuing surrogate licenses for other companies to use the patented technology in a particular space.[74]

III. ALTERNATIVE PAYMENT SYSTEMS

A. Payer Issues

The high cost of gene-therapy treatments challenges the traditional U.S. reimbursement system. Although current medical care is replete with examples of expensive treatments and pharmaceuticals, gene-therapy treatments are somewhat unique in their elevated, one-time costs. It is unclear whether insurers will cover gene-therapy treatments across the board.[75] Given the one-time high cost, insurers may exclude coverage of gene-therapy treatments altogether, or they may provide coverage for such technologies on a case-by-case basis.[76] There are several reasons why insurers are disincentivized from providing coverage for such treatments.

First, insurance policyholders may change their insurance coverage due to changes in employment, life situation, or geographic location. For example, the current median length of stay with an

71. *See* Louis P. Garrison, Jr. et al., *Private Sector Risk-Sharing Agreements in the United States: Trends, Barriers, and Prospects*, 21 AM. J. MANAGED CARE 632, 632, 636 fig.2 (2015) [hereinafter Garrison et al., *Private Sector*].

72. Orkin & Reilly, *supra* note 43, at 1060. However, the authors of that article are affiliated with the industry, and therefore other estimates of research and development costs could conceivably be lower.

73. Sherkow, *supra* note 70, at 668.

74. Jorge Contreras & Jacob S. Sherkow, *CRISPR, Surrogate Licensing, and Scientific Discovery*, 355 SCI. MAG. 698, 698–99 (2017).

75. Carr & Bradshaw, *supra* note 43, at 381; Sherkow, *supra* note 70, at 668–69.

76. Sherkow, *supra* note 70, at 669.

employer is 4.2 years,[77] and since many Americans receive their insurance through their employers, they may switch insurers at that rate as well. Other individuals may switch between different specific insurance plans, switch plan options within their employer offerings at open enrollment, or shift from one type of insurance, such as Medicaid, to another, such as a private individual plan. Indeed, it is estimated that the average person stays with their medical insurance provider for "less than 6 years."[78] Given the distinct possibility that a current policyholder will no longer be a customer in a few years, a private insurer has little incentive to invest in treatments with long-term benefits but immediate one-time costs in the hundreds of thousands of dollars.[79]

Second, insurers may be less likely to cover therapies because there is a lack of evidence that the treatments will be successful long term.[80] Gene-editing treatments come into the market with the promise and hope of lasting cures, but the technology is new enough that developers have not gathered data on a full generation of patients undergoing the treatment. Additionally, given the one-and-done nature of the treatment, there is not an option to discontinue treatment that proves to be ineffective for the patient, as is the case for other expensive, but more long-term, treatments.[81] The regulatory-approval process focuses on safety and analytical and clinical validity; however, to get approval, it is not necessary to demonstrate clinical utility.[82] Thus, a treatment can enter the market as a safe product but run into barriers of reimbursement as insurers are wary of paying for untested technology.[83] Without

77. Press Release, Bureau of Labor Statistics, Employee Tenure in 2018 (Sept. 20, 2018, 10:00 AM), https://www.bls.gov/news.release/pdf/tenure.pdf [https://perma.cc/KGY9-6CZ6].

78. Evans, *supra* note 10, at 2671.

79. This is analogous to a situation where an insurer has little incentive to pay for an expensive preventive treatment because it would likely not be the insurance company paying for the treatment for any potential developed symptoms. Anya E.R. Prince, *Prevention for Those Who Can Pay: Insurance Reimbursement of Genetic-Based Preventive Interventions in the Liminal State Between Health and Disease*, 2 J.L. & BIOSCIENCES 365, 373–74 (2015).

80. Sherkow, *supra* note 70, at 668.

81. Carr & Bradshaw, *supra* note 43, at 384.

82. Lori Knowles, Westerly Luth & Tania Bubela, *Paving the Road to Personalized Medicine: Recommendations on Regulatory, Intellectual Property and Reimbursement Challenges*, 4 J.L. & BIOSCIENCES 453, 498 (2017).

83. This is a familiar problem with new technologies. For example, multigene panel testing is increasingly being offered to patients with the promise that it is cheaper to test many genes at once rather than to test each individually. However, insurers have been slow to adopt coverage for these tests due to the lack of data on clinical utility. *See, e.g.*,

reimbursement, treatments are more likely to go the way of Glybera and fail before ever really making it onto the market, despite crossing necessary regulatory hurdles and spending the initial research and development costs.[84]

Third, even if insurers are interested in and willing to cover gene-editing treatments, the reimbursement system may be overwhelmed by the upfront high cost of treatments.[85] This is a foreseeable problem as the "ever-growing development pipeline of gene therapies on the horizon" begins to enter the market.[86] Relatively conservative estimates of uptake of gene therapy show the impact of cost on the insurance system:

> Even if gene therapies are developed to treat only one in ten patients with a genetic condition—approximately 1% of the total US population—the cumulative budget impact at that price could rise to US$3 trillion, as much as is currently spent in a year on all health care in the USA.[87]

Given that insurers may not be driven to cover these treatments or may be unable to afford them, the treatment developers will likely be motivated to find creative ways to obtain reimbursement. Kymriah's introduction into the U.S. market provides an example of the developer's willingness to think creatively about potential payment models. On the same day the FDA approved Kymriah, priced at $475,000, the Centers for Medicare and Medicaid Services ("CMS") announced that it would work with stakeholders to explore "innovative payment arrangements."[88] The goal of innovating would

Julia R. Trosman et al., *Payer Coverage for Hereditary Cancer Panels: Barriers, Opportunities, and Implications for the Precision Medicine Initiative*, 15 J. NAT'L COMPREHENSIVE CANCER NETWORK 219, 220 (2017).

