THE PICK-AND-SHOVEL PLAY: BIOETHICS FOR GENE-EDITING VECTOR PATENTS*

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Concerns over patent protection covering new forms of gene editing have largely focused on the intellectual property covering the editing mechanism itself, most notably CRISPR (clustered regularly interspaced short palindromic repeats), but also ZFNs (zinc finger nucleases) and TALENs (transcription activator-like effector nucleases). Some of the most important technical advances in these areas, however, relate not to these technologies themselves but to vectors—the means for introducing the gene-editing machinery into human cells. In this Article, we discuss the implications of one intellectual property strategy used by some commercial developers of gene-editing vectors: a divided strategy of keeping some of the most significant information about vectors secret while patenting, cryptically, other aspects. We liken this to the business strategy of a "pick-and-shovel play": using secrecy as informational arbitrage to sell gene editing's necessary equipment. Such a strategy raises specific ethical and safety issues pertaining to many gene therapy interventions—namely, the uncertainty of risk, a reliance on insufficient preclinical evidence, the detriment of patient-physician decisionmaking, and increases in monetary costs. At the same time, these bioethical issues seem to illuminate the importance of patents' disclosure function to, perhaps surprisingly, consumers, users, and standards developers.

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INTRODUCTION

> *Huck Finn, did you ever hear of a prisoner having picks and shovels, and all the modern conveniences in his wardrobe to dig himself out with? Now I want to ask you—if you got any reasonableness in you at all—what kind of a show would that give him to be a hero? Why, they might as well lend him the key, and done with it. Picks and shovels—why, they wouldn't furnish 'em to a king.*
> —*Mark Twain,* Adventures of Huckleberry Finn[1]

Much has been made about recent developments in genome-editing technologies such as CRISPR that, depending upon one's

1. MARK TWAIN, ADVENTURES OF HUCKLEBERRY FINN (TOM SAWYER'S COMRADE) 306 (Collectors Reprints Inc. 1991) (1885).

perspective, promise both the salvation and destruction of humankind.[2] But perhaps an equal amount of commentary on the technologies has been reserved for the patent estates covering them. Bioethicists, legal scholars, and the popular press have dissected, analyzed, and critiqued the genome-editing patent landscape in minute detail across a wide variety of publications that rival the number of papers describing uses of the technologies themselves.[3] A substantial reason for this interest lies in the amount of money involved in patent licensing and litigation in this area: patent licenses for gene-editing technologies routinely command tens of millions of dollars that, in total, are likely worth many billions.[4] The four principal companies, all publicly traded, that are today closest to delivering a genome-editing product are collectively

2. *Compare, e.g.*, Giedrius Gasiunas & Virginijus Siksnys, *RNA-Dependent DNA Endonuclease Cas9 of the CRISPR System: Holy Grail of Genome Editing?*, 21 TRENDS MICROBIOLOGY 562, 562 (2013) ("Targeted genome editing technology that enables the generation of site-specific changes in the genomic DNA of cellular organisms is a Holy Grail for genome engineers."), *with* Sheila Jasanoff, J. Benjamin Hurlbut & Krishanu Saha, *CRISPR Democracy: Gene Editing and the Need for Inclusive Deliberation*, 32 ISSUES SCI. & TECH., Fall 2015, http://issues.org/32-1/crispr-democracy-gene-editing-and-the-need-for-inclusive-deliberation/ [https://perma.cc/WKN4-KRWM] ("CRISPR raises basic questions about the rightful place of science in governing the future in democratic societies."). CRISPR is an acronym for "clustered regularly interspaced short palindromic repeats." Francisco J.M. Mojica et al., *Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements*, 60 J. MOLECULAR EVOLUTION 174, 174 (2005).

3. *See, e.g.*, Knut J. Egelie et al., *The Emerging Patent Landscape of CRISPR–Cas Gene Editing Technology*, 34 NATURE BIOTECHNOLOGY 1025, 1025 (2016) (discussing some ethical issues with the CRISPR patent landscape); Jacob S. Sherkow, *The CRISPR Patent Landscape: Past, Present, and Future*, 1 CRISPR J. 1, 3–4 (2018) [hereinafter Sherkow, *CRISPR Patent Landscape*] (opining on the future of the CRISPR patent landscape); *see also* Sharon Begley, *As CRISPR Patent Fight Nears the Endgame, Where Are Settlement Talks?*, STAT (May 2, 2018), https://www.statnews.com/2018/05/02/crispr-patent-fight-settlement-talks/ [https://perma.cc/3VB3-HDQK (dark archive)] (reporting on the global CRISPR patent landscape).

4. *See* Caroline Chen & Doni Bloomfield, *Gene-Editing Tool on Every Drugmaker's 2016 Wish List*, BLOOMBERG (Dec. 24, 2015), http://www.bloomberg.com/news/articles/2015-12-24/the-gene-editing-tool-on-every-drugmaker-s-wish-list-this-year [https://perma.cc/U8EP-5CDS (dark archive)] (reporting on value of license payments); Jacob S. Sherkow, *How Much Is a CRISPR Patent License Worth?*, FORBES (Feb. 21, 2017, 5:00 AM), https://www.forbes.com/sites/jacobsherkow/2017/02/21/how-much-is-a-crispr-patent-license-worth/#786147e6b777 [https://perma.cc/38QL-EWY4] (estimating the value of a CRISPR patent license).

worth roughly $5.5 billion.[5] With no sense of understatement, genome-editing intellectual property has been described as a new "gold rush."[6]

But as the adage goes, the best business to be in during a gold rush isn't mining but selling picks and shovels.[7] The same may ultimately be true for gene-editing intellectual property: the best bet may be licensing patents that make gene editing possible.[8] In particular, gene-editing technologies rely on critically important pieces of necessary equipment—vectors—that catalyze the introduction of the editing

5. As of the end of trading on May 8, 2019, Sangamo Therapeutics, Inc. had a market cap of $1.31 billion, *Stock Quote: Sangamo Therapeutics, Inc.*, BLOOMBERG, https://www.bloomberg.com/quote/SGMO:US [https://perma.cc/L9CF-M9CN (dark archive)] (last updated May 8, 2019), Editas Medicine, Inc., $1.24 billion, *Stock Quote: Editas Medicine, Inc.*, BLOOMBERG, https://www.bloomberg.com/quote/EDIT:US [https://perma.cc/3YBY-3GPH (dark archive)] (last updated May 8, 2019), CRISPR Therapeutics AG, $2.11 billion, *Stock Quote: CRISPR Therapeutics AG*, BLOOMBERG, https://www.bloomberg.com/quote/CRSP:US [https://perma.cc/WC46-Y92A (dark archive)] (last updated May 8, 2019), and Intellia Therapeutics Inc., $751 million, *Stock Quote: Intellia Therapeutics, Inc.*, BLOOMBERG, https://www.bloomberg.com/quote/NTLA:US [https://perma.cc/UR7E-M2XN (dark archive)] (last updated May 8, 2019).

6. Deborah Netburn, *UC Berkeley Suffers Big Loss in CRISPR Patent Fight: What's Next for the Powerful Gene-Editing Technology?*, L.A. TIMES (Feb. 15, 2017, 8:00 PM), http://www.latimes.com/science/sciencenow/la-sci-sn-crispr-patent-decision-20170215-story.html [https://perma.cc/3TNH-4SGY (staff-uploaded archive)] ("CRISPR is a gold mine, and that's why you are seeing a gold rush.").

7. G. Thomas Goodnight & Sandy Green, *Rhetoric, Risk, and Markets: The Dot-Com Bubble*, 96 Q.J. SPEECH 115, 125 (2010) ("The [new] gold rush is following the classic pattern. It is not the diggers themselves who make the first money, but the manufacturers of picks and shovels.''); Elicia Maine, Sarah Lubik & Elizabeth Garnsey, *Process-Based vs. Product-Based Innovation: Value Creation by Nanotech Ventures*, 32 TECHNOVATION 179, 184 (2012) (describing fuel cell test equipment as a "'pick and shovel' niche strategy"); Christine Williamson, *Cryptocurrency Concerns Keeping Investors at Bay*, 45 PENSIONS & INV. 4, 6 (2017) ("As the old adage goes: In a gold rush, money is made by selling picks and shovels."); Julia Fortier, *There's More than One Way to Make It in Biotech*, BOS. GLOBE, Sept. 3, 1985, at B39 ("But hitting the pay dirt is still years in the future for most biotech companies. In the meantime, just as in the 1849 California Gold Rush, it's the 'picks and shovels' people who are quietly raking in sales.").

8. *See* Claudia Carbone et al., *Lipid-Based Nanocarriers for Drug Delivery and Targeting: A Patent Survey of Methods of Production and Characterization*, 2 PHARMACEUTICAL PAT. ANALYST 665, 667–75 (2013) (analyzing patents covering lipid-based nanocarriers); Virgínia Picanço-Castro, Elisa Maria de Sousa Russo-Carbolante & Dimas Tadeu Covas, *Advances in Lentiviral Vectors: A Patent Review*, 6 RECENT PATENTS ON DNA & GENE SEQUENCES 82, 82–90 (2012) (surveying the patent landscape of lentiviral vectors); Christopher Thomas Scott, *The Zinc Finger Nuclease Monopoly*, 23 NATURE BIOTECHNOLOGY 915, 917 (2005) [hereinafter Scott, *ZFN Monopoly*] ("How did Sangamo reach its catbird's seat? Credit CEO Edward Lanphier. In 1995, Lanphier was head of business development and chief financial officer of Alameda, California's Somatix Therapy, a vector-based gene therapy company. . . . Somatix's proprietary core was a gene vector delivery system.").

equipment into cells that do not normally have them.[9] And like most pick-and-shovel businesses, the companies responsible for gene-editing vectors operate by strategically using secrecy to their advantage[10]—if everyone knew how to procure a gold rush's necessary equipment, they would do it themselves. This Article explores a few of the ethical problems with this approach and what it says more generally about patent policy.

While the phrase "pick-and-shovel play" sounds suggestive of unethical profiteering, the term is used today in a much more anodyne fashion simply to describe businesses that sell necessary equipment or services to other, often flashier, businesses.[11] Internet network

9. James E. DiCarlo, Anurag Deeconda & Stephen H. Tsang, *Viral Vectors, Engineered Cells and the CRISPR Revolution*, *in* ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY 3 (Stephen H. Tsang ed., 2017); Christopher E. Nelson & Charles A. Gersbach, *Engineering Delivery Vehicles for Genome Editing*, 7 ANN. REV. CHEMICAL & BIOMOLECULAR ENGINEERING 637, 640–49 (2016); Christopher Thomas Scott & Laura DeFrancesco, *Gene Therapy's Out-of-Body Experience*, 34 NATURE BIOTECHNOLOGY 600, 601–04 (2016); Gayong Shim et al., *Therapeutic Gene Editing: Delivery and Regulatory Perspectives*, 38 ACTA PHARMACOLOGICA SINICA 738, 739–40 (2017); Hao Yin, Kevin J. Kauffman & Daniel G. Anderson, *Delivery Technologies for Genome Editing*, 16 NATURE REV. DRUG DISCOVERY 387, 388–90 (2017).

10. *See, e.g.*, Sergey Anokhin & Joakim Wincent, *Technological Arbitrage Opportunities and Interindustry Differences in Entry Rates*, 29 J. BUS. VENTURING 437, 440 n.6 (2014) ("[E]ffective information exchange may even be purposefully sabotaged by innovator firms."); Andrei Shleifer & Robert W. Vishny, *The Limits of Arbitrage*, 52 J. FIN. 35, 40 (1997) ("[A]rbitrageurs do not share all their knowledge with investors, and cultivate secrecy to protect their knowledge from imitation."); Wesley Gray, *Information Exchange and the Limits of Arbitrage* 4 (Munich Pers. RePEc Archive, Paper No. 11918, 2008), https://mpra.ub.uni-muenchen.de/11918/1/MPRA_paper_11918.pdf [https://perma.cc/M9UT-UFKE] ("Why are arbitragers telling other arbitragers about their investment opportunities? According to efficient market logic, the rational arbitrager should act alone, drive the price to the fundamental level, and reap all the rewards of the arbitrage he has found." (citation omitted)). *See generally* Matteo Acquilina et al., *Asymmetries in Dark Pool Reference Prices* 10 (Fin. Conduct Auth., Occasional Paper No. 21, Sept. 2016), https://www.fca.org.uk/publication/op16-21.pdf [https://perma.cc/5LMX-RM7N] (concluding that "dark pools" of traded equities take advantage of price information "[l]atency [to] give rise to arbitrage opportunities"); Huy N. Chau, Andrea Cosso & Claudio Fontana, *The Value of Informational Arbitrage* (arXiv, Paper No. 1804.00442v1), https://arxiv.org/pdf/1804.00442v1 [https://perma.cc/4MKX-G737] (modeling the value of information asymmetries in arbitrage opportunities).

11. Jason Stutman, *Who's Making the Picks and Shovels of Tech?*, WEALTH DAILY (Jan. 20, 2017, 7:00 PM), https://www.wealthdaily.com/articles/whos-making-the-picks-and-shovels-of-tech/8495 [https://perma.cc/95SR-WY93] ("A pick-and-shovel play is, at its core, a company that sells products needed for a larger, overarching industry to operate."); *Pick-And-Shovel Play*, INVESTOPEDIA, https://www.investopedia.com/terms/p/pick-and-shovel-play.asp [https://perma.cc/Q37F-WUWH] ("A pick-and-shovel play is an investment strategy that invests in the underlying technology needed to produce a good or service instead of in the final output. It is a way to invest in an industry without having to endure

equipment, product testing services, oil and gas storage, railcar equipment, and chemical manufacturers are all modern examples of pick-and-shovel plays.[12] The origins of the phrase, however, are perhaps more instructive as to both why and how pick-and-shovel plays are often profitable ventures. In 1848, Samuel Brannan, a store owner at Sutter's Fort, California, bought tin pans for 20¢ and sold them to prospectors for $15 each, all while publicizing the discovery of gold on the American River outside Sacramento.[13] He quickly became a millionaire.[14] But the core of his success was not so much his skills as a salesman but his knowledge—hidden from his customers—about where to obtain the equipment they otherwise needed.[15] If everyone knew where to buy tin pans for 20¢, no one would have bought them from Sam Brannan for $15. The lesson of Brannan's sale of tin pans is this: at the core of most good pick-and-shovel plays lies a devil's bargain of secrecy and publicity.[16]

If gene-editing technologies are gold, then the vectors used to implement the technologies are picks and shovels. Most gene-editing technologies rely on enzymes—typically DNA-cutting enzymes called nucleases—that are not naturally expressed in human cells.[17] Physically getting those enzymes into human cells is a recurrent challenge in genetic engineering, and the vehicles used to do so are the enzymes' vectors.[18] Recent advances in vector technology have eased this process and appear to be especially promising in the implementation of gene-

the risks of the market for the final product. It is named after the tools needed to take part in the California Gold Rush.").

12. *E.g.*, Goodnight & Green, *supra* note 7, at 125; Maine et al., *supra* note 7, at 184; AnnaLisa Kraft, *A Golden Portfolio with 5 Pick-and-Shovel Stocks*, MOTLEY FOOL (Oct. 18, 2013, 6:00 PM), https://www.fool.com/investing/general/2013/10/18/five-picks-and-shovel-stocks-that-get-er-done.aspx [https://perma.cc/KU2F-RQQH].

13. FRANK K. MARTIN, A DECADE OF DELUSIONS: FROM SPECULATIVE CONTAGION TO THE GREAT RECESSION 21 n.9 (2011) ("A metal pan that sold for 20 cents a few days earlier was now available from Brannan for 15 *dollars*."); Douglas S. Watson, *Herald of the Gold Rush: Sam Brannan*, 10 CAL. HIST. SOC'Y Q. 298, 301 (1931) ("Rushing into San Francisco's Plaza, he doffed his broad-brimmed black hat, and holding aloft a bottle of glittering particles in his left hand, he bellowed in his great bull voice: 'GOLD! GOLD! GOLD! From the American River!' The Gold Rush was born that instant.").

14. Newell G. Bringhurst, *Samuel Brannan and His Forgotten Final Years*, 79 S. CAL. Q. 139, 139 (1997).

15. *See id.* at 145 ("Before Brannan allowed word of the discovery to leak out, the enterprising businessman scoured northern California purchasing and stocking his store with any and all merchandise of any conceivable use to the gold seekers.").

16. *See supra* note 10 and accompanying text.

17. *See supra* text accompanying note 9.

18. *See supra* text accompanying note 9.

editing technologies like CRISPR.[19] Given the interest—and likely profitability—of gene-editing therapies, underlying vector technologies are especially valuable.[20] As such, vector technology companies have deployed a strategy reminiscent of Brannan: they have publicized and patented the basic contours of some aspects of their technology while keeping others entirely secret. For example, uniQure touts a "Best-in-Class" vector delivery system,[21] protected by a host of patents that cover its technology.[22] But—by uniQure's own admission—"significant aspects of the process by which we manufacture our gene therapies are based on unpatented trade secrets and know-how."[23] MaxCyte, another vector company, similarly provides a "patented, high-performance cell-engineering platform."[24] But its patent applications do not disclose critical aspects of the platform, such as important manufacturing details.[25] And Spark Therapeutics—a gene-therapy company proud of its "cutting-edge vector design," with several pending patent applications to boot—quietly makes use of an important safety-enhancing trade-secret technology owned by another company, Selecta Biosciences.[26]

19. *See supra* text accompanying note 9; *see also infra* Section I.A.

20. *See* Scott, *ZFN Monopoly*, *supra* note 8, at 917 (discussing the profitability of Somatix); Scott & DeFrancesco, *supra* note 9, at 603 (noting bluebird bio's then market cap of $1.35 billion). In addition, Spark Therapeutics, a viral vector platform company, has a market cap of almost $4.16 billion. *Stock Quote: Spark Therapeutics, Inc.*, BLOOMBERG, https://www.bloomberg.com/quote/ONCE:US [https://perma.cc/7BYY-2S3S (dark archive)] (last updated May 8, 2019).

21. *uniQure's Technology: Excellence in Gene Therapy Through Innovative Modular Technology, Proprietary Manufacturing and the Experience to Achieve Success*, UNIQURE, http://www.uniqure.com/gene-therapy/uniqure-technology.php [https://perma.cc/6F8N-9B6E] [hereinafter *uniQure's Technology*].

22. *Gene Therapy: Intellectual Property*, UNIQURE, http://www.uniqure.com/gene-therapy/gene-therapy-intellectual-property.php [https://perma.cc/69UM-4GJ6].

23. UNIQURE N.V., ANNUAL REPORT 2017, at 16 (2018), http://www.uniqure.com/uniQure%20Annual%20Accounts%202017.pdf [https://perma.cc/AJD3-5TZK].

24. *About Us: Driving a New Generation of Cell-based Medicines*, MAXCYTE, https://www.maxcyte.com/about-us/ [https://perma.cc/7SQF-9WE3] [hereinafter *About Us*].

25. *See, e.g.*, U.S. Patent No. 9,132,153 (filed May 24, 2013) (claiming methods of modifying certain cells with mRNA, without disclosing specific mRNA sequences); U.S. Patent No. 8,450,112 (filed Apr. 9, 2009) (same).

26. Selecta Biosciences, Inc., Annual Report 4 (Form 10-K) (Mar. 27, 2017), http://ir.selectabio.com/static-files/35d1c085-9947-4d8d-aa61-dd3c05d0b280 [https://perma.cc/3C4F-P7N5]; Spark Therapeutics, Inc., Annual Report 19 (Form 10-K) (Feb. 27, 2018), http://ir.sparktx.com/static-files/28cb5c84-8bf4-4aea-b028-60a3d5278b8b [https://perma.cc/5DFR-HTT3].

This divided strategy of patenting, commercialization, and secrecy is not atypical in the biotechnology space.[27] But it poses some specific ethical problems for gene editing as a therapeutic. First, it makes the risk of gene-editing therapies wholly uncertain and difficult to assess.[28] Given gene editing's recent successes, and the horrifying nature of many genetic diseases, patients and subjects may be pressured into experimental therapies with imperfect information about a vector's overall safety profile.[29] Historically, it is difficulties with gene therapies' vectors—not the therapies' genetic modifications themselves—that have resulted in trial subjects' deaths and adverse events.[30] Second, where patent information does exist, it may not be trustworthy—for a number of reasons, the information disclosed in patents tends to be unreliable and based on entirely insufficient preclinical evidence.[31] Third, the lack of sufficient information about the mechanisms and

27. Karl F. Jorda, *Patent and Trade Secret Complementariness: An Unsuspected Synergy*, 48 WASHBURN L.J. 1, 29 (2008) (describing the case of Premarin (conjugated estrogens)); W. Nicholson Price II, *Expired Patents, Trade Secrets, and Stymied Competition*, 92 NOTRE DAME L. REV. 1611, 1624–26 (2017) (describing this dynamic for biologics); Brenda M. Simon & Ted Sichelman, *Data-Generating Patents*, 111 NW. U. L. REV. 377, 406 (2017) (discussing the "use of patents and trade secrets as complements . . . in fields in which some disclosure of post-patenting data is required for regulatory purposes, such as medical devices or pharmaceuticals").

28. *See* Clare E. Thomas, Anja Ehrhardt & Mark A. Kay, *Progress and Problems with the Use of Viral Vectors for Gene Therapy*, 4 NATURE REV. GENETICS 346, 346 (2003) (reviewing "the advances in the development of viral vectors, as well as discussing the substantial challenges that remain before gene therapy can truly fulfil all of its promises"); Aaron D. Levine, *Revolutionary New Cancer Therapies Come with Big Risks. Drug Makers Must Be Prepared*, STAT (Nov. 8, 2017), https://www.statnews.com/2017/11/08/car-t-cancer-death-pharma-companies/ [https://perma.cc/G3QM-ZWDE] (discussing some of the risks of immunotherapy vectors).

29. *See* NAT'L ACADS. OF SCIS., ENG'G, & MED., HUMAN GENOME EDITING: SCIENCE, ETHICS, AND GOVERNANCE 7 (2017) [hereinafter NASEM, HUMAN GENOME EDITING] (noting gene editing's potential to create "social pressure[s] for people to use technologies they would not otherwise choose"); *id.* at 49–51 (listing some of the uncertainties surrounding new viral vectors); Levine, *supra* note 28 (noting "the clamor of individual patients and patient organizations to rapidly expand the use of CAR-T therapy . . . and accompanying pressures" despite clinical trial subjects' deaths).

30. *See* NASEM, HUMAN GENOME EDITING, *supra* note 29, at 88–89 (describing safety issues with gene-editing vectors); Thomas et al., *supra* note 28, at 347 (discussing adverse events of gene-editing vectors); Levine, *supra* note 28 (discussing the potential for CAR-T clinical trial deaths).

31. *See* Jacob S. Sherkow, *Patent Law's Reproducibility Paradox*, 66 DUKE L.J. 845, 883–85 (2017) [hereinafter Sherkow, *Patent Law's Reproducibility Paradox*] ("[D]rug developers often rely on early preclinical studies to bolster their patents. By design, these studies often have small sample sizes; employ little statistical power; and, of course, suffer from conflicts of interest between industrial researchers and their employers—all hallmarks of irreproducibility.").

reliability of gene-editing vectors—through published research that would fully test them—hampers physicians' ability to properly inform their patients of the benefits and burdens of a given course of treatment.[32] And fourth, having an additional layer of patent protection for gene-editing technologies is likely to contribute to relatively higher monetary costs of treatment where such therapies are available.[33] This is especially problematic where new DNA- and RNA-based therapies already routinely command close to a half-million dollars for a course of treatment, prices that threaten to break health-care payer systems.[34]

At the same time, these problems with patents' role in the pick-and-shovel play shine some light on patent law's disclosure function.[35]

32. *See* NASEM, HUMAN GENOME EDITING, *supra* note 29, at 26 ("[O]utside of a study, 'off-label' use in clinical care is entirely legal, and has become a common practice among physicians with respect to drugs, and might be available for a gene transfer product using genome editing once it is approved. Physicians use their own expertise and sources of information, as well as the advice of professional societies."); George A. Beller, *President's Page: Convocation Address*, 35 J. AM. C. CARDIOLOGY 1694, 1695 (2000) ("A second ethical challenge arises with the need to disclose to patients all the risks from potentially dangerous new treatments such as gene therapy using viral vectors. We must let patients know all the risks, and we must explain those risks in language that is easily understood."); Edmund D. Pellegrino, *Patient and Physician Autonomy: Conflicting Rights and Obligations in the Physician-Patient Relationship*, 10 J. CONTEMP. HEALTH L. & POL'Y 47, 52 (1994) (arguing that "physician's autonomy as a physician is also grounded in the possession of expert knowledge needed by sick people and society"); Scott, *ZFN Monopoly*, *supra* note 8, at 918 (reporting that some "physician-scientists" support an "open resource" of gene-editing information); *see also* Dianne Nicol et al., *Key Challenges in Bringing CRISPR-Mediated Somatic Cell Therapy into the Clinic*, 9 GENOME MED. 85, 87 (2017) ("Issues surrounding patent ownership and validity feed into clinical delivery.").

33. *See* 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, 492–94 (2017) (describing the literature on the connection between personalized medicine and patents); Jacob S. Sherkow, *CRISPR, Patents, and the Public Health*, 90 YALE J. BIOLOGY & MED. 667, 667–68 (2017) [hereinafter Sherkow, *Public Health*] (discussing patents' contribution to gene-therapy drug pricing).

34. Robert Cook-Deegan, *Gene Patents*, *in* FROM BIRTH TO DEATH AND BENCH TO CLINIC: THE HASTINGS CENTER BIOETHICS BRIEFING BOOK FOR JOURNALISTS, POLICYMAKERS, AND CAMPAIGNS 69 (Mary Crowley ed., 2008) ("One concern is that patents might make the cost of genetic tests and genetic therapies unacceptably high."); Sherkow, *Public Health*, *supra* note 33, at 668–69 (discussing genetic therapies in the context of insurance reimbursement); Meghana Keshavan, *We May Soon Have Our First $1 Million Drug. Who Will Pay for It? And How?*, STAT (Oct. 13, 2017), https://www.statnews.com/2017/10/13/gene-therapy-pricing/ [https://perma.cc/SAB8-5CCT] (reporting that a gene vector company's patented treatment "could cost $1 million per patient" and asking whether private insurers or "taxpayers, via Medicaid and Medicare," would be willing to pay).

35. *See* Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1022 (1989) ("This enabling disclosure becomes

Ideally, patents' disclosure function goes beyond merely a tit-for-tat trade of technical information—it allows markets and physicians to critically assess whether, how, and to what extent to adopt a new technology, and how much to pay for it.[36] Contrary to pick-and-shovel strategies, generally, robust disclosure in patents also allows users to assess the costs of inventing around a particular technology rather than licensing from the patent owner—that is, to decide whether to find tin pans on one's own or buy them from Sam Brannan.[37] And lastly, it

freely available to the public as soon as the patent issues; the patent holder may not thereafter monitor or control access to it."); Jeanne C. Fromer, *Patent Disclosure*, 94 IOWA L. REV. 539, 548 (2009) ("[Patent disclosure] permits society at large to apply the information by freely making or using the patented invention after the expiration of the patent."); Timothy R. Holbrook, *Possession in Patent Law*, 59 SMU L. REV. 123, 131 (2006) ("[T]he public benefits from the disclosure of the invention because the public storehouse of knowledge is thus enhanced, allowing others to rely upon the teachings of the patent to generate even further, follow-on innovation."); Sean B. Seymore, *The Teaching Function of Patents*, 85 NOTRE DAME L. REV. 621, 624 (2010) ("[T]he technical information disclosed in the patent document has potential immediate value to the public, which can use the information for any purpose that does not infringe upon the claims.").

36. *See* J. Jonas Anderson, *Nontechnical Disclosure*, 69 VAND. L. REV. 1573, 1575 (2016) ("[A] patent can inform innovators, investors, and consumers about the value of an inventive idea."); Alan Devlin, *The Misunderstood Function of Disclosure in Patent Law*, 23 HARV. J.L. & TECH. 401, 425 (2010) ("Disclosure may provide a better justification [of the patent system]. . . . [T]hese inventions are presumably of some worth to third parties as well, be they competitors, scientists, or consumers."); Fromer, *supra* note 35, at 548–49 ("[D]isclosure can stimulate others to design around the invention or conceive of new inventions—either by improving upon the invention or by being inspired by it—even during the patent term."); Shubha Ghosh, *Decentering the Consuming Self: Personalized Medicine, Science, and the Market for Lemons*, 5 WAKE FOREST J.L. & POL'Y 299, 337–38 (2015) ("As information flourishes in personalized medicine, disclosures for consumers can become more meaningful and provide guidance in how to respond to identified disease proclivities and risk. This more liberal patent regime, combined with disclosure solutions, may provide the best set of regulations to allow the market for personalized medicine to mature and the field to progress for the benefits of patients.").

37. *See* Kevin Emerson Collins, *The Structural Implications of Inventors' Disclosure Obligations*, 69 VAND. L. REV. 1785, 1786 (2016) ("From the moment patent disclosures are published, the public has a privilege to freely engage in activities such as disseminating the disclosed knowledge and employing the disclosed knowledge as an input into the creative cognition that conceives yet further innovation, including both improvements and design-arounds."); Fromer, *supra* note 35, at 541 ("[P]atent disclosure indirectly stimulates future innovation by revealing the invention's design so that others can use it fruitfully when the patent term expires and design around, improve upon, or be inspired by the invention, even during the patent term."); Jorda, *supra* note 27, at 26 ("Patent applications and patents, after they are published and the invention is disclosed, often spur competitors to invent around and develop improved products. These products may be separately patented, may not be dominated, and may become commercially more important than the earlier, more basic invention."); Dmitry Karshtedt, *The Completeness Requirement in Patent Law*, 56 B.C. L. REV. 949, 996 (2015) (noting that a "completeness" requirement in patent disclosures "would encourage productive design-arounds"); Sean B. Seymore, *Uninformative Patents*,

shows that poor disclosure may lead to suboptimal and early platform standardization—users being locked into a particular iteration of a required technology because it is one of few widely available.[38] With respect to gene-editing vectors, this means letting information about vectors, rather than knowledge of diseases and the biology of vector-payload systems, control which therapies are ultimately developed.[39]

This Article proceeds in four parts. Part I gives a brief overview of gene editing, vectors, and intellectual property, including a discussion of the importance of vectors for gene-editing technologies and historical concerns about their safety. Part II then describes the gene-editing vector pick-and-shovel play at the core of this Article. On this foundation, Part III explores several ethical issues arising from this pick-and-shovel play—namely its unwarranted risk to patients and clinical subjects, its reliance on unreliable preclinical evidence, its effects on physician-patient decisionmaking, and its increased cost of

55 HOUS. L. REV. 377, 395–96 (2017) ("Theory posits that disclosure inspires others to learn about the invention, design around it, improve upon it, or conceive of entirely new inventions—all during the patent term."); Ted Sichelman & Stuart J.H. Graham, *Patenting by Entrepreneurs: An Empirical Study*, 17 MICH. TELECOMM. & TECH. L. REV. 111, 135 (2010) (discussing the connection between patents' disclosure and entrepreneur's decisions to avoid licensing); Gerald Sobel, *Patent Scope and Competition: Is the Federal Circuit's Approach Correct?*, 7 VA. J.L. & TECH. 3, 59 n.181 (2002) ("Disclosure may permit competitors to 'invent around' or invent improvements of the patented invention.").

38. *Cf.* Jonathan M. Barnett, *The Host's Dilemma: Strategic Forfeiture in Platform Markets for Informational Goods*, 124 HARV. L. REV. 1861, 1865 (2011) (identifying the "host's dilemma" as attempts to "platform" the host's technology without expropriating user investment); Jorge L. Contreras, *Much Ado About Hold-Up*, 2019 U. ILL. L. REV. (forthcoming 2019) [hereinafter Contreras, *Much Ado*] (manuscript at 7–8), https://dc.law.utah.edu/cgi/viewcontent.cgi?article=1106&context=scholarship [https://perma.cc/C522-HM3D] ("[T]he manufacturer's cost of switching from the standardized technology to an alternative may be prohibitive (a situation often referred to as 'lock-in')."); Mark A. Lemley, *Patenting Nanotechnology*, 58 STAN. L. REV. 601, 606–13 (2005) (recounting the history of early patents on "building blocks" of nascent technologies); Joseph Scott Miller, *Standard Setting, Patents, and Access Lock-In: RAND Licensing and the Theory of the Firm*, 40 IND. L. REV. 351, 386 (2007) ("[A] central licensing entity [is] an example of the corporate form as an access lock-in governance mechanism."); Jesse L. Reynolds, Jorge L. Contreras & Joshua D. Sarnoff, *Solar Climate Engineering and Intellectual Property: Toward a Research Commons*, 18 MINN. J.L. SCI. & TECH. 1, 58–59 (2017) (describing how patent platforming risks "technological lock-in" for solar climate engineering).