84. Louis P. Garrison Jr. et al., *Performance-Based Risk-Sharing Arrangements—Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force*, 16 VALUE HEALTH 703, 704 (2013) [hereinafter Garrison et al., *Performance-Based*] ("If payers are reluctant to adopt, manufacturers face the risk of reduced revenue for a product they regard as delivering value."); *see also* Szymon Jarosławski & Mondher Toumi, *Market Access Agreements for Pharmaceuticals in Europe: Diversity of Approaches and Underlying Concepts*, 11 BMC HEALTH SERVICES RES., no. 259, Oct. 8, 2011, at 1, 1.

85. E. Hanna et al., *Funding Breakthrough Therapies: A Systematic Review and Recommendation*, 122 HEALTH POL'Y 217, 225–26 (2018).

86. Carr & Bradshaw, *supra* note 43, at 382.

87. Hampson et al., *supra* note 8, at 18.

88. Press Release, Ctrs. for Medicare & Medicaid Servs., CMS: Innovative Treatments Call for Innovative Payment Models & Arrangements (Aug. 30, 2017), https://www.cms.gov/newsroom/press-releases/cms-innovative-treatments-call-innovative-payment-models-and-arrangements [https://perma.cc/TW42-QD3X].

be to help pay for treatments that provide high patient value with a high one-time cost.[89] Indeed, CMS has been a driver of exploring alternative payment structures as part of a broader increased focus on value-based medicine in lieu of fee-for-service care.[90] Beyond just CMS, however, many different innovative pricing models have been introduced or suggested in the United States and internationally.[91] These pricing models range from financial agreements (such as discounts) to health-outcomes-based agreements (such as pay for performance).[92] The models have been introduced across a wide variety of drugs and treatments but, in anticipation of the costs of gene therapy and gene editing, a number of these new pricing models have been suggested to ease the burden of covering gene-editing technologies.[93]

B. Innovative Payment Models

The goals of different payment schemes can be broadly categorized as lowering the costs of the therapy and expanding the insurance pool.[94] Lowering costs will increase the likelihood that insurers will cover the treatment and that individuals can access the treatment. Absent lowering costs, expanding the pool spreads the high cost of care across a broader group, making it easier for insurance companies to absorb the cost into the system and, therefore, more likely that they will opt for coverage. As discussed above, sometimes insurers loathe covering expensive one-off treatment since the policyholder may not be a customer in a couple years.[95] Spreading the risk of requests for high-cost gene-therapy coverage across a broader risk pool limits the impetus for insurers to avoid the difficulty associated with paying for coverage for policyholders possibly in transition. Three alternative payment structures—pay for performance, indication-based pricing, and discounts—primarily aim to lower the cost paid to the developer for the treatment.[96] Annuities and reinsurance, on the other hand, primarily seek to spread the risk either temporally or across people and policies.[97]

89. *Id.*
90. Hanna et al., *supra* note 85, at 218.
91. *Id.*
92. *Id.*
93. *Id.*
94. *See id.*
95. *See supra* Section II.B.
96. Hanna et al., *supra* note 85, at 228.
97. *Id.*

This section discusses the five alternative payment structures mentioned above that have been implemented, discussed, or recommended in the context of expensive gene-therapy treatments: (1) pay for performance, (2) indication-based pricing, (3) discounts, (4) annuity payments, and (5) reinsurance. For example, the Institute for Clinical and Economic Review ("ICER") identified these alternative structures as options for use in gene therapy at the 2016 ICER Membership Policy Summit.[98] This summit brought together representatives, including drug manufacturers, pharmacy benefit management, and insurers, to discuss various payment options.[99] Since then, there have been efforts to implement most of these alternative structures within a gene-therapy context, as will be discussed more below.[100]

1. Pay for Performance

Pay-for-performance models, also called outcome-based or risk-sharing models,[101] require the patient, the payer, or both to pay the full cost of the treatment only if it is effective—thereby lowering the cost of the treatment for some individuals and for payers in the aggregate, while keeping the overarching list price high.[102] There are several goals to setting up such a system. For one, insurers may be more likely to agree to cover a treatment when they are only paying for value.[103] From a societal perspective, pay for performance would also be beneficial because it will ideally spur the collection of evidence of effectiveness and encourage the pharmaceutical community (or in this case the gene-therapy community) to focus on marketing to those populations where the drug or treatment is likely to be most effective. This raises two primary questions: What would the ongoing payment mechanism look like, and how will effectiveness be measured?[104]

98. ICER REPORT, *supra* note 43, at 8–10; Hampson et al., *supra* note 8, at 20.

99. *See* ICER REPORT, *supra* note 43, at 1.

100. *See infra* Sections IV.B.1–5.

101. Peter J. Neumann et al., *Risk-Sharing Arrangements that Link Payment for Drugs to Health Outcomes Are Proving Hard to Implement*, 30 HEALTH AFF. 2329, 2329 (2011).

102. *See* Jarosławski & Toumi, *supra* note 84, at 2.