39. *See, e.g.*, Luigi Naldini, *Gene Therapy Returns to Centre Stage*, 526 NATURE 351, 351 (2015) (noting the importance of vector biology in making gene therapy successful); Michael F. Naso et al., *Adeno-Associated Virus (AAV) as a Vector for Gene Therapy*, 31 BIODRUGS 317, 317 (2017) ("There has been a resurgence in gene therapy efforts that is partly fueled by the identification and understanding of new gene delivery vectors."); Thomas et al., *supra* note 28, at 346 ("The message we have extracted from a history of anticipation and disappointment is that the future success of gene therapy will be founded on a thorough understanding of vector biology and pharmacology.").

treatment. Finally, Part IV uses this analysis to illuminate several aspects of patents' disclosure function including consumer assessment, the costs of inventing around, and early platform standardization.

I. GENE EDITING, VECTORS, AND IP

A. Gene-Editing Technologies

Genome editing is "a powerful new tool for making precise additions, deletions, and alterations to the genome—an organism's complete set of genetic material."[40] Since 1997, a suite of new gene-editing approaches has emerged, with the CRISPR/Cas9 system perhaps the most promising.[41] This system—guided by flexible and "programmable" strands of RNA, DNA's molecular cousin—has made editing of the genome more precise, efficient, feasible, and less costly relative to previous protein-based technologies such as zinc finger nucleases ("ZFNs") or transcription activator-like effector nucleases ("TALENs").[42]

With these advances has come an explosion of interest in the possible applications of genome editing, both in conducting basic research and the potential to prevent, treat, and cure disease and disability. Genome editing could provide insights into reproductive failures and improve contraception and fertility treatments.[43] In embryos, CRISPR has been used to study the genetics of early human

40. NASEM, HUMAN GENOME EDITING, *supra* note 29, at 1; *see also* NUFFIELD COUNCIL ON BIOETHICS, GENOME EDITING: AN ETHICAL REVIEW 4 (2016), http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf [https://perma.cc/H6QF-7N9U] ("What we will refer to as 'genome editing' is the practice of making targeted interventions at the molecular level of DNA or RNA function, deliberately to alter the structural or functional characteristics of biological entities."); Jin-Soo Kim, *Genome Editing Comes of Age*, 11 NATURE PROTOCOLS 1573, 1573 (2016).

41. *See* Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCIENCE 819, 819–22 (2013); Jennifer A. Doudna & Emmanuelle Charpentier, *The New Frontier of Genome Engineering with CRISPR-Cas9*, 346 SCIENCE 1077, 1077 (2014); Patrick D. Hsu, Eric S. Lander & Feng Zhang, *Development and Applications of CRISPR-Cas9 for Genome Engineering*, 157 CELL 1262, 1263–64 (2014).

42. Rajat M. Gupta & Kiran Musunuru, *Expanding the Genetic Editing Tool Kit: ZFNs, TALENs, and CRISPR-Cas9*, 124 J. CLINICAL INVESTIGATION 4154, 4156–57 (2014); *see also* Jeffrey C. Miller et al., *A TALE Nuclease Architecture for Efficient Genome Editing*, 29 NATURE BIOTECHNOLOGY 143, 143 (2011); Fyodor D. Urnov et al., *Genome Editing with Engineered Zinc Finger Nucleases*, 11 NATURE REVIEWS GENETICS 636, 636 (2010).

43. Meizhu Bai et al., *Spermatogenic Cell-Specific Gene Mutation in Mice via CRISPR/Cas9*, 43 J. GENETICS & GENOMICS 289, 290–92 (2016).

development.[44] In ex vivo approaches—that is, in cells physically outside of an organism—editing platforms have been used to deliver "gene-free" gene therapy for animals,[45] revert genetic defects such as hemophilia A in stem cells,[46] and functionally correct genetic mutations of human Duchenne muscular dystrophy.[47]

This interest extends beyond correcting currently existing defects—it also includes curiosity into fixing such errors before they take root: editing eggs, sperm, and embryos (i.e., the human "germline") to prevent genetic disease in future children and their descendants.[48] Recently, controversial experiments by researchers using nonviable and viable human embryos used germline editing in genetic disease, examining the safety and feasibility of CRISPR.[49] In a review published in June, scientists connected the cellular repair process to "mosaicism"—a patchwork of edited and unedited cells.[50] Other researchers have found that similar techniques resulted in incomplete editing and "off-target effects," edits to subjects' DNA that were otherwise unintended.[51] And even when gene editing does work as technically intended, it may result in unpredictable and harmful effects. In a recent study, U.K. researchers found significant numbers of on-target mutations, but with potentially pathogenic consequences.[52] In the United States, ex vivo clinical trials for cancer and sickle cell

44. Norah M.E. Fogarty et al., *Genome Editing Reveals a Role for OCT4 in Human Embryogenesis*, 550 NATURE 67, 67 (2017).

45. *See* Thomas Gaj et al., *Targeted Gene Knockout by Direct Delivery of Zinc-Finger Nuclease Proteins*, 9 NATURE METHODS 805, 805, 807 (2012).

46. Chul-Yong Park et al., *Functional Correction of Large Factor VIII Gene Chromosomal Inversions in Hemophilia A Patient-Derived iPSCs Using CRISPR-Cas9*, 17 CELL STEM CELL 213, 213 (2015).

47. Courtney S. Young et al., *A Single CRISPR-Cas9 Deletion Strategy that Targets the Majority of DMD Patients Restores Dystrophin Function in hiPSC-Derived Muscle Cells*, 18 CELL STEM CELL 533, 533 (2016).

48. NASEM, HUMAN GENOME EDITING, *supra* note 29, at 91–93.

49. *See generally* Xiangjin Kang et al., *Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR/Cas-mediated Genome Editing*, 33 J. ASSISTED REPROD. & GENETICS 581 (2016) (discussing viable embryos); Puping Liang et al., *CRISPR/Cas9-mediated Gene Editing in Human Tripronuclear Zygotes*, 6 PROTEIN & CELL 363 (2015) (discussing nonviable embryos); Hong Ma et al., *Correction of a Pathogenic Gene Mutation in Human Embryos*, 548 NATURE 413 (2017) (discussing nonviable embryos).

50. Stella Baliou et al., *CRISPR Therapeutic Tools for Complex Genetic Disorders and Cancer*, 53 INT'L J. ONCOLOGY 443, 450 (2018).

51. *E.g.*, Shim et al., *supra* note 9, at 747 (noting the risk of unsafe off-target effects for some vectors).

52. 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).

anemia are set to commence, though the Food and Drug Administration ("FDA") has placed a hold on the sickle cell trial sponsored by CRISPR Therapeutics.[53] Despite substantial concerns over the safety of in vivo approaches, China has treated over eighty subjects with CRISPR interventions.[54] This now includes news of Chinese researcher He Jiankui, who "engineered" the birth of two CRISPR-edited twins, with a third baby on the way. (In dramatic fashion, this was announced in December 2018 at an international human genome-editing summit in Hong Kong.) He's procedure was deceptive, violated Chinese law, flaunted international ethical norms, and put the babies at physical risk. Dr. He has since been fired from his university, and Dr. He, his mentors, and his collaborators are now under investigation.[55] Nonetheless, the outrage from the international scientific and bioethics communities was unanimous, and such limitations have the potential to stand as major hurdles facing eventual clinical applications.

B. Invention, Disclosure, and the Gene-Editing Patent Estate

Despite this potential for peril, the promise of CRISPR and other gene-editing technologies has yielded substantial patent estates. The U.S. Patent and Trademark Office ("USPTO") has issued over 450 patents to core aspects of CRISPR as of the date of this writing.[56] A more thorough landscaping analysis by researchers in Scandinavia and Colorado found hundreds more patent families on CRISPR components worldwide.[57] Currently, fundamental aspects of one

53. Rich Haridy, *FDA Hits Pause on One of the First US Human Clinical Trials to Use CRISPR*, NEW ATLAS (May 31, 2018), https://newatlas.com/us-crispr-human-trial-hold-fda/54862/ [https://perma.cc/9W4N-J78D].

54. Preetika Rana, Amy Dockser Marcus & Wenxin Fan, *China Races Ahead in Gene Editing*, WALL ST. J., Jan. 22, 2018, at A1, A10.

55. *Id.*; Christopher Thomas Scott & Cynthia Selin, *What to Expect When Expecting CRISPR Baby Number Four*, AM. J. BIOETHICS, Mar. 2019, at 7, 7–9; Todd Ackerman, *Lawyers Say Rice Professor Not Involved in Controversial Gene-Edited Babies Research*, HOUS. CHRON. (Dec. 13, 2018, 9:11 PM), https://www.houstonchronicle.com/news/houston-texas/houston/article/Lawyers-say-Rice-professor-not-involved-in-13465277.php/ [https://perma.cc/496Z-Z9VC]; Antonio Regalado, *The Chinese Scientist Who Claims He Made CRISPR Babies Is Under Investigation*, MIT TECH. REV. (Nov. 26, 2018), https://www.technologyreview.com/s/612466/the-chinese-scientist-who-claims-he-made-crispr-babies-has-been-suspended-without-pay/ [https://perma.cc/PH8G-WG9E]; Christopher Thomas Scott, Opinion, *Gene-Edited Babies Have Been Born. Now What*?, HOUS. CHRON. (Dec. 4, 2018, 10:24 AM), https://www.houstonchronicle.com/local/gray-matters/article/gene-edited-babies-crispr-ethics-research-13439892.php [https://perma.cc/8ZG7-8PWN].

56. Sherkow, *CRISPR Patent Landscape*, *supra* note 3, at 3.

57. Egelie et al., *supra* note 3, at 1027–28.

variant of CRISPR—applications using the Cas9 enzyme—are the subject of a particularly heated patent dispute between the University of California, Berkeley, and the Broad Institute of MIT and Harvard.[58] The dispute has raised a host of concerns about the future of CRISPR research and commercial development as well as the role of patenting in modern universities and research centers.[59] Similar controversies are ongoing for ZFNs and TALENs, alike.[60]

At the same time, these technologies are undergoing a literal renaissance—a "rebirthing"—despite, or perhaps because of, the patent estates covering their earlier versions. New enzymes have been found and in some cases engineered to use the technologies' basic components without treading on the claims of ongoing patent disputes.[61] Developing synthetic or recombinant enzymes is also used to further improve the technology—to make gene editing more or less error prone, available to more portions of the genome, or increasingly precise.[62] In describing CRISPR, for example, the moniker "gene editing" has accordingly conjured up metaphors of word processing, with Cas9, the enzyme that kicked off the CRISPR craze in 2012, being likened to cut-and-paste.[63] To further the analogy, new enzymes, to date, can find-and-replace, randomly delete, and highlight text.[64]

58. Regents of the Univ. of Cal. v. Broad Inst., Inc., 903 F.3d 1286, 1289–90 (Fed. Cir. 2018).

59. *E.g.*, Jorge L. Contreras & Jacob S. Sherkow, *CRISPR, Surrogate Licensing, and Scientific Discovery*, 355 SCIENCE 698, 698 (2017); Sherkow, *Public Health*, *supra* note 33, at 668–69 (noting the potential effects of the dispute on insurance coverage); Jacob S. Sherkow, *Pursuit of Profit Poisons Collaboration*, 532 NATURE 172, 172 (2016).

60. *E.g.*, Helga Schinkel & Stefan Schillberg, *Genome Editing: Intellectual Property and Product Development in Plant Biotechnology*, 35 PLANT CELL REP. 1487, 1488 (2016) (discussing TALEN patent controversies); Scott, *ZFN Monopoly*, *supra* note 8, at 915–16 (discussing ZFN patent controversies).

61. Sherkow, *CRISPR Patent Landscape*, *supra* note 3, at 4 ("New applications for CRISPR . . . continue to arise at a rapid pace. . . . This includes the continual discovery of new nucleases, such as CasX, CasY, and Cas13a, that belong to new types and subtypes of CRISPR-Cas systems.").

62. *See generally* Jason M. Gehrke et al., *High-Precision CRISPR-Cas9 Base Editors with Minimized Bystander and Off-Target Mutations* (bioRXiv, Working Paper No. 273938, 2018), https://www.biorxiv.org/content/biorxiv/early/2018/03/01/273938.full.pdf [http://perma.cc/D89Y-FTUH (staff-uploaded archive)] (using CRISPR/Cas9 technology to improve the precision of base editors).

63. *See, e.g.*, Sharon Begley, *Meet One of the World's Most Groundbreaking Scientists. He's 34.*, STAT (Nov. 6, 2015), https://www.statnews.com/2015/11/06/hollywood-inspired-scientist-rewrite-code-life/ [https://perma.cc/EPL6-72RT] (containing a video analogizing CRISPR to a word processor).

64. *See* Jonathan S. Gootenberg et al., *Multiplexed and Portable Nucleic Acid Detection Platform with Cas13, Cas12a, and Csm6*, 360 SCIENCE 439, 439 (2018) (using the nonspecificity of some enzymes to randomly delete other nucleic acid segments); Charleston

In virtually all of these cases, these technologies—including the original CRISPR/Cas9 technology—have been widely disclosed. Researchers have published thousands of papers on CRISPR since its advent in 2012.[65] As an example of how quickly the field is moving, genome-editing publications increased by 1453% from 2011–2016.[66] There is video, using high-speed atomic-force microscopy, of Cas9 cleaving a piece of DNA.[67] CRISPR has been so thoroughly adopted that it has become an internet meme—"CRISPR/Cas9: So Hot Right Now"[68]—and investors in companies working with CRISPR have complained of "CRISPR fatigue."[69] Researchers have largely made their materials freely available through a revolutionary nonprofit organization, AddGene, which supplies CRISPR materials—namely constructs of DNA that code for CRISPR components—and materials transfer agreements and documentation to use the technology for academic scientists.[70] Patents in this area most thoroughly disclose the science undergirding their claims; whatever deficiencies exist are

Noble et al., *Evolutionary Dynamics of CRISPR Gene Drives*, 3 SCI. ADVANCES, no. e1601964, Apr. 5, 2017, at 1, 1 (likening CRISPR gene drives to a search-and-replace function); Lei S. Qi et al., *Repurposing CRISPR as an RNA-Guided Platform for Sequence-Specific Control of Gene Expression*, 152 CELL 1173, 1173 (2013) (showing that catalytically inactive CRISPR enzymes can regulate gene expression, akin to highlighting text to increase its visibility).

65. *CRISPR*, ELSEVIER, https://www.elsevier.com/research-intelligence/campaigns/crispr [https://perma.cc/YU62-MYKP].

66. *STAT's Stats of the Year: 2016 by the Numbers*, STAT (Dec. 28, 2016), https://www.statnews.com/2016/12/28/stat-stats-year-in-numbers/ [https://perma.cc/6F62-A866].

67. Sarah Zhang, *An Astonishing Video Shows CRISPR Editing DNA in Real Time*, ATLANTIC (Nov. 13, 2017), https://www.theatlantic.com/science/archive/2017/11/crispr-video-real-time/545603/ [https://perma.cc/6CMT-WVWE].

68. *Mugatu So Hot Right Now*, IMGFLIP, https://imgflip.com/i/1fdwb4 [http://perma.cc/U6R6-WBLF]; *cf.* ZOOLANDER (Paramount Pictures 2001) (movie from which the meme originated). And, in a remarkable, surreal example of life imitating art, scientists have put a "meme" in bacterial cells using CRISPR. Taylor Hatmaker, *Scientists Have Inserted a GIF of a Horse into Living Bacteria — Did Your Brain Just Explode?*, TECHCRUNCH (July 12, 2017), https://techcrunch.com/2017/07/12/harvard-nature-crispr-cas1-cas2-horse-gif/ [https://perma.cc/PP5H-Y4WM].

69. Max Nisen, *CRISPR Therapeutics IPO: Bad Timing is Costly*, BLOOMBERG (Oct. 20, 2016), https://www.bloomberg.com/gadfly/articles/2016-10-20/crispr-therapeutics-ipo-bad-timing-is-costly [https://perma.cc/C6W5-QUV4 (dark archive)].

70. ADDGENE, https://www.addgene.org/ [http://perma.cc/9SXP-Y2PG]; *see also* Neil C. Thompson & Samantha Zyontz, Who Tries (and Who Succeeds) in Staying at the Forefront of Science: Evidence from the DNA-Editing Technology, CRISPR 9–10 (Nov. 17, 2017) (unpublished manuscript), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3073227 [http://perma.cc/VUN3-9237].

readily ascertainable from the scientific literature.[71] Patent estates and patent disputes notwithstanding, basic information about CRISPR has been disclosed to all.

C. The Importance of Vectors

Whichever fundamental gene-editing technology is used, it needs a way to deliver its machinery into cells—"vectors."[72] The concept of gene editing as therapy for genetic disease is straightforward: a vector carrying a gene-editing enzyme, or DNA coding for a gene-editing enzyme, delivers its payload to a cell.[73] This is frequently accompanied by DNA or RNA to replace the defective gene (a "knock-in" approach) or, more simply, introduce a mutation into a functioning gene (a "knock-out" strategy).[74] Gene editing can be accomplished using vectors ex vivo: the transference of genetic material to cells that have been removed from a patient.[75] After editing, the corrected cells are then subsequently reintroduced.[76] Alternatively, a vector carrying the functional gene copy is directly injected into the body to achieve in vivo gene transfer.[77] In either case, for gene-editing technology to actually work as therapy it must be accompanied by a safe, effective, and suitable vector.[78]

To date, a handful of experiments have shown the safety and efficacy of several vectors that may ultimately prove useful for gene therapy.[79] These can largely be grouped into two types: nonviral

71. *See* Egelie et al., *supra* note 3, at 1028–29 (assessing the technical disclosures of CRISPR patent families).

72. *See* DiCarlo et al., *supra* note 9, at 3; Nelson & Gersbach, *supra* note 9, at 640–49; Scott & DeFrancesco, *supra* note 9, at 601–04; Yin et al., *supra* note 9, at 388–90.

73. *See* DiCarlo et al., *supra* note 9, at 3–4.

74. *See id.* at 5–6.

75. Nelson & Gersbach, *supra* note 9, at 647; Scott & DeFrancesco, *supra* note 9, at 600; Shim et al., *supra* note 9, at 740; Thomas et al., *supra* note 28, at 348; Yin et al., *supra* note 9, at 390.

76. *See* Nelson & Gersbach, *supra* note 9, at 647; Scott & DeFrancesco, *supra* note 9, at 600; Shim et al., *supra* note 9, at 740; Thomas et al., *supra* note 28, at 348; Yin et al., *supra* note 9, at 390.

77. Shim et al., *supra* note 9, at 740; Thomas et al., *supra* note 28, at 350; Yin et al., *supra* note 9, at 392–94.

78. Nelson & Gersbach, *supra* note 9, at 637; *see also* Roland W. Herzog, Ou Cao & Arun Srivastava, *Two Decades of Clinical Gene Therapy—Success Is Finally Mounting*, 9 DISCOVERY MED. 105, 105–06 (2010).

79. *See* Thomas et al., *supra* note 28, at 351–52 (reviewing some of the most promising vectors). *See generally* Jacob S. Sherkow, Patricia J. Zettler & Henry T. Greely, Peer Commentary, *Is It 'Gene Therapy'?*, J.L. & BIOSCIENCES, no. lsy020, Sept. 18, 2018, at 1 (defining "gene therapy" and reviewing the safety of some vectors).

vectors, those that do not make use of viruses; and viral vectors, those that do.[80] Each has demonstrated some successes in laboratory experiments. CRISPR systems, for example, have given promise that delivery of DNA, RNA, or an active enzyme to the target tissue or cells of interest can be achieved nonvirally.[81] Ex vivo studies—those editing cells once removed from the body—currently lead the way for advances in nonviral vectors. The same applies to most preclinical experiments. Such studies use diverse mechanisms to achieve editing nonvirally through methods like direct injections of plasmid DNA or RNA.[82] In one experiment using human-induced pluripotent stem cells carrying the Duchenne muscular dystrophy mutation, plasmid delivery of a CRISPR protein restored the cells' dystrophin function.[83] In another, a similar approach successfully corrected deficiencies in the human β-thalassemia gene in mice.[84] Physically disrupting cells is yet another ex vivo delivery method through electroporation or cell-penetrating peptides and could conceivably be used in localized in vivo cases.[85] Liposomes, yet another nonviral method, have long been used to transfect DNA and RNA into cells and, after thirty years of development, have advanced into gene-therapy trials, most notably for cystic fibrosis and cancer.[86] Chinese researchers have reportedly used liposomes to deliver CRISPR into mice with solid tumors, improving their survival.[87] Finally, protein-based systems can deliver a functional CRISPR complex—the Cas9 enzyme along with guide RNA—directly inside target cells.[88]

80. Nelson & Gersbach, *supra* note 9, at 637, 640–42, 646–47.

81. *Id.* at 642.

82. *See id.* at 649. These pose technical hurdles, however: nonviral vectors must be engineered to protect their DNA and RNA from degradation by other enzymes during transport. Yin et al., *supra* note 9, at 391 ("[B]are nucleic acid is subject to degradation by endogenous nucleases in the blood.").

83. Young et al., *supra* note 47, at 533.

84. Zhanhui Ou et al., *The Combination of CRISPR/Cas9 and iPSC Technologies in the Gene Therapy of Human β-Thalassemia in Mice*, 6 SCI. REP., no. 32463, Sept. 1, 2016, at 1, 1.

85. Kim, *supra* note 40, at 1575–76; Shim et al., *supra* note 9, at 740; Yin et al., *supra* note 9, at 394.

86. Eric W. F. W. Alton et al., Correspondence, *A Phase I/IIa Safety and Efficacy Study of Nebulized Liposome-Mediated Gene Therapy for Cystic Fibrosis Supports a Multidose Trial*, 192 AM. J. RESPIRATORY & CRITICAL CARE MED. 1389, 1389–90 (2015).

87. Zeming Chen et al., *Targeted Delivery of CRISPR/Cas9-Mediated Cancer Gene Therapy via Liposome-Templated Hydrogel Nanoparticles*, 27 ADVANCED FUNCTIONAL MATERIALS, no. 1703036, Oct. 16, 2017, at 1, 1–2.

88. *See* Nelson & Gersbach, *supra* note 9, at 638–40.

Nonetheless, the most widely used and studied gene delivery vehicles are viral vectors.[89] Viruses, by their nature, have evolved ways to efficiently deliver their genetic payload to the cells; that is how all viruses operate, from the benign to the malignant.[90] Viral vectors for gene therapy are differentiated by the form in which they carry their genetic material, widely known as the Baltimore classification system.[91] Viruses that use double-stranded DNA—like DNA found in the genome—are Class I.[92] Some viruses that use single-stranded RNA—like the Human Immunodeficiency Virus—are Class VI.[93] But in all cases, the principle of using viruses for gene editing is the same: genetic material is inserted into a target cell and makes use of the cell's own machinery to edit the cell's genome.[94] Further, many viral vectors—like Class VI viruses—make such modifications permanent.[95] And despite billions of years of evolution and five decades of research, much about their manufacture, safety, and how the human body responds to their molecular machinery remains unknown.[96]

D. Gene-Editing Vectors and Safety

Although excitement about gene editing feels new and hopeful, gene editing as therapy has a long and checkered history, with significant safety issues arising from the vectors used.[97] Adeno-associated viral vectors ("AAVs"), for example, are among the most well-studied tools used in gene-therapy trials.[98] While some attempts

89. *See* ADDGENE, VIRAL VECTORS 101: A DESKTOP RESOURCE 8 (2018) (ebook), https://info.addgene.org/sign-up-to-receive-addgenes-viral-vectors-101-ebook [https://perma.cc/AY93-EKPY] ("One well-established and widely popular technology (that scientists love to discuss) is virus—specifically, using viruses as research tools.").

90. Thomas et al., *supra* note 28, at 346 ("Viruses are highly evolved biological machines that efficiently gain access to host cells and exploit the cellular machinery to facilitate their replication.").

91. LINDA BRUSLIND, MICROBIOLOGY 144 (2018), https://open.umn.edu/opentextbooks/textbooks/microbiology-2017 [https://perma.cc/FJ65-3SJ6]; JANE FLINT ET AL., PRINCIPLES OF VIROLOGY 21 (4th ed. 2015).

92. BRUSLIND, *supra* note 91, at 144–45.

93. HARVEY LODISH ET AL., MOLECULAR CELL BIOLOGY § 6.3 (4th ed. 2000).

94. Thomas et al., *supra* note 28, at 346.

95. ADDGENE, *supra* note 89, at 105 ("Viruses of the Retroviridae or Retrovirus family, which includes the gamma-retrovirus and lentivirus genera, have the unique ability to integrate permanently into the host genome and thereby enable long-term stable gene expression.").

96. *See* Yin et al., *supra* note 9, at 397.

97. Thomas et al., *supra* note 28, at 346 ("The science of gene therapy has a turbulent history.").

98. Nelson & Gersbach, *supra* note 9, at 646.

with AAVs were successful, the most notable result was the first death of a gene-therapy clinical-trial volunteer. In a 1999 Phase I trial to study corrections to a significant metabolic disorder, one participant, Jesse Gelsinger, died shortly after administration of the vector and the replacement gene; he developed a severe immune reaction to the infusion.[99] The tragedy laid bare a host of ethical shortcomings of first-in-human gene-editing trials, including overzealous investigators, financial conflicts of interest, improper informed consent, and insufficient attention paid to preclinical data.[100] It also demonstrated that one of gene editing's principal dangers was not the delivered genes themselves but the vectors used to deliver them.[101]

Other ex vivo gene-therapy trials carried out in Severe Combined Immunodeficiency Disease ("SCID") patients experienced similar issues. The first trials suffered from limited efficacy; they made use of mouse-related viral vectors, which poorly engrafted the stem cells used for transformation.[102] As a result, these early studies were written off as largely unsuccessful.[103] Later attempts to improve efficacy had troubling results. Trials in France and the United Kingdom in 2000 cured nine boys with SCID but caused leukemia in five children.[104] The culprit, again, was the vector: a gamma retroviral vector ("γ-RV") used in the study inserted its genetic payload within an oncogene. This gene, when disrupted, increases the body's propensity to develop cancer.[105]

"These events precipitated what is recognized as the field's nadir."[106] Though no participants in the U.S. retroviral trials suffered adverse events, in 2003 the FDA halted twenty-seven other gene-therapy trials.[107] The tendencies of certain viruses like γ-RVs to cause

99. Nikunj Somia & Inder M. Verma, *Gene Therapy: Trials and Tribulations*, 1 NATURE REV.: GENETICS 91, 95 (2000).

100. James M. Wilson, *Lessons Learned from the Gene Therapy Trial for Ornithine Transcarbamylase Deficiency*, 96 MOLECULAR GENETICS & METABOLISM 151, 153–56 (2009).

101. *See* David A. Williams & Adrian J. Thrasher, *Concise Review: Lessons Learned from Clinical Trials of Gene Therapy in Monogenic Immunodeficiency Diseases*, 3 STEM CELLS TRANSLATIONAL MED. 636, 637 (2014).

102. Thomas et al., *supra* note 28, at 355.

103. *See id.*

104. *See* Scott & DeFrancesco, *supra* note 9, at 600–02; Williams & Thrasher, *supra* note 101, at 636–37; *see also* Marina Cavazzana-Calvo et al., *Gene Therapy of Human Severe Combined Immunodeficiency (SCID)-X1 Disease*, 288 SCIENCE 669, 669–70 (2000); Salima Hacein-Bey-Abina et al., *A Serious Adverse Event After Successful Gene Therapy for X-Linked Severe Combined Immunodeficiency*, 348 NEW ENG. J. MED. 255, 255 (2003).

105. Scott & DeFrancesco, *supra* note 9, at 601–02.

106. *Id.* at 602.

107. *Id.* at 604.

cancer, combined with the death of Jesse Gelsinger, led to a massive retreat from gene-therapy development.[108] By the early 2000s, simply the term "'gene therapy' took on a more negative connotation as a dangerous and unproven technology."[109]

The recent elucidation of gene-editing technologies, however, has reinvigorated interest in "gene therapy," even while the safety of their concomitant vectors remains unproven. One recent gene-therapy trial—one of the first since the FDA's 2003 stop order—resulted in the vector-related death of several clinical trial subjects.[110] Another gene-therapy trial similarly killed yet another clinical trial subject.[111] Nonetheless, gene editing—with or without safe vectors—now continues apace.[112]

Besides toxicity—the likely culprit of some trial subjects' gene-editing deaths—gene editing and its attendant vectors raise three principal safety concerns: mosaicism, efficiency, and off-target effects. Mosaicism is the effect of gene-editing technologies only editing some of the target cells in a given tissue.[113] This creates a mosaic of edited and unedited cells, the persistence of which is unclear.[114] Recently, Chinese scientists attempted the CRISPR technique in viable human embryos and managed to correct gene mutations half the time. However, the study revealed that one of two edited embryos was a mosaic—a mixture of edited and unedited cells. It appears that CRISPR made repairs *after* DNA replication so that when the single-

108. *See* Sherkow et al., *supra* note 79, at 4.

109. *Id.*

110. Laura DeFrancesco, *CAR-Ts Forge Ahead, Despite Juno Deaths*, 35 NATURE BIOTECHNOLOGY 6, 6 (2017).

111. Lisa LaMotta, *Death in Cellectis CAR-T Trial Leads to Clinical Hold*, BIOPHARMADIVE (Sept. 5, 2017), https://www.biopharmadive.com/news/cellectis-cart-trial-death-clinical-hold/504185/ [https://perma.cc/H7QV-VMV5].

112. *See* François Baylis & Marus McLeod, *First-in-Human Phase 1 CRISPR Gene Editing Cancer Trials: Are We Ready?*, 17 CURRENT GENE THERAPY 309, 309 (2017); DeFrancesco, *supra* note 110, at 6; 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/7DSF-X2HF]; Sara Reardon, *First CRISPR Clinical Trial Gets Green Light from US Panel*, NATURE (June 22, 2018), https://www.nature.com/news/first-crispr-clinical-trial-gets-green-light-from-us-panel-1.20137 [https://perma.cc/R37U-LFWQ].

At the same time, the difficult ethical problems—such as investigative zeal, professional and institutional conflicts of interest, proper informed consent, and inattention to preclinical evidence—that plagued first-generation gene therapies were again raised as expert groups pondered recommendations for the first U.S. ex vivo CRISPR clinical trial. Baylis & McLeod, *supra*, at 309.

113. NASEM, HUMAN GENOME EDITING, *supra* note 29, at 89.

114. *Id.*

celled embryos continued to divide, some of the daughter cells inherited unrepaired DNA.[115] Other groups have reduced levels of mosaicism by carefully timing the addition of the enzyme during fertilization or certain phases of cell division, or by shortening the half-life of the Cas9 protein.[116]

Editing efficiency is another stumbling block. In a 2015 study, only 14.3% of nonviable human embryos were edited.[117] Since then, vector efficiencies have improved somewhat.[118] The controversial Chinese experiment that produced engineered human babies underscored these two shortcomings of efficiency: the twins were both mosaics, and one was incompletely edited, with cuts in one chromosome but not another.[119] Other work identified a potential flaw in the editing process, which leaves cells "transiently vulnerable to the introduction of chromosomal rearrangements and other [cancer-causing] mutations."[120] Selecting cells whose DNA has been modified by CRISPR, it seems, may also select cells with a mutated cancer-suppressor gene.[121] And now it is known that CRISPR can produce on-target effects, causing large deletions and gene shuffling.[122] After editing, imperfections in the cell's repair mechanism can rearrange segments of DNA or incorporate unwanted stretches of DNA into the chromosome.[123]

Finally, detecting off-target events—when the nucleases mutate unintended stretches of DNA—will be essential to any calculation of clinical readiness. Various methods have emerged for detecting and measuring off-target mutations, including genome-wide profiling in

115. Lichun Tang et al., *CRISPR/Cas9-Mediated Gene Editing in Human Zygotes Using Cas9 Protein*, 292 MOLECULAR GENETICS & GENOMICS 525, 532 (2017). It appears as if the engineered babies in the controversial He Jiankui case are indeed mosaics.