103. ELIZABETH SEELEY & AARON S. KESSELHEIM, COMMONWEALTH FUND, OUTCOMES-BASED PHARMACEUTICAL CONTRACTS: AN ANSWER TO HIGH U.S. DRUG SPENDING? 1–2 (2017), https://www.commonwealthfund.org/sites/default/files/documents/___media_files_publications_issue_brief_2017_sep_seeley_outcomes_based_pharma_contracts_ib.pdf [https://perma.cc/N2ER-8UD8]; Neumann et al., *supra* note 101, at 2330.

104. These are by no means the only questions that must get sorted before such payment schemes can be successful. For example, other potential issues include the absence of suitable data infrastructure and high implementation costs. SEELEY &

Pay-for-performance models can either be set up where insurers buy the full cost of treatment up front and then receive rebates if the treatment is not effective long term.[105] Alternatively, insurers could pay an initial amount and have some form of continuing payments for as long as the treatments work.[106] One of the most difficult parts of this scenario is that it creates a long-term payment relationship between a treatment developer, the payer, and the patient for a single event that has already occurred. Thus, potential complications arise if and when the patient changes insurance companies.[107] Does the new insurer now accept responsibility to pay for the remaining costs of a treatment they did not initially approve or cover? Does the old insurance company continue to have an obligation to cover costs for a patient who is no longer their policyholder? If the insurer is expecting rebates, how do they continue to track the health of a patient who is no longer their policyholder? It is perhaps no wonder that many examples of implemented pay-for-performance contracts have arisen in countries with single-payer systems, where this problem of switching insurance plans does not arise.[108]

A rebate may be the best way to address this scenario, especially if the treatment developer assesses performance across a patient population rather than for a specific patient.[109] Thus, the relevant data would be the aggregate success of a treatment rather than data particular to one patient—a situation that would also encourage

KESSELHEIM, *supra* note 103, at 4–5; Garrison et al., *Private Sector*, *supra* note 71, at 634; Neumann et al., *supra* note 101, at 2329.

105. Rachel Sachs, Nicholas Bagley & Darius N. Lakdawalla, *Innovative Contracting for Pharmaceuticals and Medicaid's Best-Price Rule*, 43 J. HEALTH POL. POL'Y & L. 5, 10 (2017).

106. *Id.*

107. *See* Orkin & Reilly, *supra* note 43, at 1061; Ted Slocomb et al., *New Payment and Financing Models for Curative Regenerative Medicines*, IN VIVO, July–Aug. 2017, at 1, 3–4, https://www.hklaw.com/files/Uploads/Documents/Articles/ARM_Curative_Regenerative_IV1707_LRS.pdf [https://perma.cc/DX52-KFBX].

108. *See, e.g.*, Garrison et al., *Private Sector*, *supra* note 71, at 633 (noting that of the 148 worldwide risk-sharing agreements, including pay-for-performance agreements, as of 2013, only eighteen were from the United States and only seven were implemented in the private sector). The authors also note that most of these arrangements were implemented in single-payer systems in Europe, Canada, and Australia. *Id.*; *see also* Josh J. Carlson, Louis P. Garrison, Jr. & Sean D. Sullivan, Commentary, *Paying for Outcomes: Innovative Coverage and Reimbursement Schemes for Pharmaceuticals*, 15 J. MANAGED CARE PHARMACY 683, 685–86 (2009) (highlighting other potential barriers to implementation in the United States that could also be present in single-payer systems); Neumann et al., *supra* note 101, at 2332 (noting that another benefit of the European systems is that they have more leverage to contract such plans).

109. Sachs et al., *supra* note 105, at 12.

broad data collection on effectiveness of the treatment overall.[110] Another potential solution is to place the initial payment into a type of escrow account until the success of the drug has been determined.[111] If it does not succeed, as defined by the parties, the payer will get the money back from escrow.[112] If it does succeed, the manufacturer will get the money.[113] Although this would address many of the back-end challenges of long-term follow-up, it would not ease the initial payments made by payers and therefore may still lead payers to opt not to cover the expensive treatment due to high upfront costs.

As discussed previously, the pay-for-performance model has already made a brief debut in the U.S. gene-therapy markets when CMS announced its willingness to develop an alternative payment model for Kymriah.[114] This first attempt showed little promise, since less than one year after the initial announcement CMS ended negotiations over the payment deal, ostensibly out of concern that Novartis, the maker of Kymriah, had too much influence over the negotiations.[115]

This raises the second major question of a pay-for-performance model: How and when should effectiveness be measured?[116] During the CMS negotiations for Kymriah, Novartis advocated for an assessment of effectiveness one month after treatment.[117] Others argued that this was too short a time period to properly measure success or to determine if there will be any complications or adverse

110. Garrison et al., *Performance-Based*, *supra* note 84, at 709, 711–13. (discussing use of performance-linked reimbursement at the patient level as opposed to part of broader research).

111. Of course, as discussed later, what counts as "success" must be determined ahead of time. *See infra* text accompanying notes 116–24.

112. Hanna et al., *supra* note 85, at 227.

113. This was discussed in the context of coverage with evidence development but is equally applicable to pay for performance. *Id.*

114. Sarah Karlin-Smith & David Pittman, *CMS Quit Test of Pricey Cancer Treatment Amid Concerns Over Industry Role*, POLITICO (July 9, 2018, 3:22 PM), https://www.politico.com/story/2018/07/09/cms-quit-test-of-pricey-cancer-treatment-amid-concerns-over-industry-role-674086 [https://perma.cc/2FFA-C2RN].