116. Hong Ma et al., *Correction of a Pathogenic Gene Mutation in Human Embryos*, 548 NATURE 413, 413 (2017); Zhuchi Tu et al., *Promoting Cas9 Degradation Reduces Mosaic Mutations in Non-Human Primate Embryos*, 7 SCI. REP., no. 42081, Feb. 3, 2017, at 1, 1.

117. Liang et al., *supra* note 49, at 366.

118. *See* Ma et al., *supra* note 116, at 413.

119. Katarina Zimmer, *CRISPR Scientists Slam Methods Used on Gene-Edited Babies*, SCIENTIST (Dec. 4, 2018), https://www.the-scientist.com/news-opinion/crispr-scientists-slam-methods-used-on-gene-edited-babies--65167 [https://perma.cc/YVP6-Y6J2].

120. Emma Haapaniemi et al., *CRISPR-Cas9 Genome Editing Induces a p53-Mediated DNA Damage Response*, 24 NATURE MED. 927, 930 (2018).

121. *See id.*

122. Kosicki et al., *supra* note 52, at 765.

123. *Id.* at 765–70.

bulk populations of cells.[124] Other strategies include minimizing off-target mutations by improving genome-wide specificity of CRISPR/Cas9.[125]

It is important to note that these experiments, and others designed to optimize the eventual clinical use of CRISPR and other genome-editing technologies, will likely require the use of many thousands of human embryos. The use of scarce and morally fraught resources such as unwanted, donated embryos from IVF clinics and embryos made expressly for research were dominant features of the human embryonic-stem-cell debate.[126] These controversies will continue as CRISPR-mediated approaches march toward the clinic. As an example, the CRISPR study on viable embryos conducted at Oregon Health Sciences University used hundreds of embryos during the course of the experiments.[127] Taken together, these reports and others underscore the dangers of a rush to the clinic for both in vivo and ex vivo applications—including those reported in China and trials contemplated in other countries.[128]

How are these safety risks being weighed in new gene-editing trials? There are several places to look for clues, including the National Institute of Health's ("NIH") Recombinant DNA Advisory Committee ("RAC") clinical trial approvals database.[129] Until August of 2018, the RAC reviewed gene-editing experiments in somatic

124. Taeyoung Koo, Jungjoon Lee & Jin-Soo Kim, *Measuring and Reducing Off-Target Activities of Programmable Nucleases Including CRISPR-Cas9*, 38 MOLECULES & CELLS 475, 475–78 (2015).

125. Shengdar Q. Tsai & J. Keith Joung, *Defining and Improving the Genome-Wide Specificities of CRISPR-Cas9 Nucleases*, 17 NATURE REVIEWS: GENETICS 300, 300 (2016).

126. CHRISTOPHER THOMAS SCOTT, STEM CELL NOW: FROM THE EXPERIMENT THAT SHOOK THE WORLD TO THE NEW POLITICS OF LIFE 6–9, 123–30 (2006).

127. Ma et al., *supra* note 116, at 414–17.

128. In May 2018, the FDA put a hold on CRISPR Therapeutics Phase I/II clinical trial for sickle-cell disease. Emily Mullin, *FDA Halts One of the First Human CRISPR Studies Before It Begins*, MIT TECH. REV. (May 30, 2018, 7:02 PM), https://www.technologyreview.com/the-download/611271/fda-halts-one-of-the-first-human-crispr-studies-before-it-begins/ [https://perma.cc/9LCQ-AXFR].

129. *GeMCRIS*, NAT'L INSTITUTES HEALTH, http://gemcris.od.NIH.gov [https://perma.cc/5978-XNXK]. The RAC is a federal advisory committee that provides recommendations to the Director of the NIH related to basic and clinical research involving recombinant or synthetic nucleic acid molecules, including new genome-editing technologies. *See* 42 U.S.C.A. § 282(b)(16) (Westlaw through Pub. L. No. 116-16); NAT'L INSTS. OF HEALTH, CHARTER: RECOMBINANT DNA ADVISORY COMMITTEE (2017), https://osp.od.nih.gov/wp-content/uploads/RAC_Charter_2017_508.pdf [https://perma.cc/87HN-35YF]. Recently, health officials announced plans to do away with the RAC's gene-therapy oversight function. *See* Francis S. Collins & Scott Gottlieb, *The Next Phase of Human Gene-Therapy Oversight*, 379 NEW ENG. J. MED. 1393, 1395 (2018).

cells.[130] Prior to its diminishment, the RAC database listed eleven gene-editing protocols: one concerning CRISPR, seven for ZFNs, and none for TALENs.[131] Another database that may provide clues as to the trials and vectors being used for gene editing are investigational new drug applications ("INDs") filed with the FDA.[132] For gene-editing trials to cure inherited diseases, the FDA has approved several INDs for leukemia, using lentiviral vectors, and β-thalassemia, using AAVs. At the same time, the FDA has placed "clinical holds" on other sickle cell and Duchenne muscular dystrophy programs using AAVs.[133] The FDA, meanwhile, has approved gene therapies for retinal blindness—Luxturna, an AAV therapy—and two products for leukemia, one using lentiviruses and the other using retroviruses.[134]

Beyond these resources are listings of clinical trials currently being conducted, mainly housed at NIH's Clinical Trials website.[135] Simple keyword searches yield twenty-four CRISPR trials (thirteen in China,

130. *See* Collins & Gottlieb, *supra* note 129, at 1395 (announcing the new policy). While U.S. law prohibits the RAC from considering and the NIH from funding trials that would edit the germline (i.e., eggs and sperm) to make an edited trait heritable, it does review editing experiments in somatic cells. *See* Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2242, 2283 (2015).

131. *See GeMCRIS*, *supra* note 129.

132. *IND Activity*, USDA, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/default.htm [https://perma.cc/J92T-MNS9].

133. *See* Jorge Mansilla-Soto et al., *Cell and Gene Therapy for the Beta-Thalassemias: Advances and Prospects*, 27 HUM. GENE THERAPY 295, 296–97 (2016); Sherkow et al., *supra* note 79, at 7 (discussing the leukemia approvals); Meghana Keshavan, *FDA Slaps Clinical Hold on Seattle Genetics After Four Patients Die in Cancer Drug Trial*, STAT (Dec. 27, 2016), https://www.statnews.com/2016/12/27/fda-seattle-genetics-patient-deaths/ [https://perma.cc/JMJ9-D76R]; Kate Sheridan, *Sarepta Halts Early-Stage Gene Therapy Trial for DMD*, STAT (July 25, 2018), https://www.statnews.com/2018/07/25/sarepta-clinical-gene-therapy-dmd/ [https://perma.cc/8BE7-VSGF].

134. *Approved Cellular and Gene Therapy Products: Kymriah (tisagenlecleucel)*, USDA, https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm573706.htm [https://perma.cc/4EM4-9GQX]; *Approved Cellular and Gene Therapy Products: Luxturna*, USDA, https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm589507.htm [https://perma.cc/YA9H-QYM3]; *Approved Cellular and Gene Therapy Products: Yescarta (axicabtagene ciloleucel)*, USDA, https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm581222.htm [https://perma.cc/4QDY-W2AX].

135. CLINICALTRIALS.GOV, https://clinicaltrials.gov [https://perma.cc/K4S3-9SBF]. Simply because a trial appears on a U.S. federal registry, however, does not mean it is subject to or has passed ethical and regulatory oversight in the United States. *See* 42 U.S.C.A. § 282(j) (Westlaw through Pub. L. No. 116-16) (requiring registration of all applicable clinical trials).

ten in the United States, and one in Germany);[136] two TALENs studies (both in China);[137] and fourteen ZFN trials (ten in the United States, three in China, and one in Australia).[138] In the last case, it is interesting to note that China is taking an aggressive approach to developing CRISPR therapies, while the United States seems to be exhibiting more caution.[139] Whether this is due to safety concerns related to vectors or intellectual property issues regarding ZFNs as a first-generation editing platform remains unclear. Finally, NIH requires all funded academic and research institutions to review all experiments involving human subjects through Institutional Review Boards ("IRBs").[140] How these IRBs will assess safety issues related to vectors is also an open question. Will they equate the risks of the gene-editing protocols themselves with the risks—and tragic outcomes—seen by early iterations of their vectors? Advances in the technology may have shifted the risk-benefit profile of gene-editing technologies, but memories of their failures are long and poignant.[141] As with mines in the Gold Rush, there is no single hand to police the safety of gene-editing vectors.[142] But more information about their mechanisms seems better than less.

136. *Search Results: CRISPR*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/results?cond=&term=CRISPR&cntry=&state=&city=&dist= [http://perma.cc/4ZNS-TZR2 (staff-uploaded archive)].

137. *Search Results: Talen*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/results?cond=&term=talen&cntry=&state=&city=&dist= [https://perma.cc/2A9H-3VRA].

138. *Search Result: Zinc Finger*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/results?term=%22zinc+finger%22&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&recrs=m&age_v=&gndr=&type=&rslt= [http://perma.cc/6ZTQ-T4KG (staff-uploaded archive)].

139. *See* NASEM, HUMAN GENOME EDITING, *supra* note 29, at 41 ("[I]n vitro research on embryos has already proceeded in China (using nonviable embryos).").

140. *See* Carol A. Heimer & JuLeigh Petty, *Bureaucratic Ethics: IRBs and the Legal Regulation of Human Subjects Research*, 6 ANN. REV. L. & SOC. SCI. 601, 602 (2010) (discussing the NIH's IRB requirement).

141. *Compare* Collins & Gottlieb, *supra* note 129, at 1395 (announcing that advances in "the general framework for medical product safety" are "well suited" to gene-editing research), *with* NASEM, HUMAN GENOME EDITING, *supra* note 29, at 7 ("It would be essential for this research to be approached with caution, and for it to proceed with broad public input.").

142. *See* Daniel Cornford, *"We All Live More Like Brutes than Humans": Labor and Capital in the Gold Rush*, *in* A GOLDEN STATE: MINING AND ECONOMIC DEVELOPMENT IN GOLD RUSH CALIFORNIA 78, 91 (James J. Rawls & Richard J. Orsi eds., 1999) (noting that individuals, not the government or employers, owed responsibility for mine safety).

II. THE GENE-EDITING VECTOR PICK-AND-SHOVEL PLAY

A. Secrecy in Pick-and-Shovel Plays

Today, a pick-and-shovel business simply means "a company that sells products needed for a larger, overarching industry to operate."[143] Businesses that sell pressurized tanks for the storage of natural gas, for example, provide "picks and shovels" to the otherwise highly volatile natural gas industry.[144] Internet server storage and processing—Amazon Web Services, for example—sells pick-and-shovel equipment and services to internet companies.[145] And industrial manufacturers of chemicals—needed for a host of industries—could also be considered pick-and-shovel operations.[146] In finance, pick-and-shovel businesses are widely believed to be safe if not profitable investments as long as the overarching technology is commonly used and there is a constant demand for materials and know-how to implement it.[147]

This rather mundane sector of business operations belies a more canny history of its namesake's origins—and why, of all pieces of equipment, picks and shovels are tools after which it is named. In 1848, near Sutter's Mill, California, Samuel Brannan—newspaper publisher, Mormon exile, and general store owner—noticed that workers from a nearby sawmill were keen to purchase Brannan's mining equipment.[148] After pressing them as to their interest, one teamster produced a pocket of gold dust found at Coloma on the American River outside of Sacramento.[149] At that moment, Brannan seized on an idea, one of the greatest singular acts of capitalistic zeal in American history: he would simultaneously publicize the existence of gold in the Coloma-Lotus Valley and, owning the only store for dozens of miles around, sell the equipment needed to pan it.[150] Brannan commissioned several letters

143. Stutman, *supra* note 11.

144. *Picks and Shovels for Natural Gas: These 3 Companies Will Make Money*, SEEKING ALPHA (Apr. 20, 2012, 11:53 AM), https://seekingalpha.com/article/513861-picks-and-shovels-for-natural-gas-these-3-companies-will-make-money [https://perma.cc/PSZ5-VJLY].

145. James Barnes, *What's Your Pick-and-Shovel Play of 2017?*, MEDIUM (Sept. 26, 2017), https://medium.com/@JamesBarnesEsq/whats-your-pick-and-shovel-play-of-2017-5a7c3a594e87 [https://perma.cc/FP92-GM6U].

146. Kraft, *supra* note 12.

147. *See* Stutman, *supra* note 11 ("[I]nternal component providers are the foundation of everything you see and experience on the surface. Without them, the industry simply wouldn't exist, which makes them incredibly secure from the standpoint of demand.").

148. Watson, *supra* note 13, at 299.

149. *Id.*

150. Bringhurst, *supra* note 14, at 145 ("Before Brannan allowed word of the discovery to leak out, the enterprising businessman scoured northern California purchasing and

to the editor in newspapers around the United States about the gold find and California's mild climate—"the forerunner of all California promotion literature."[151] And, later, as business picked up, Brannan "[r]ush[ed] into San Francisco's Plaza[,] . . . doffed his broad-brimmed black hat, and holding aloft a bottle of glittering particles in his left hand, he bellowed in his great bull voice: 'GOLD! GOLD! GOLD! From the American River!' The Gold Rush was born that instant."[152]

Back at his store, Brannan purchased cheap metal pans from every possible retailer and wholesaler in the United States.[153] Retailing for 20¢ each, Brannan sold them to desperate miners for $15 dollars. Miners, not knowing where else to buy the necessary equipment for their endeavors, gladly paid.[154] At the operation's peak, Brannan was netting "$150,000 a month in business"—$4.8 million today.[155] Brannan quickly became the richest man in California, purchasing virtually all of Calistoga, California; funding the Mexican Revolution of 1860; and, in a tale apt for a story about the Gold Rush, dying "a penniless drunkard—shunned by his former friends and forgotten by his enemies."[156] All from selling picks and shovels.

There are many good lessons to be learned from Brannan's tale about marketing, pricing, and cornering a hot market. But like Brannan's knowledge about wholesalers of mining equipment, at the core of most good pick-and-shovel plays lies secrecy.[157] If miners possessed the same knowledge as Brannan on where to purchase tin pans, Brannan would not have been able to sell them at a 7400% markup.

This axiom is instructive about the relationship between modern-day pick-and-shovel companies and secrecy. Older theories of the firm

stocking his store with any and all merchandise of any conceivable use to the gold seekers."). Indeed, prior to Brannan's announcement, "it was not the social custom [in California] for miners to share information of a gold strike." Douglas W. Allen, *Information Sharing During the Klondike Gold Rush*, 67 J. ECON. HIST. 944, 961 (2007). Interestingly, Douglas W. Allen chalks up the difference between information sharing during the California and Klondike gold rushes to the absence and presence, respectively, of institutionalized property norms. *Id.* at 946–47.

151. Watson, *supra* note 13, at 300.

152. *Id.* at 301.

153. MARTIN, *supra* note 13, at 21 n.9.

154. *See id.*

155. Bringhurst, *supra* note 14, at 145; *see also U.S. Inflation Rate, $150,000 in 1848 to 2018*, CPI INFLATION CALCULATOR, https://www.officialdata.org/1848-dollars-in-2018?amount=150000 [https://perma.cc/RV5A-SLNU].

156. Bringhurst, *supra* note 14, at 140.

157. *See supra* note 10.

suggest that the size and cohesiveness of a company is defined by transaction costs.[158] But in truth, these costs have as much to do with tacit knowledge—know-how—as price efficiency.[159] In this sense, pick-and-shovel plays are forms of "informational arbitrage": keeping secret information developed from one source to use it more profitably on another source.[160] This is analogous to the most classic form of arbitrage, currency arbitrage, where sellers purchase currency from one market and sell it in another, taking advantage of a difference in price across markets.[161] In some circumstances, the same applies to physical goods that are both standardized and resalable: oil, precious metals, and even corn may be utilized for "physical arbitrage."[162] But in all of these cases, the core of arbitrage remains secrecy: once information about price differences becomes public knowledge, sellers demand higher prices, purchasers demand lower prices, and competitors drive profit margins to efficiency levels, i.e., close to zero. For this reason, "arbitrageurs do not share all their knowledge with investors, and cultivate secrecy to protect their knowledge from imitation."[163] So do vector developers.

B. The Pick-and-Shovel Play, Gene-Editing Vectors, and Patents

Like tin pans, natural gas storage, or cloud computing resources, the business of gene-editing vectors constitutes a form of the pick-and-shovel play. Developers of gene-editing vectors provide tools, resources, and a great deal of technical know-how to companies more concerned with developing gene therapies than the viruses and

158. R.H. Coase, *The Nature of the Firm*, 4 ECONOMICA 386, 394–95 (1937).

159. Peter Lee, *Transcending the Tacit Dimension: Patents, Relationships, and Organizational Integration in Technology Transfer*, 100 CALIF. L. REV. 1503, 1545 (2012) ("In light of market failure, organizational integration emerges as a viable option for conveying tacit knowledge, even in the presence of patents.").

160. *See* Chau et al., *supra* note 10, at 2–3 (defining "informational arbitrage").

161. Shleifer & Vishny, *supra* note 10, at 35–36.

162. *See, e.g.*, Andrew Coleman, *Storage, Transport and the Law of One Price: Theory with Evidence from Nineteenth Century U.S. Corn Markets*, 91 REV. ECON. & STAT. 332, 332 (2009); André Plourde & G.C. Watkins, *Crude Oil Prices Between 1985 and 1994: How Volatile in Relation to Other Commodities?*, 20 RESOURCE & ENERGY ECON. 245, 247 (1998).

163. Shleifer & Vishny, *supra* note 10, at 40; *see also* Anokhin & Wincent, *supra* note 10, at 440 n.6 ("[E]ffective information exchange may even be purposefully sabotaged by innovator firms that try to exploit the better resource combinations by pursuing a 'monopolistic excess of price over cost.'").

liposomes packaging their breakthroughs.[164] And like Brannan himself, gene-editing vector companies advertise their wares through promotional literature and conference presentations, to be sure, but also through patents.[165]

Patents, among other forms of advertising, allow vector companies to disclose their technology to others while, like Brannan, fending off competition.[166] But these disclosures are often incomplete, providing just enough information about the vector's basic contours to understand them but not enough to move the technology in-house.[167] It is true that this seems to violate patent law's statutory requirement that inventions must be sufficiently disclosed in patent specifications to enable others to "make and use the same."[168] Also true: this double protection runs against the maxim that inventors must choose between protecting their inventions through patents or trade secrets, but not both.[169] But, as scholars have long noted, patent law's disclosure requirement is increasingly honored only in the breach,[170] and "layering" patent protection with trade secrecy—the mutually

164. *See, e.g.*, Nicole Faust, *Addressing the Challenges of Commercial-Scale Viral Vector Production*, 4 CELL & GENE THERAPY INSIGHTS 31, 31–32 (2018) (describing the services provided by viral developer CEVEC).

165. *E.g.*, Press Release, CEVEC, CEVEC Intensifies Its Marketing Activities, Presenting at Various Renowned Scientific Conferences in Europe and the US (Feb. 22, 2016), https://cevec.com/news/press-releases/cevec-intensifies-its-marketing-activities/ [https://perma.cc/Q8KZ-6GGC]; *About Us*, *supra* note 24; *Gene Therapy: Intellectual Property*, *supra* note 22; *see also* Jason Rantanen & Sarah E. Jack, *Patents as Credentials*, WASH. & LEE L. REV. (forthcoming 2019) (manuscript at 1–4), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3013780 [http://perma.cc/MP6N-7UV3] (discussing the reputational incentives behind patenting and patent advertising).

166. Anderson, *supra* note 36, at 1593 ("Companies use their patents as a type of advertising, extolling the virtues of a product or company."); Ann Bartow, *Separating Marketing Innovation from Actual Invention: A Proposal for a New, Improved, Lighter, and Better-Tasting Form of Patent Protection*, 4 J. SMALL & EMERGING BUS. L. 1, 3 (2000) ("[P]atents may be good marketing tools (irrespective of the specific inventions they define), they may enhance the image of the patenting entity (creating an aura of creativity and technological proficiency), and they may add fiber to patent portfolios."); Dan L. Burk, *Patent Silences*, 69 VAND. L. REV. 1603, 1627 (2016) ("Some view [a patent] as a marketing asset or as an advertising feature.").

167. *See* Burk, *supra* note 166, at 1628 ("[P]atent doctrine preserves multiple spaces in which patents remain[] silent, maintaining ambiguities that may be satisfied or imbued with meanings as needed at different points in the life of the document. The patent provides a natural point of mediation, which largely occurs in the interstices between the local meanings of the document's disclosure."); Lee, *supra* note 159, at 1545.

168. 35 U.S.C. § 112(a) (2012).

169. *See, e.g.*, W. Nicholson Price II, *Regulating Secrecy*, 91 WASH. L. REV. 1769, 1774 (2016) ("Inventors face a stark choice between two intellectual property systems of protecting innovative ideas: patents and trade secrecy.").

170. *See id.* at 1781–83.

exclusive nature of the two protections notwithstanding—seems to be the modern state of affairs.[171]

For vector developers, the layering of patenting with trade secrecy provides developers with a higher quantum of protection than either patents or pure secrecy would alone: insufficiently disclosed patents, without a primer to the technology's know-how, are unlikely to attract high prices or attention.[172] Nor are they likely to require the continual reengagement of the patent-holding firm.[173] Perfectly disclosed patents, meanwhile, are likely to be victims of their own success by informing potential purchasers how to invent around them. And secrecy alone is unlikely to assuage potential purchasers' fears of the patented technology's replicability or reliability.[174] Patents in this sense operate as a form of informational arbitrage: informational assets obtained through the company's own research that, although disclosed, are nonetheless restricted to command higher prices elsewhere.[175]

Take, for example, uniQure's Vector Delivery System.[176] By its own account, uniQure makes a "modular technology platform" utilizing AAVs that in theory could be used with virtually any therapeutic gene cassette desired by licensed developers, such as Bristol-Myers Squibb.[177] To encourage developers to partner with it, uniQure discloses substantial aspects of its system both through its patents and through investor and partner communications.[178] For example, uniQure has patented methods of using its technology in

171. *Id.* at 1774 n.21; *see also* Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 491–92 (1974) (noting that patent protection does not readily conflict with—nor preempt—state law patent protections). At the same time, there is the possibility that the "tying" of a slate of products protected by both trade secrets and patents may be violative of the antitrust laws; that is, simply, outside the scope of this Article.

172. *See* Lee, *supra* note 159, at 1545.

173. *See infra* Section IV.C.

174. *See infra* Section IV.B.

175. *Cf.* Anokhin & Wincent, *supra* note 10, at 439 (describing this in the context of informational arbitrage based on technical knowledge); Gray, *supra* note 10, at 4 ("According to efficient market logic, the rational arbitrager should act alone, drive the price to the fundamental level, and reap all the rewards of the arbitrage he has found." (internal citation omitted)).

176. *uniQure's Technology*, *supra* note 21.

177. *Id.*; *About: Partners*, UNIQURE, http://www.uniqure.com/about/partners.php [https://perma.cc/FEN2-SZAN].

178. *See, e.g.*, U.S. Patent No. 9,988,645 (disclosing a method of AAV preparation); U.S. Patent No. 9,885,022 (disclosing another method of AAV preparation); U.S. Patent No. 9,840,694 (disclosing a method of AAV purification); *Investors & Newsroom: Events & Presentations*, UNIQURE, http://uniqure.com/investors-newsroom/events-presentations.php [https://perma.cc/D4A9-9K5F] (listing uniQure's investor communications).

certain cell lines and further advertises its system as using one specific AAV variant—AAV5—that uniQure claims is more effective than other technologies.[179] But a substantial quantity of information about uniQure's manufacturing and development processes remains unknown such that gene-editing companies interested in using uniQure's technology have little choice but to partner with the company directly.[180] These gaps in the information disclosed by uniQure include the sequences of uniQure's AAV5 construct itself—important in assessing various safety aspects of uniQure's platform.[181]

MaxCyte is another vector company that markets a "patented, high-performance cell-engineering platform" for the development of various aspects of gene therapy.[182] According to MaxCyte, their "platform offers the potential to deliver therapy to the patient in a fraction of the time with less complexity of other autologous [chimeric antigen T-cells ("CAR-T")] products . . . due to a more streamlined manufacturing process without the complexity of virus-based products."[183] MaxCyte's patents, meanwhile, disclose an electroporation technique using stably transfected mRNA, rather than DNA, to express the recombinant proteins needed to engage in CAR-T work.[184] One would be forgiven, therefore, for thinking that such patents sufficiently disclosed MaxCyte's technology to potential licensees. But MaxCyte's patents elide over important details such as sequence listings and manufacturing details of its electroporation

179. *Gene Therapy: Hemophilia*, UNIQURE, http://uniqure.com/gene-therapy/hemophilia.php [https://perma.cc/3SEJ-RS7Y] ("We believe these factors contribute to making AAV5 a potential best-in-class vector for delivering gene therapies more effectively and safely to a greater portion of patients in need of treatment.").

180. UNIQURE N.V., *supra* note 23, at 16 ("[S]ignificant aspects of the process by which we manufacture our gene therapies are based on unpatented trade secrets and know-how. We seek to protect our proprietary technology and processes and obtain and maintain ownership of certain technologies, in part, through confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial collaborator[s].").

181. *See* Irene Gil-Farina et al., *Improving AAV Gene Therapy Safety Analysis: Multiplex LAM-PCR Provide New Insights into AAV Vector Integration*, 23 MOLECULAR THERAPY (SUPP. 1) S264, S264 (2015) (cataloging some AAV5 safety issues).

182. *About Us*, *supra* note 24.

183. *CARMA Platform*, MAXCYTE, https://www.maxcyte.com/car/car-platform/ [https://perma.cc/H3SK-GXM2].

184. U.S. Patent No. 9,669,058 ("Certain embodiments involve the use of electroporation to facilitate the entry of one or more nucleic acid molecules into cells of the immune system, such as natural killer (NK) cells.").

technologies.[185] This is, of course, proprietary information, allowing MaxCyte to advertise its product as "patented" even while failing to disclose precisely how it works.

Spark Therapeutics provides yet another example of a gene-therapy company wishing to establish itself at the forefront of "vector design," the DNA sequences that enable vectors to operate safely and permanently.[186] To demonstrate their vector's potential to licensees, Spark chose perhaps an unorthodox route: it sought and received FDA approval for a gene-therapy product of its own, Luxturna, an AAV therapy indicated to treat a rare form of genetic blindness.[187] In an effort to further entice and inform partners, Spark has filed several pending patent applications describing components of its vector technology.[188] But regulatory filings note that Spark also quietly makes use of a trade-secreted platform, Selecta Biosciences' SVP platform, to ensure the safety of Spark's vectors.[189] These are critical for Spark's vector technology: Selecta's SVP platform is designed to mitigate the potential for overactive immune responses to the viral vector used by Spark, lessening the likelihood that patients suffer extreme—and in some cases fatal—immune attacks.[190] Precisely how such technology works with Spark's platform, however, is unknown despite the FDA's approval of Luxturna and Spark's patents seemingly disclosing its technology.[191]

These lacunae in vector developers' patents and technical disclosures are significant given the recent, almost insatiable interest in gene editing; not much information is needed to froth investor interest

185. *See, e.g.*, *id.* (claiming methods of modifying certain cells with mRNA, without disclosing specific mRNA sequences); U.S. Patent No. 9,132,153 (same); U.S. Patent No. 8,450,112 (same).

186. *See* BioSci Capital Partners, *Rounds Report: Spark Therapeutics Ironically Topped Our Featured List Despite Its Depreciation*, SEEKING ALPHA (Aug. 8, 2016), https://seekingalpha.com/article/4196276-rounds-report-spark-therapeutics-ironically-topped-featured-list-despite-depreciation [https://perma.cc/UA8J-FS8M] ("The company is leveraging on the cutting-edge viral vector design via adeno-associated virus.").

187. *Luxturna*, *supra* note 134.

188. U.S. Patent Application No. 20,180,135,097 (filed Nov. 7, 2017); U.S. Patent Application No. 20,170,216,408 (filed Mar. 17, 2017).

189. Selecta Biosciences, Inc., *supra* note 26, at 47; Spark Therapeutics, Inc., *supra* note 26, at 19.

190. *SVP™ for Immune Tolerance*, SELECTA BIOSCIENCES, http://selectabio.com/platform/svp-for-immune-tolerance/ [https://perma.cc/A7PR-AMCE].

191. *See* Spark Therapeutics, Inc., *supra* note 26, at 19.

and massage fears of past failures.[192] The vector-platform industry has responded to this demand by touting efforts to develop a new generation of vectors with better efficacy, higher potency, and reduced integration problems.[193] In developing γ-RVs, for example, industry efforts included removing sequences that would detrimentally activate nearby genes.[194] This was an important first step in the field; later studies showed that these so-called self-inactivating ("SIN") viruses improved safety in SCID therapy.[195] At the same time, the possibility that SIN γ-RVs could integrate into promoter regions of genes provided the impetus for the development of a different type of gene ferry, lentiviral vectors ("LVs").[196] LVs do not readily integrate in nearby genes, thus reducing the probability of "insertional mutagenesis"—the mutation of genes through the accidental "insertion" of the vector's payload.[197] Newly engineered versions of LVs are, in theory, transcriptionally inactive; many are used in some ongoing gene-therapy trials.[198] And AAVs have perhaps become the most widely used gene-therapy interventions to date with over 173 clinical trials recorded in 2017 alone.[199] As with Spark's use of Selecta's SVP platform, however, host immune response to AAVs remains a major obstacle.[200] Finally, CAR-T therapies, using retroviral vectors in an ex vivo setting, have emerged as a potential treatment for malignant cancers.[201] And even despite some fatal failures in the CAR-T

192. *See* Max Nisen, *Playing with Crispr, Investors Get Burned*, BLOOMBERG (June 13, 2018, 4:21 PM), https://www.bloomberg.com/opinion/articles/2018-06-11/crispr-gene-editing-setback-offers-reminder-of-biotech-risks [https://perma.cc/5YKW-ZSBT (dark archive)].

193. Naldini, *supra* note 39, at 351.

194. S. Hacein-Bey-Abina et al., *A Modified γ-Retrovirus Vector for X-Linked Severe Combined Immunodeficiency*, 371 NEW ENG. J. MED. 1407, 1407–08 (2014).

195. *Id.* at 1408.

196. *See* NASEM, HUMAN GENOME EDITING, *supra* note 29, at 225 (discussing integrase-defective lentiviral vectors); Shim et al., *supra* note 9, at 744 fig.4.

197. Melissa A. Kotterman, Thomas W. Chalberg & David V. Schaffer, *Viral Vectors for Gene Therapy: Translational and Clinical Outlook*, 17 ANN. REV. BIOMEDICAL ENGINEERING 63, 65–68 (2015). To be clear, naturally occurring LVs do carry the risk of insertional mutagenesis, but this is likely due to a single virally encoded gene, integrase, that, once removed, strongly mitigates this effect. *Id.* at 67–68.

198. *See* Daniela Cesana et al., *Uncovering and Dissecting the Genotoxicity of Self-Inactivating Lentiviral Vectors* In Vivo, 22 MOLECULAR THERAPY 774, 774 (2014).

199. DiCarlo et al., *supra* note 9, at 15.

200. Roberto Calcedo & James M. Wilson, *Humoral Immune Response to AAV*, 4 FRONTIERS IMMUNOLOGY, no. 341, Oct. 18, 2013, at 1, 1; Nelson & Gersbach, *supra* note 9, at 646–47.

201. Yin et al., *supra* note 9, at 391–92.

space[202]—the equivalent of a mine collapse, if you will—CAR-T development rapidly continues, with Gilead acquiring Kite Pharmaceuticals[203] and Novartis also investing heavily in the technology.[204] Like early advertisements for the Gold Rush, the potential for vectors' success seems to paint a much rosier picture than can be readily ascertained from patents' literature. And advertisements of safety, efficacy, and potential treatment and cures, as we have learned from other frontier biotechnologies, raise significant bioethical concerns.