115. *Id.* Private payers may still be exploring these types of payment arrangements for their policies with Novartis.

116. *See, e.g.*, Garrison et al., *Private Sector*, *supra* note 71, at 635–36.

117. Rachel Sachs, *CMS Abandonment of Outcomes-Based Payment Deal with Novartis Is a Missed Opportunity*, HARV. L. PETRIE-FLOM CTR.: BILL OF HEALTH BLOG (July 12, 2018), https://blogs-test.harvard.edu/billofhealth/2018/07/12/what-does-cms-withdrawal-of-its-kymriah-deal-mean-for-cms-and-outcomes-based-contracts/ [https://perma.cc/SX8D-QM32].

events.[118] There is a balance, however, to selecting an appropriate time frame to measure the outcomes of a treatment. Shorter time frames are generally recommended for pay-for-performance systems, since longer time frames increase the administrative costs and complexity of implementing the model.[119] Of course, too short of time frames may not convince payers that a treatment is truly successful and therefore will not be successful in bringing gene therapies to market.

To be successful, pay for performance should incorporate relatively easy-to-measure outcomes.[120] These should be "objective, clearly defined, reproducible, . . . difficult to manipulate," and not influenced by other situations or patient characteristics.[121] Gene therapy specifically, however, may not have easy-to-measure outcomes available. As one commentary discussing the challenges of alternative payment models describes:

> [U]nlike hypertension whereby reduction in blood pressure is an easy to understand end point for an antihypertensive and could be used in a pay-for-performance . . . , there are difficulties in demonstrating outcomes via hard end points in genetic diseases, even on a patient level as population studies are difficult given the small numbers, and there is also the additional time lag (sometimes years) between administration and any apparent clinical benefit.[122]

Additionally, since each gene-therapy treatment is unique, the outcomes assessment will need to be renegotiated between developers and payers for each new treatment.[123]

These complications of negotiating pay-for-performance models have led to fairly low and stagnant uptake of these types of agreements in the private sector across a variety of treatments.[124] Gene therapy has increased calls for implementation of pay for performance in this area, but it remains to be seen whether the private sector will increasingly negotiate these arrangements.

118. *Id.*
119. Neumann et al., *supra* note 101, at 2333.
120. *Id.*
121. *Id.*
122. Carr & Bradshaw, *supra* note 43, at 385.
123. *Id.* at 386.
124. Garrison et al., *Private Sector*, *supra* note 71, at 632.

2. Indication-Based Pricing

When a drug is introduced into the market, it may be prescribed for a number of different conditions, whether on or off label.[125] However, the drug is likely to have different levels of effectiveness, especially when the conditions, or indications, are quite different.[126] This variable effectiveness across different patient populations is behind original calls for indication-based pricing. Under indication-based pricing, the most effective uses of the treatment cost more than those uses that have less effectiveness.[127] The economic motivations for patients paying more for those treatments that provide higher value is that, by successfully segmenting patient markets, access to the drug will increase across patient populations.[128] The lower costs for some segments of the population will make it more likely that they can access treatment.[129] This method, however, has been criticized, with those against the practice arguing that this will not lower costs but increase health-care spending through greater utilization of less effective treatments.[130]

Indication-based pricing was utilized for Kymriah in the gene-therapy context.[131] About a year after its initial approval, the FDA gave Kymriah a new approval, expanding it from a therapy intended only for young adults and children with acute lymphoblastic leukemia to a treatment for large B-cell lymphoma in all patients, including adults.[132] The cost of the same drug for this different patient population is $373,000, compared to the original $475,000.[133] Whether this type of pricing will increase access to helpful treatment or simply increase utilization of less effective treatments remains to be seen.

3. Discounts

A third way to lower the cost of treatments is, well, to lower the cost of treatments. Drug manufacturers have utilized discounts or

125. Sachs et al., *supra* note 105, at 9.

126. *Id.*

127. Amitabh Chandra & Craig Garthwaite, *The Economics of Indication-Based Drug Pricing*, 377 NEW ENG. J. MED. 103, 103 (2017).

128. *See id.* at 104.

129. *See id.*

130. *See id.* at 103–04.

131. *See* Lydia Ramsey, *A Cutting-Edge New Cancer Treatment Has Two Different Price Tags, and It Could Be the Future of How We Pay for Drugs*, BUS. INSIDER (May 7, 2018, 7:30 AM), https://www.businessinsider.com/indication-based-pricing-for-novartis-car-t-cell-therapy-kymriah-2018-5 [https://perma.cc/7NG5-Z5NL (dark archive)].

132. *See id.*

133. *Id.*

rebates as a way to increase uptake of a pharmaceutical product by charging a lower price tag than the list price of the good.[134] In the context of gene-therapy treatments, developers may opt to provide discounts to certain patients or a specific insurance plan in order to encourage uptake and coverage.[135] Discounts can be beneficial because they lower the cost of the treatment—thus minimizing a significant barrier to access.[136] Additionally, payers generally prefer discounts because they are much simpler to manage than the complex administration of other systems like pay for performance.[137]

However, the implementation of discounts may still create problems for two reasons. First, discounts have been critiqued because, unlike pay-for-performance and indication-based pricing, the decreased costs are not associated with the value the treatment or drug carries.[138] Thus, discounts do little to motivate treatment developers to improve the efficiency of their product.