III. BIOETHICS OF VECTOR PICK-AND-SHOVEL PLAYS

This combination of patents and the pick-and-shovel play in the gene-editing vector space raises several specific ethical issues. Vector patents' partial technical disclosures add uncertainty to patients' and research subjects' medical risk, especially for viral vectors. It also perpetuates risky clinical trials on shaky foundations of preclinical evidence. The vector pick-and-shovel play also complicates issues of informed consent between patients and clinicians. And assuming therapies are approved by the FDA using a partially secretive vector as a backbone, this may ultimately drive up costs, exacerbating access and affordability issues currently plaguing advanced therapies.[205] Vector developers' employment of pick-and-shovel strategies may be good for business, but they stand counter to some core principles of bioethics.

202. DeFrancesco, *supra* note 110, at 6; Roni Dengler, *Cancer Immunotherapy Company Tries to Explain Deaths in Recent Trial*, SCIENCE (Nov. 16, 2017, 5:45 PM), http://www.sciencemag.org/news/2017/11/cancer-immunotherapy-company-tries-explain-deaths-recent-trial [https://perma.cc/P5SG-3672]; Keshavan, *supra* note 133; Levine, *supra* note 28; Rebecca Robbins, *Patient Dies from Severe Brain Swelling After Taking Kite's CAR-T Therapy*, STAT (May 8, 2017), https://www.statnews.com/2017/05/08/patient-dies-kite-car-t-therapy/ [https://perma.cc/9FQQ-S3HP]; Mark Terry, *Patient Dies in Cellectis' Groundbreaking CAR-T Trial, Forcing a Halt to Trials*, BIOSPACE (Sept. 11, 2017), https://www.biospace.com/article/patient-dies-in-cellectis-groundbreaking-car-t-trial-forcing-a-halt-to-trials-/ [https://perma.cc/BT9Z-TN3T] [hereinafter Terry, *Patient Dies*].

203. Press Release, Gilead Sciences, Inc., Gilead Completes Acquisition of Kite Pharma, https://www.gilead.com/news-and-press/company-statements/kite-pharma [https://perma.cc/29R3-WRT2].

204. *See* DeFrancesco, *supra* note 110, at 6.

205. *See* Scott & DeFrancesco, *supra* note 9, at 606.

A. Uncertain Risk

Any human testing of a new medical technology has inherent risk.[206] But with enough technical information about the technology itself, such risk can—at least ideally—be quantified and managed.[207] Typically, clinicians engage in such analyses by using empirical data to assess the clinical effectiveness of a given intervention and weigh that effectiveness against the potential harm by treatment.[208] This requires some detailed knowledge about the mechanism of the intervention itself; it is difficult to quantify a treatment's potential risk if it is unclear how the treatment works.[209] Failures to appreciate the molecular mechanisms behind certain treatments have led to spectacular failures in medicine.[210]

Partial and incomplete technical disclosures for certain gene-editing vectors—in combination with their adoption by the field—makes the risk of many potential gene-editing therapies uncertain. Those advising potential clinical trial subjects may not know in which cell lines the subject vectors are produced, important for immunogenicity studies.[211] If the sequence of the vector is unknown, clinicians may similarly be unaware of the risks of oncogenic genomic

206. *See, e.g.*, M.J.H. Kenter & A.F. Cohen, *Establishing Risk of Human Experimentation with Drugs: Lessons from TGN1412*, 368 LANCET 1387, 1387 (2006) ("Administration of a chemical or biological compound to a human being is never without risk.").

207. *See* A. Brett Hauber, Angelyn O. Fairchild & F. Reed Johnson, *Quantifying Benefit–Risk Preferences for Medical Interventions: An Overview of a Growing Empirical Literature*, 11 APPLIED HEALTH ECONS. & HEALTH POL'Y 319, 319, 325 (2013) (mentioning technology as but one factor used to elicit benefit-risk preferences).

208. *Id.* at 320.

209. *See, e.g.*, W. Nicholson Price II, *Black-Box Medicine*, 28 HARV. J.L. & TECH. 419, 458–60 (2015) (describing this principle in the context of "black box" algorithmic diagnostic tests).

210. *See, e.g.*, Waqas Rehman, Lisa M. Arfons & Hillard M. Lazarus, *The Rise, Fall and Subsequent Triumph of Thalidomide: Lessons Learned in Drug Development*, 2 THERAPEUTIC ADVANCES HEMATOLOGY 291, 291, 294–95 (2011) (noting that the thalidomide disaster arose, in part, from a lack of understanding of the drug's mechanism of action).

211. *See, e.g.*, Jennifer M. Audsley & Gregory A. Tannock, *Cell-Based Influenza Vaccines*, 68 DRUGS 1483, 1486–87 (2008) (noting that GlaxoSmithKline uses a proprietary cell line for some influenza vaccine development); Jiemiao Hu & Shulin Li, *Electroporation Formulation for Cell Therapy*, *in* ELECTROPORATION PROTOCOLS 55, 57 (Shulin Li et al. eds., 2014) ("[A]s a trade secret, the components in each [proprietary electroporation] buffer are unknown, which is inconvenient when researchers try to transfect a new cell line."); Ana F. Rodrigues et al., *Viral Vaccines and Their Manufacturing Cell Substrates: New Trends and Designs in Modern Vaccinology*, 10 BIOTECHNOLOGY J. 1329, 1336 (2015) (recounting the history of PER.C6, the first proprietary "designer-cell substrate").

integration.[212] And if organ tropism is unknown—such as selective integration in the liver—this may increase organ toxicity in patients with already-damaged immune systems.[213] This makes granular risk assessments—other than "kill or cure"—all but impossible.[214]

This can be seen from a recent reset of the vector-design field that has experienced both startling successes and catastrophic failures. At the same hospital in France where X-linked SCID trials occurred nearly twenty years ago, clinicians recently transplanted engineered stem cells and apparently "cured" a teenager with sickle cell disease.[215] An in vivo trial using an AAV vector has similar effects on six of seven patients with severe Hemophilia A.[216] And a 2018 β-thalassemia trial using LV-engineered stem cells reduced or stopped the need for blood transfusions in all twenty-two patients.[217]

At the same time, issues concerning vectors and manufacturing—the bulk of which remain trade secrets despite being patented—are likely responsible for a spate of deaths in trials advancing CAR-T.[218] A gene-therapy trial sponsored by Juno Therapeutics resulted in the deaths of five clinical trial subjects, all from toxicities likely related to the treatment itself.[219] While the ultimate cause of such toxicities remains unclear, the likely culprit stems from a portion of the vector construct used to create Juno's therapy—something called the costimulatory domain.[220] Cellectis, another company developing

212. *See, e.g.*, Axel Schambach et al., *Biosafety Features of Lentiviral Vectors*, 24 HUM. GENE THERAPY 132, 133 (2013) (discussing the need to thoroughly understand the sequence of γ-RVs to assess safety).

213. *See* Takehiro Ura, Kenji Okuda & Masaru Shimada, *Developments in Viral Vector-Based Vaccines*, 2 VACCINES 624, 624 (2014).

214. *See* Scott & DeFrancesco, *supra* note 9, at 600 ("*Ex vivo* γ-Moloney murine leukemia RV-mediated transfer of the γc-chain cDNA (common to several interleukin receptors) to autologous [hematopoietic stem cells] cured boys with X-linked SCID. However, four of ten children and one of ten children in a similar UK trial developed leukemia.").

215. Jean-Antoine Ribeil et al., *Gene Therapy in a Patient with Sickle Cell Disease*, 376 NEW ENG. J. MED. 848, 848–49 (2017).

216. *See* Savita Rangarajan et al., *AAV5-Factor VII Gene Transfer in Severe Hemophilia A*, 377 NEW ENG. J. MED. 2519, 2519 (2017).

217. Alexis A. Thompson et al., *Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia*, 378 NEW ENG. J. MED. 1479, 1479 (2018).

218. *See supra* Section II.B.

219. *See* DeFrancesco, *supra* note 110, at 6; Clara Rodríguez Fernández, *A Cure for Cancer? How CAR-T Therapy Is Revolutionizing Oncology*, LABIOTECH.EU (Jan. 16, 2018), https://labiotech.eu/features/car-t-therapy-cancer-review/ [https://perma.cc/6X8F-BGTU].

220. Fernández, *supra* note 219; Mark Terry, *A Look at the Deaths that Plagued Juno and Kite Pharma's CAR-T Trials*, BIOSPACE (June 29, 2017), https://www.biospace.com/

products in the CAR-T space, similarly reported nine deaths from its trial "not related . . . to disease progression."[221] This is despite robust patenting from both Juno and Cellectis.[222] These trials and travails underscore how individual disease, different delivery systems, and gene-transfer technology make the risk-benefit calculation difficult for these first-in-human trials.[223]

This uncertainty of risk seems especially problematic in the context of gene-editing vectors because it allows the benefit side of the risk-benefit equation to increase while keeping the risk side dark. To date, gene-editing trials have justifiably focused on last-option patients with deadly disease.[224] As a consequence, there are significant pressures to translate CRISPR and other gene-editing technologies to clinical applications—deeper understandings of how they're introduced into cells be damned.[225] Even with imperfect understandings of how gene-editing vectors work, this has changed the risk-benefit ratio for single-gene (i.e., "monogenic") diseases that seem potentially curable but are otherwise deadly.[226] This is especially true in developing countries with high health-care burdens, and even in developed countries, like the United States, with high health-care costs.[227] Marina Cavazzana, head of biotherapy at the Necker Hospital for Sick Children in Paris where she conducts X-linked SCID trials, stated that "[i]f one compares the cost of gene therapy to conventional therapy and transplantation in economic terms, it is absolutely the least

article/a-look-at-the-deaths-that-plagued-juno-and-kite-pharma-s-car-t-trials-/ [https://perma.cc/9XAH-TZE7] [hereinafter Terry, *A Look at the Deaths*].

221. *See* Terry, *A Look at the Deaths*, *supra* note 220.

222. *See, e.g.*, U.S. Patent No. 7,446,190 (claiming specific CAR-T sequences); U.S. Patent No. 9,855,297 (claiming certain endonucleases for use in CAR-T preparation); U.S. Patent No. 9,890,393 (same).

223. *See* Robbins, *supra* note 202; Terry, *Patient Dies*, *supra* note 202.

224. *See* NASEM, HUMAN GENOME EDITING, *supra* note 29, at 47 ("First-in-human trials make compliance with [informed consent] provisions difficult, given that by definition, it is very difficult to assess the degree of uncertainty that pertains when research is moving from preclinical models to human interventions.").

225. *See* Nicol et al., *supra* note 32, at 87.

226. *See* Luigi Naldini, Ex Vivo *Gene Transfer and Correction for Cell-Based Therapies*, 12 NATURE REVIEWS: GENETICS 301, 301 (2011) ("[Monogenic diseases treated with] early-generation retroviral vectors, now provide a comprehensive analysis of a sizeable number of patients, allowing a reliable assessment of long-term immune system reconstitution and the risk/benefit ratio . . . . The verdict is favourable, with a clear long-term therapeutic benefit evident in most treated patients despite the occurrence of vector-related leukaemia in a few.").

227. *See* Stuart H. Orkin & Philip Reilly, *Paying for Future Success in Gene Therapy*, 352 SCIENCE 1059, 1060 (2016).

expensive system. It is a cure for patients, with no continued therapy, no immunosuppression, and no infections."[228] This assumes, of course, that deadly diseases are viewed as infinitely harmful, and discounts to zero—because they are unknown—the likely adverse events that may arise from aggressive treatment using less than well-characterized vectors.

Patenting and secrecy issues for vectors notwithstanding, perhaps this calculus *is* ethically appropriate: Is the promise of the technology changing or just our perceptions of it? Like the CAR-T example, it is true that the first trials have killed some patients faster than the underlying disease otherwise would have. But the trials have also wonderfully cured others.[229] Nonetheless, risk assessments for clinical trial subjects and patients should not be kept in the shadows. It does not excuse the hocking of the new technology's vectors and the subsequent secreting away of important information about them.

B. Insufficient Preclinical Evidence

Some of the vector patents' secrecy gap stems from structural issues in patent doctrine: patent law's incentives—if not requirements—for early patenting.[230] Patent law's novelty requirement, for example, contains within it a series of "statutory bars," prohibitions on developers patenting their own inventions if the inventions had been disclosed "in a printed publication, or in public use, on sale, or otherwise available to the public" for more than one year prior to filing a patent application.[231] Beyond this legal requirement, developers engage in early patenting for traditional reasons having to do with competitive advantage and defensive strategy.[232]

228. *See* Scott & DeFrancesco, *supra* note 9, at 606.

229. *E.g.*, Levine, *supra* note 28.

230. Christopher A. Cotropia, *The Folly of Early Filing in Patent Law*, 61 HASTINGS L.J. 65, 93–96 (2009) (describing this phenomenon); Sherkow, *Patent Law's Reproducibility Paradox*, *supra* note 31, at 883–84 (linking this to scientific irreproducibility).

231. *See* 35 U.S.C. § 102(a)(1), (b)(1) (2012); Robert P. Merges, *Priority and Novelty Under the AIA*, 27 BERKELEY TECH. L.J. 1023, 1024–27 (2012) (discussing the statutory bars).

232. *See, e.g.*, Stuart J.H. Graham et. al., *High Technology Entrepreneurs and the Patent System: Results of the 2008 Berkeley Patent Survey*, 24 BERKELEY TECH. L.J. 1255, 1288 (2009) ("[P]atenting plays a substantial role for many high-technology startups in securing competitive advantage from their technology innovations."); Sean B. Seymore, *Rethinking Novelty in Patent Law*, 60 DUKE L.J. 919, 944 (2011) ("Savvy third-party patentees accordingly have an incentive to purposely create novelty hurdles for subsequent inventors by strategically disclosing unclaimed, unmade compounds in their patents."); Sean B.

This means, however, that patents—even at their best—are frequently grounded in early-stage preclinical evidence, much of which is unlikely to be replicable.[233] For some drugs, this means basing a patents' claims on treating human therapy like small-sample-size animal trials.[234] For gene-editing vectors, this means that patents are similarly filed early, long before any clinical trials have been run.[235] Whatever does end up disclosed may ultimately not work as claimed.[236] As a result, many of the safety issues arising from vector design are unlikely to be found out until long after patents have been filed. The clinical trial deaths from treatment studies obviously came as surprises to the companies themselves.[237] Other problematic safety issues are likely more predictable, however, such as cellular "chimerism," tissues with mixtures of genomic material,[238] and off-target effects, changes to the code of genes not sought to be edited.[239] Some of these can be

Seymore, *The Null Patent*, 53 WM. & MARY L. REV. 2041, 2073 (2012) ("[A] research organization might engage in defensive publication, which occurs when information '[is] intentionally made available to the public as prior art in order to render any subsequent claims of invention or discovery ineligible for a patent.'" (second alteration in original) (quoting STEPHEN A. HANSEN & JUSTIN W. VANFLEET, TRADITIONAL KNOWLEDGE AND INTELLECTUAL PROPERTY: A HANDBOOK ON ISSUES AND OPTIONS FOR TRADITIONAL KNOWLEDGE HOLDERS IN PROTECTING THEIR INTELLECTUAL PROPERTY AND MAINTAINING BIOLOGICAL DIVERSITY 24 (2003), https://community-wealth.org/sites/clone.community-wealth.org/files/downloads/book-hansen-vanFleet.pdf [https://perma.cc/B7T7-DY7Y])).

233. *See generally* Sherkow, *Patent Law's Reproducibility Paradox*, *supra* note 31 (exploring this phenomenon with four case studies).

234. *E.g.*, *In re* '318 Patent Infringement Litig., 583 F.3d 1317, 1321 (Fed. Cir. 2009) (criticizing a patent's basis on animal studies); Sherkow, *Patent Law's Reproducibility Paradox*, *supra* note 31, at 890 ("[T]he basis for the '197 patent's claims rests only on the thinnest reed of data: a preclinical, prophylactic trial in baboons—and even then, only ten baboons.").