Second, for the extremely large payments of gene therapies, discounts are likely to be negotiated on a case-by-case—or at least a health-plan-by-health-plan—basis, if provided at all. Case-by-case negotiations place a lot of discretion with the developers to control who has access to the treatment. For example, StatNews recently published a story about two siblings in the Amish community who carry the specific gene mutation that Luxturna is approved to treat.[139] The catch is that the Amish community pools resources to pay for the community's health needs—it does not have private insurance policies to cover even a portion of the expenses of gene therapy.[140] Additionally, since there are two children who would need the treatment in the community, the total cost would be $1.7 million.[141] The families are working with the maker of Luxturna, Spark

134. ICER REPORT, *supra* note 43, at 30–31.

135. *Id.* at 29 (highlighting the goal to meet optimal levels of coverage).

136. *Id.* at 30–31 (noting that the goal of discounts is to lower the individual level costs to within the ability to pay).

137. *See* Jarosławski & Toumi, *supra* note 84, at 5–6 (citing the statement of the chair of the U.K. National Institute for Health and Care Excellence ("NICE") that "a simple discount may eliminate the need to put in place complicated schemes that require substantial management input"); *see also* Garrison et al., *Private Sector*, *supra* note 71, at 634 (identifying barriers to implementing alternative payment schemes linked to outcome, like pay for performance).

138. Neumann et al., *supra* note 101, at 2332–33.

139. *See* Eric Boodman, *The Amish Pool Resources for Their Medical Care. A Budget-Busting Gene Therapy Puts Them in a Bind*, STAT (May 8, 2018), https://www.statnews.com/2018/05/08/luxturna-gene-therapy-price-amish [https://perma.cc/M792-JFBY].

140. *See id.*

141. *See id.*

Therapeutics, to negotiate a discount for the drug, similar to that an insurer might get; although at the time of the story, the company was not willing to give any discounts.[142] Here again, as with pay-for-performance schemes, a larger payer or single-payer may be better able to negotiate discounts for their policyholders than individuals themselves or a smaller health plan.[143]

4. Reinsurance

Pay-for-performance pricing, indication-based pricing, and discounts are all alternative payment systems that seek to lower the cost of treatment for at least some segment of the population—those whose treatment was ineffective, those disease or indication groups experiencing different treatment effectiveness, and those whose payers have negotiated reduced rates, respectively. Other alternative payment models seek to spread the cost across a broader risk pool. By spreading the risk of a high payment across a larger insurance pool, payers minimize the potential harm of having several high-cost payments within one plan year. For example, an insurance pool of ten people is much more likely to be impacted if one needs an $800,000 treatment than an insurance pool of one hundred. Therefore, insurance companies can try to grow their risk pools—generally, they aim to increase the number of relatively healthy policyholders in their risk pool.[144]

Alternatively, insurers can seek reinsurance as another way to spread their risk even without contracting with more policyholders. Reinsurance is effectively an insurance policy for the insurance company, which covers the risk of a high one-time payment.[145] In this way, individual companies are protected against an unanticipated number of high payouts and spread the cost across what is effectively pooled risk for insurance companies.[146] As a way to pool risk across insurances, reinsurance is an especially attractive solution in countries, like the United States, that have a fragmented health-care system.[147] Reinsurance, however, is not necessarily expected to decrease costs since it reduces incentives for drug developers to lower

142. *See id.*
143. *See id.*
144. *See* ICER REPORT, *supra* note 43, at 31.
145. *See id.*
146. *See id.*
147. Hanna et al., *supra* note 85, at 227.

prices.[148] Additionally, some reinsurers have explicitly begun to exclude gene therapies from their coverage.[149]

5. Annuity Payments

Another proposed solution to high insurance payouts is to set up reimbursement as a series of payments over time, rather than require the full cost all at once.[150] Called annuity payments, or alternatively amortization, these models would tend to make costs for an insurance company more consistent and less random.[151] Such models have also been analogized to a home mortgage system—rather than pay for the good up front and reap the benefit for years to come, homeowners instead enter into mortgages to set costs over time and defray the initial up-front cost.[152] Whereas reinsurance spreads cost across a greater number of people, annuity payments spread cost temporally.

Annuity payments require an up-front loan that the patient or insurer then pays off over time—much like a mortgage company loaning the initial money to pay for the house.[153] This loan could come from the treatment developer, a third-party financer, or a consumer loan, but some also suggest that it could be done through an initial government-issued loan.[154] The annuity payment model can also be combined with a pay-for-performance model, where the annuity payments only continue as long as the treatment remains effective for the patient.[155] Of course, similar, if not more complex, problems arise due to the long-term payment relationship between insurer, drug manufacturer, and patient. Questions of what happens when a patient switches insurance plans remain an issue,[156] along with new questions of what happens if the payments go into default and what implications this would have to the overall cost of the system.[157]

148. *Id.*

149. *Id.*

150. ICER REPORT, *supra* note 43, at 32; SCOTT GOTTLIEB & TANISHA CARINO, AEI RESEARCH, ESTABLISHING NEW PAYMENT PROVISIONS FOR THE HIGH COST OF CURING DISEASE 4 (2014), https://www.aei.org/wp-content/uploads/2014/07/-establishing-new-payment-provisions-for-the-high-cost-of-curing-disease_154058134931.pdf [https://perma.cc/9ZCZ-B9YK]; Slocomb et al., *supra* note 107, at 3.

151. *See* Slocomb et al., *supra* note 107, at 3.

152. Sachs et al., *supra* note 105, at 14.

153. *Id.*

154. ICER REPORT, *supra* note 43, at 32–33; Hampson et al., *supra* note 8, at 21–22.

155. *See* Carr & Bradshaw, *supra* note 43, at 385; Orkin & Reilly, *supra* note 43, at 1061.

156. *See* Carr & Bradshaw, *supra* note 43, at 385.

157. Sachs et al., *supra* note 105, at 14.

Additionally, while annuities may help to bring gene therapies onto the market, they essentially push health-care costs down the road without effectively lowering costs.[158] This may strain health-care budgets in the future and continue to threaten the health-care systems.[159]

C. Patient Issues

Even if innovative pricing models are adopted and work to lower the cost of new gene-editing treatments or to spread the expense temporally or across a broader risk pool, cost may still be an issue for patients—a perennial problem in our broken health-care system. For example, even with insurance coverage, out-of-pocket costs for gene-editing treatments may be prohibitive for many individuals. Additionally, in a society where there is inequitable access to health insurance itself, there will be many people for whom reimbursement policies are irrelevant, and this problem will be magnified if changes to the Affordable Care Act ("ACA") remove protections for preexisting conditions. Thus, it is foreseeable that cost will be a significant barrier to access as somatic gene-editing therapies enter clinical care.[160]

1. Out-of-Pocket Expenses

For any large-cost treatment, out-of-pocket costs, such as co-pays and coinsurance, can prevent individuals from accessing care, even if that care is covered in part by insurance.[161] Indeed, even small co-pays

158. *See* Hanna et al., *supra* note 85, at 227.

159. *Id.*

160. Of course, we can expect that other health-care inequalities will lead to barriers to access. For example, there is already a dearth of genetic services across the country, especially in rural areas far from academic medical centers that generally handle genetic services. *See, e.g.*, Alice K. Hawkins & Michael R. Hayden, *A Grand Challenge: Providing Benefits of Clinical Genetics to Those in Need*, 13 GENETICS MED. 197, 197 (2011). This inequality can be further exacerbated with regard to gene-editing treatment since the FDA sometimes grants approval contingent on the treatment being provided by specifically trained facilities or doctors. *See, e.g.*, FDA Kymriah Press Release, *supra* note 17. This has also been recommended in the gene-therapy arena where treatments may need to be given at specific hospitals or treatment facilities. Hampson et al., *supra* note 8, at 19. Additionally, problematic racial disparities regarding referral to genetic testing create differential outcomes across patients of different ethnicities and races. *See, e.g.*, Molly Quinn & Victor Fujimoto, *Racial and Ethnic Disparities in Assisted Reproductive Technology Access and Outcomes*, 105 FERTILITY & STERILITY 1119, 1119 (2016).

161. *See, e.g.*, *Preventive Services Covered by Private Health Plans Under the Affordable Care Act*, HENRY J. KAISER FAM. FOUND. (Aug. 4, 2015), https://www.kff.org/health-reform/fact-sheet/preventive-services-covered-by-private-health-plans/ [https://perma.cc/G3VJ-DTK6].

can be a barrier to care—one of the reasons why the ACA included preventive care free of all out-of-pocket costs to policyholders.[162] High out-of-pocket costs can lead to disparities in access to care.[163] For example, in part due to the high costs associated with in vitro fertilization ("IVF"), minorities and persons of low-to-middle socioeconomic status are less likely to get care for infertility.[164] It is especially important to continue to consider out-of-pocket costs and barriers of access for patients because society could implement several innovative pricing systems described above but still not improve equitable access since innovative models will not help those that choose not to undergo a treatment due to out-of-pocket costs.[165]

Out-of-pocket expenses are also a problem for those who do not have insurance coverage. As the example of the Amish seeking discounts for Luxturna highlights, individuals and even communities without insurance reimbursement can find the high costs of gene-therapy treatments a significant barrier.[166] Even for those with insurance coverage, getting access to high-cost gene-therapy treatments can be difficult.[167] High out-of-pocket costs could prevent a patient from getting care or can necessitate finding other sources of money, such as from a crowdfunding website like GoFundMe.[168] Additionally, until therapies are covered by existing insurance policies, the new treatments will essentially have to be covered via self-pay.[169]

2. Preexisting Conditions

Currently, individuals with genetic conditions are protected against discrimination in access to health insurance principally by two laws—the ACA and the Genetic Information Nondiscrimination Act ("GINA"). GINA prohibits health insurers from denying an individual health insurance based on genetic information, including genetic test results and family medical history.[170] One catch, however,

162. *See id.*
163. *See id.* fig.1.
164. *See* Quinn & Fujimoto, *supra* note 160, at 1120.
165. SEELEY & KESSELHEIM, *supra* note 103, at 5.
166. *See* Boodman, *supra* note 139.
167. *See id.*
168. *See id.*
169. *See, e.g.*, Antonio Regalado, *Two Sick Children and a $1.5 Million Bill: One Family's Race for a Gene Therapy Cure*, MIT TECH. REV. (Oct. 23, 2018), https://www.technologyreview.com/s/612259/two-sick-children-and-a-15-million-bill-one-familys-race-for-a-gene-therapy-cure/ [https://perma.cc/J2BV-W2DV].
170. *See* Genetic Information Nondiscrimination Act of 2008, 29 U.S.C. § 1182(b) (2012).

is that GINA's protections do not cover manifested symptoms, even if they have an underlying genetic cause.[171] Enter the ACA, which prohibits health insurers from considering preexisting conditions and symptoms when determining insurance coverage and setting rates.[172] Protection for preexisting conditions is simultaneously one of the most popular provisions of the law and one of the most endangered.[173] For example, currently the Trump administration has declined to defend the ACA in an ongoing lawsuit that argues that the preexisting condition protections are unconstitutional.[174] Given existing political threats to the preexisting condition protections of the ACA, it is worth noting how genetics in general and gene-editing treatments in particular may challenge the scope of protections provided by GINA were the ACA's protections to disappear.

If the preexisting condition clause of the ACA no longer applies, then GINA will return as the primary health insurance protection for individuals with gene-based risks and predispositions. However, it is difficult, if not impossible, to draw a clear distinction between a predisposition and a disease. For example, if a patient has a variant in a Lynch-Syndrome-associated gene that indicates that he or she is at increased risk for colon cancer, this alone would be protected genetic information.[175] If the same patient developed colon cancer, this would be a manifested condition.[176] But does the initiation of preventive measures, like screening for what doctors and genetic counselors identify as a "cancer predisposition syndrome," indicate that what was a predisposition is now a disease? Does finding a polyp qualify as manifesting? Virtually every genetic condition not fully penetrant at birth poses some variant of this conundrum.

GINA itself does not define "manifestation" of disease.[177] However, GINA's regulations related to health insurance state that a disease is manifest when

> an individual has been or could reasonably be diagnosed with the disease, disorder, or pathological condition by a health care

171. *See* Anya E.R. Prince & Benjamin E. Berkman, *When Does an Illness Begin: Genetic Discrimination and Disease Manifestation*, 40 J.L. MED. & ETHICS 655, 655 (2012).

172. *See* Patient Protection and Affordable Care Act, 42 U.S.C. § 18001(a), (d) (2012).

173. *See* Julie Rovner & Julie Appleby, *Administration Challenges ACA's Preexisting Conditions Protection in Court*, KAISER HEALTH NEWS (June 8, 2018), https://khn.org/news/administration-challenges-acas-preexisting-conditions-protection-in-court [https://perma.cc/8PXL-YXCZ].

174. *See id.*

175. 26 C.F.R. § 54.9802-3T(a)(6)(ii) ex. 2 (2018).

176. *Id.* § 54.9802-3T(a)(6)(ii) ex. 3.

177. *See* Prince & Berkman, *supra* note 171, at 655.

> professional with appropriate training and expertise in the field of medicine involved. For purposes of this section, a disease, disorder, or pathological condition is not manifest if a diagnosis is based principally on genetic information.[178]

Gene-editing therapies will likely continue to blur the bounds between genotype and phenotype—that is, between a person's genes and their actual self: the collection of features, characteristics, and tendencies that presents itself to the world. Indeed, with gene editing, it is the genotype itself that is the manifestation of disease being treated, sometimes in advance of any symptomology at all. Many potential gene-therapy targets, such as metabolic diseases, are progressive and show effects over time, although the genetic variant responsible for the disease could be identified in utero or at birth. In many scenarios, presymptomatic treatment may be one of the advantages of gene therapy, which could allow us to act before the disease inflicts damage that cannot be undone. For this reason, we emphasize the second part of the definition of manifestation in the regulations—that if a diagnosis is based principally on genetic information it is not considered a manifest condition. If this protection is lost (and without the ACA protections), and if clinical genetic testing and preventive gene-editing therapies become more mainstream, some people would be at risk of losing their health insurance simply because of their genetic makeup.

Unfortunately, if the ACA protections are repealed, many individuals who could benefit from gene-therapy or gene-editing treatments could be denied coverage based on existing symptoms.[179] For example, without ACA protection, if an individual has been experiencing vision loss, a new individual insurance policy could deny the patient health insurance based on the preexisting condition or refuse to cover the cost of Luxturna due to a preexisting condition exclusion. While other insurance, such as Medicaid, may be an option (assuming that state Medicaid had opted to cover the expensive treatment), this would push more patients needing extremely expensive medical care into already stretched public systems rather than pooling risks throughout private and public insurance. Ideally, of course, both the protections of the ACA and GINA should remain in place in order to have continuity of protection across the murky boundary between genotype and phenotype.

178. 26 C.F.R. § 54.9802-3T(a)(6)(i) (2018). The EEOC regulations in the employment context include a similar definition of manifestation. *See* 29 C.F.R. § 1635.3(g) (2018).

179. *See* Sherkow, *supra* note 70, at 669.

IV. ACCESS AND DISPARITIES

Disparities in access to care are not unique to gene therapy; there is nothing new about health-care disparities. Other health-care treatments raise concerns related to high costs and one-time treatments. For example, Sovaldi, a treatment for Hepatitis C, costs as much as $84,000 for a twelve-week dose.[180] However, it is still important to examine these issues in the gene-therapy space as treatments grow, given the social implications of having some able to access a cure and others left without the possibility to pay for desired treatment.

The introduction of a powerful new class of high-priced therapies with the potential to considerably reduce the burden of inherited disease brings the issue to a new level. Obviously, anytime an individual is denied access to care it is lamentable. Systemically, it translates into something broader: an issue of social justice.

We often see diseases where incidence as well as outcome are related to poverty, from cardiovascular disease to tropical diseases such as dengue fever.[181] Systematic analysis has shown that diseases that occur primarily in low-income populations are less likely to be the focus of research and pharmaceutical development.[182] Examples like malaria and tuberculosis generally expose differences between developing and developed nations; gene therapy has the potential to divide the population of a given nation into at-risk and not-at-risk subcultures. How this affects the division of health and community resources remains to be seen, but an ebbing of empathic or self-interest-based motivation for controlling diseases is one possible result.

As a policy statement from the American Society of Human Genetics ("ASHG") puts it,

> Unequal access and cultural differences affecting uptake could create large differences in the relative incidence of a given condition by region, ethnic group, or socioeconomic status.

180. Olga Khazan, *The True Cost of an Expensive Medication*, ATLANTIC (Sept. 25, 2015), https://www.theatlantic.com/health/archive/2015/09/an-expensive-medications-human-cost/407299/ [https://perma.cc/T674-XURG].

181. Peter J. Hotez, Kristy O. Murray & Pierre Buekens, *The Gulf Coast: A New American Underbelly of Tropical Diseases and Poverty*, 8 PLOS, e2760, May 15, 2014, at 1, 1; Sanjat Kanjilal et al., *Socioeconomic Status and Trends in Disparities in 4 Major Risk Factors for Cardiovascular Disease Among US Adults*, *1971-2002*, 166 ARCHIVES INTERNAL MED. 2348, 2348 (2006).

182. Patrice Trouiller, *Drug Development for Neglected Diseases: A Deficient Market and a Public-Health Policy Failure*, 359 LANCET 2188, 2188 (2002).

> Genetic disease, once a universal common denominator, could instead become an artifact of class, geographic location, and culture.[183]

In this instance the ASHG working group was discussing changes to the human germline—eggs, sperm, or embryos[184]—but the point is relevant to somatic treatments as well. A treatment that is an effective cure for some and not others could adversely affect our willingness to find funds for resources and care to help those who remain affected, as well as funding for research into less glamorous but more affordable conventional treatments.[185]

No one likes to imagine that there could be a lack of empathy for individuals without access to care, but both health-care and research dollars are finite and competitive. It is easier to imagine an empathy deficit when the community-building aspect of our shared risk is no longer in play. It has the potential to increase the sort of stigma often discussed by advocates for disability rights who described how affected individuals can be viewed as "other."[186] "Genetic disease has always been our shared vulnerability. When one part of society can opt out of risk, will they continue to feel the same obligation to provide support and resources to those who remain [vulnerable] . . . ?"[187]

This is not to say that everyone should undergo gene therapy—there are some who may choose not to get this treatment for a myriad of valid reasons.[188] Nor is this necessarily where society's limited health-care dollars should be focused. However, as these technologies are inevitably rolled into clinical care, there are problematic implications if only those with independent funding are able to cure disease. Currently, this lack of access affects only a handful of individuals as somatic gene-therapy treatment reaches a small patient population. However, as gene-therapy offerings grow, so too will the impact for those left out of the system due to cost. Now, at the dawn of gene therapy, is a ripe time to consider both access and cost.

183. Kelly E. Ormond et al., *Human Germline Genome Editing*, 101 AM. J. HUM. GENETICS 167, 172 (2017).

184. *See id.*

185. *See id.*; Laura Hercher, Innovations in Prenatal Testing and the Ghettoization of Genetic Disease (July 5, 2017) (unpublished manuscript) (on file with the North Carolina Law Review).

186. Aisling de Paor & Peter Blanck, *Precision Medicine and Advancing Genetic Technologies—Disability and Human Rights Perspectives*, 5 LAWS 1, 8 (2016).

187. Hercher, *supra* note 185.

188. Ormond et al., *supra* note 183, at 171.

CONCLUSION

Gene therapy will never be the underlying cause of health-care inequities; access to care is a systemic issue within our health-care system. However, gene therapy threatens to exacerbate existing disparities in substantial ways. Generally, though this may not be true in every instance, there are three characteristics of gene therapy that have social justice implications: they are extremely expensive as a one-time cost, they are intended as a cure rather than a treatment or risk-reducing measure, and they are specific to a given genotype. Successful applications of gene therapy with limited access will not just improve outcomes for individuals who receive the intervention but essentially create a class of persons who are at risk for these diseases and a class of persons who are not. And while success for the early adopters who have insurance or can self-pay may pave the way for others down the road, the individualized nature of gene therapy is such that scale or practice may not radically bring the prices down, as has often been the case with other innovations.

Our recommendation, therefore, is for the importance of equitable access. Access can be improved either by increasing reimbursement or decreasing costs, and greater equality of access will no doubt require both. Because insurers are not incentivized to pay for expensive one-time therapies under our current system, we will need to consider a variety of alternative payment systems that lower costs, reduce uncertainties relative to value, and create a broader pool of shared risk.

The advent of successful gene therapy is a long-sought goal of medical research and may prove to be a blessing for many families affected by genetic disease. The economics of gene therapy, however, are challenging and may reduce access for broad swaths of the population. Without a commitment to ensuring access, gene therapy may fail to live up to its potential. Individuals may be unable to pay for treatment or denied it because their disease is too rare or their prognosis is too uncertain to make gene therapy economically viable. In consequence, we run the risk of creating a world of haves and have-nots and that those who cannot find the means of obtaining treatment face more in the way of stigma with less in the way of resources and support. For all of these reasons, the success of gene therapy must be considered as inextricable from issues of cost and coverage.