235. *See* U.S. Patent No. 9,132,153 (filed May 24, 2013) (MaxCyte's Patent); U.S. Patent No. 8,450,112 (filed Apr. 9, 2009) (same); U.S. Patent No. 9,988,645 (filed Feb. 3, 2017) (uniQure's patent); U.S. Patent No. 9,885,022 (filed Nov. 25, 2015) (same); U.S. Patent No. 9,840,694 (filed Sept. 7, 2012) (same); U.S. Patent Application No. 20,180,135,097 (filed Nov. 7, 2017) (Spark Therapeutics' patent application); U.S. Patent Application No. 20,170,216,408 (filed Mar. 17, 2017) (same).

236. *Cf.* Sherkow, *Patent Law's Reproducibility Paradox*, *supra* note 31, at 886–98 (analyzing four case studies of this in the context of small molecule drugs).

237. *See* Jennifer Couzin-Frankel, *Worries, Confusion After Cancer Trial Deaths*, 354 SCIENCE 1211, 1211 (2016). One researcher reacted, "Why would we see this now? We don't know, period." *Id.*

238. *See* Maria Pia Cicalese & Alessandro Aiuti, *Clinical Applications for Gene Therapy for Primary Immunodeficiencies,* 26 HUM. GENE THERAPY 210, 214 (2015) (discussing safety issues with partial chimerism).

239. A common definition of "off-target effects" is changes to the code of genes not sought to be edited. *See* Shim et al., *supra* note 9, at 747 (noting the risk for unsafe off-target effects for some vectors).

especially concerning—some have the propensity to cause cancer and some cause large deletions of otherwise necessary genes.[240]

As a consequence, vector developers file for patents covering their wares before they can reasonably know whether clinical trials will even be safe.[241] This gives vector patents—along with corporate advertising of their technology's patent protection—the false imprimatur of good technological disclosure useful for green lighting clinical trials.[242] This unfortunately traffics on the current framework used for such analyses, which prioritizes technical disclosures, above all others, as sufficient for informed consent.[243] In 2010, the bioethicist Jonathan Kimmelman developed a risk-assessment framework for novel gene therapies to help reviewers and investigators decide when the distance between preclinical and clinical research is sufficiently narrow to green light a first-in-human experiment.[244] Under this framework, measurements of scientific validity—such as whether animal data are good representations of the human condition under study, the level of disclosures' experimental reproducibility and replicability, a study's statistical power, and tests of the vector platform—can give confidence to reviewers and oversight committees about whether to proceed.[245] Two Canadian researchers, François Baylis and Marcus McLeod, analyzed a RAC-approved Phase I CRISPR trial for cancer using the Kimmelman framework.[246] Among other major concerns about the study's validity, they found that investigators of the study did not

240. Clara Rodríguez Fernández, *Scientists Warn CRISPR Therapy Could Cause Cancer as First Human Trials Take Place*, LABIOTECH.EU (Nov. 6, 2018), https://labiotech.eu/medical/crispr-therapy-cancer-risk/ [https://perma.cc/5BT9-JXLN]; Heidi Ledford, *CRISPR Gene Editing Produces Unwanted DNA Deletions*, NATURE (July 16, 2018), https://www.nature.com/articles/d41586-018-05736-3 [https://perma.cc/K8WF-P7MD].

241. *See* U.S. Patent No. 9,132,153 (filed May 24, 2013) (MaxCyte's Patent); U.S. Patent No. 8,450,112 (filed Apr. 9, 2009) (same); U.S. Patent No. 9,988,645 (filed Feb. 3, 2017) (uniQure's patent); U.S. Patent No. 9,885,022 (filed Nov. 25, 2015) (same); U.S. Patent No. 9,840,694 (filed Sept. 7, 2012) (same); U.S. Patent Application No. 20,180,135,097 (filed Nov. 7, 2017) (Spark Therapeutics' patent application); U.S. Patent Application No. 20,170,216,408 (filed Mar. 17, 2017) (same); *see also* Sherkow, *Patent Law's Reproducibility Paradox*, *supra* note 31, at 886–98; *supra* text accompanying notes 235–36.

242. *See* JONATHAN KIMMELMAN, GENE TRANSFER AND THE ETHICS OF FIRST-IN-HUMAN RESEARCH: LOST IN TRANSLATION 40 (2010) (criticizing "[t]he tendency in clinical research and human protections . . . to conceptualize risk in technical, mono-causal terms").

243. *Id.*

244. *Id.* at 110.

245. *Id.* at 117–24.

246. Baylis & McLeod, *supra* note 112, at 311.

sufficiently test the efficacy of the lentiviral delivery system.[247] This led Baylis and McLeod to conclude that the move to a first-in-human CRISPR trial using the delivery system was "premature."[248] Nonetheless, the eighteen-patient trial, approved by an academic IRB, continued to recruit patients.[249]

To be clear, this rush to the clinic isn't solely a function of patent law's early, incomplete disclosure requirement. Rather, this example simply illustrates that gene-editing trials using unsafe vectors may—and frequently do—commence with imperfect or insufficient preclinical data.[250] Yet, patents—touted by vector developers to sell the novelty of their technologies—seem worse than nothing in their place in the Baylis-McLeod framework. A useful comparison, perhaps, can be made to stem cell research. Over the course of a decade or more, hundreds of patent disclosures complimented by a significant trove of basic and preclinical research led to greater degrees of certainty as stem cell interventions moved through trials into the clinic.[251] Yet, early efforts in these areas suffered from ethical lapses, underfunding, moving too quickly, and, still, insufficient preclinical evidence.[252] There, at least, local, national, and international agencies moved quickly to set standards for clinical research, including emphasis on preclinical data and strong scientific rationales.[253] In turn, the worth of stem cell patents has been muted.[254] But in the case of CRISPR, the

247. *Id.* at 313.

248. *Id.* at 317 ("In our view, the move to first-in-human Phase 1 CRISPR gene editing cancer trials in the United States, on the basis of pre-clinical evidence presented to the RAC, is premature insofar as it makes the leap of faith a leap too far.").

249. *NY-ESO-1-redirected CRISPR (TCRendo and PD1) Edited T Cells (NYCE T Cells)*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT03399448 [https://perma.cc/PAU2-UDMW]. The CRISPR interventional trial, sponsored by the University of Pennsylvania, uses engineered, autologous T-cells that have been edited to "disrupt expression" of native TCRα, TCRβ, and PD-1. *Id.*

250. *See* Sherkow, *Patent Law's Reproducibility Paradox*, *supra* note 31, at 883–85.

251. SCOTT, *supra* note 126, at 95–121.

252. George Q. Daley, *The Promise and Peril of Stem Cell Therapeutics*, 10 CELL STEM CELL 740, 740 (2012); Christopher Thomas Scott & David Magnus, *Wrongful Termination: Lessons from the Geron Clinical Trial*, 3 STEM CELLS TRANSLATIONAL MED. 1398, 1399 (2014).

253. Roger A. Barker et al., *The Challenges of First-in-Human Stem Cell Clinical Trials: What Does This Mean for Ethics and Institutional Review Boards?*, 10 STEM CELL REP. 1429, 1429 (2018); George Q. Daley et al., *Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines*, 6 STEM CELL REP. 778, 778 (2016); Jonathan Kimmelman & Carole Federico, *Consider Drug Efficacy Before First-in-Human Trials*, 542 NATURE 25, 26 (2017).

254. Jacob S. Sherkow & Christopher Thomas Scott, *Stem Cell Patents After the America Invents Act*, 16 CELL STEM CELL 461, 463 (2015) (noting that "new administrative

move to the clinic has come barely five years after the first reported discoveries and with virtually no attention paid to the enabling half of the possible therapeutic agents—the vector systems.[255] Pick-and-shoveling vector patents in this regard risks moving from the bench to the clinic on an unstable bedrock.

C. Opacity to Informed Consent

The gene-editing vector pick-and-shovel play presents another issue concerning patient-subject autonomy: opacity to informed consent. Transparent and voluntary informed consent is an ethical cornerstone of medical research.[256] Patients should be able to properly weigh the risks of experimental medicine based on their conversations with their physicians and make health decisions in line with their values and goals.[257] Subjects of biomedical research, in partnership with their providers, should similarly decide whether the benefits of seeking an investigational treatment outweigh the risks.[258] For a consent to be ethical and valid, the patient must be free to make a voluntary decision based on known and transparent information.[259]

procedures before the PTO make it substantially easier (and cheaper) to challenge stem cell patents as they become issued . . . [and that this] may be a natural stage in the life cycle of any rapidly developing area of law and technology").

255. Aside from the exhaustive review by Picanço-Castro, de Sousa Russo-Carbolante and Covas, *see supra* note 8, we could find no other academic articles assessing disclosures in gene-editing vector patents.

256. *See* COUNCIL FOR INT'L ORGS. OF MED. SCIS., INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS, Guideline 4 (2002) [hereinafter CIOMS GUIDELINES], https://cioms.ch/wp-content/uploads/2016/08/International_Ethical_Guidelines_for_Biomedical_Research_Involving_Human_Subjects.pdf [https://perma.cc/9PFT-KTMN] (detailing requirements for "individual informed consent" in Guideline 4); ICH HARMONISED TRIPARTITE GUIDELINE: GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) 5, 9 (1996) [hereinafter ICH GUIDELINE], https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf [https://perma.cc/8EFG-BRW3]; NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH § C.1 (1979) [hereinafter BELMONT REPORT], https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf [https://perma.cc/B88C-JZ6X]; WORLD MED. ASS'N, WMA DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS ¶¶ 25–32 (2018), https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ [https://perma.cc/BL5C-3L9Z] (setting out informed consent guidelines in paragraphs 25–32).

257. CIOMS GUIDELINES, *supra* note 256, Guideline 4.

258. BELMONT REPORT, *supra* note 256, § C.2; WORLD MED. ASS'N, *supra* note 256, ¶¶ 16–18.

259. CIOMS GUIDELINES, *supra* note 256, Guideline 4.

But if expert clinicians in the gene-therapy field are proceeding under a veil of opacity about the vectors used to mediate those therapies, informed consent turns fraught: How can providers—without a full understanding of or access to all the available evidence—properly obtain consent from their patients?[260] The pick-and-shovel play for vector patents makes this especially problematic because it gives clinicians the appearance of transparency even while information about vector platforms is intentionally being secreted from trialists. Even if evidence about the nature of certain vectors could be presented adequately and clearly, and assuming a subject's understanding of this information could be properly assessed, informed consent is still arguably lacking without full transparency about the delivery systems themselves.

This opacity to obtaining informed consent arising from the vector pick-and-shovel play exacerbates several other ethical problems endemic to modern gene-editing technologies. First, it plays on patients' susceptibility to overhyped portrayals of gene-editing technologies like CRISPR: gene-editing technologies are cures for genetic illnesses that are cheaper, easier, and more precise than other therapies.[261] Such a view discounts, of course, the uncertainties about the vectors used to operate them or minimizes the difficulties encountered during the more than twenty years of refinement of vector-based gene therapies.[262]

Second, it contributes to gene editing's hype. In a series of national and international policy reports and peer-reviewed research, bioethicists and policy researchers raised questions about public understanding of genome editing.[263] As a consequence, there is no clear path for how the public should be engaged to properly develop

260. Motoko Araki & Tetsuya Ishii, *Providing Appropriate Risk Information on Genome Editing for Patients*, 34 TRENDS BIOTECHNOLOGY 86, 86, 89 (2016).

261. *See* Jasanoff et al., *supra* note 2; *cf.* Christopher Scott, *Treading the Line Between Sensational and Groundbreaking Science*, 15 AM. J. BIOETHICS 1, 1 (2015) (discussing the merits of publishing experiment results from controversial CRISPR trials prior to meaningful relevant research).

262. *See* Naso et al., *supra* note 39, at 329 (expressing confidence in AAV therapy but noting that design challenges remain); Nelson & Gersbach, *supra* note 9, at 654–55 (listing ongoing challenges with vector technology); Shim et al., *supra* note 9, at 746–50 (listing various uncertainties concerning gene-editing safety and efficacy).

263. J. Benjamin Hurlbut, *Limits of Responsibility: Genome Editing, Asilomar, and the Politics of Deliberation*, 45 HASTINGS CTR. REP. 11, 11, 13 (2015); Jasanoff et al., *supra* note 2; Eric T. Juengst, *Crowdsourcing the Moral Limits of Human Gene Editing?*, 47 HASTINGS CTR. REP. 15, 15–17 (2017); Carolyn P. Neuhaus & Arthur L. Caplan, *Genome Editing: Bioethics Shows the Way*, 15 PLOS BIOLOGY, no. e2001934, Mar. 16, 2017, at 1, 3–5.

genome-editing policy, a normative value behind most new technologies.[264] How experts and the public should interact on crucial questions of clinical trials is also an open question.[265] As a result, existing guidance and mechanisms of governance of genome editing may not adequately reflect public beliefs and values.[266] The known and unknown risks of genome-editing technologies—including the attendant risks of vector technologies—must be communicated adequately if governance with public input is to be seriously considered.[267]

Third, it contributes to a culture of rational ignorance on the part of clinicians regarding technical and safety hurdles that must be surmounted before trials can proceed.[268] As discussed previously, essential to any assessment of risk for first-in-human trials is an exhaustive evaluation of the preclinical evidence.[269] Though new gene-editing vectors are often portrayed as a quantum leap over first generation technologies, several major questions concerning the technology's safety even in the preclinical validation phase are still unresolved.[270] The pick-and-shovel play, however, is likely to contribute to a physician's determination that such concerns are unknowable, simply because vector developers have chosen to guard their platforms as secret.[271]

D. Increased Costs

Lastly, patents covering important vectors have the ability to—indeed, the likelihood of—increasing the costs of gene-editing therapies using them if and when such therapies are marketed. By

264. *See* Hurlbut, *supra* note 263, at 13; Jasanoff et al., *supra* note 2; *see also* JAMES WILSDON & REBECCA WILLIS, SEE-THROUGH SCIENCE: WHY PUBLIC ENGAGEMENT NEEDS TO MOVE UPSTREAM 13–19 (2004) (reviewing the literature on the "[p]ublic understanding of science").

265. *See, e.g.*, Juan Pablo Domecq et al., *Patient Engagement in Research: A Systematic Review*, 14 BMC HEALTH SERVS. RES., no. 89, Feb. 26, 2014, at 1, 2 (noting that it "remains unclear who to engage or when, or how to perform this task").

266. *See* INT'L BIOETHICS COMM., REPORT OF THE IBC ON UPDATING ITS REFLECTION ON THE HUMAN GENOME AND HUMAN RIGHTS 27 (2015), http://unesdoc.unesco.org/images/0023/002332/233258E.pdf [https://perma.cc/8KB2-UQRH]; NUFFIELD COUNCIL ON BIOETHICS, *supra* note 40, at 86; Editorial, *Genome Editing: Science, Ethics, and Public Engagement*, 390 LANCET 625, 625 (2017).

267. *See* Jasanoff et al., *supra* note 2.

268. *See* Edward Lanphier et al., *Don't Edit the Human Germ Line*, 519 NATURE 410, 410–11 (2015).

269. *See supra* Section III.B.

270. *See supra* notes 233–40 and accompanying text.

271. *See supra* Section III.A.

conferring exclusive protection over a particular product—or in the case of vectors, a component of a larger product—patents give their owners the ability to charge supracompetitive prices.[272] And while this may sound like more of an economic concern than an ethical one, prices for life-saving therapies like gene therapies tend to traffic on the bioethical principle of justice: at the most extreme, patients who cannot afford gene-editing therapies may die where more well-heeled sufferers would have otherwise lived.[273] On a broader scale, this may contribute to increasing disparities in health outcomes between the rich and the poor.[274] The vector pick-and-shovel play may, in time, come to be viewed as taking advantage of the ill just the same as Brannan took advantage of Sutter's Fort miners.

Private issues of justice notwithstanding, increased costs associated with the pick-and-shovel play have public concerns as well. Increased costs, all else being equal, decrease health-care payers' bottom lines.[275] Classical modeling would suggest this has one of two effects: either insurance premiums themselves become increasingly expensive, which in turn has the effect of limiting insurance coverage (and access to health care), especially among the most price sensitive of the population;[276] or in the context of public payers, lead to health-

272. Michael J. Burstein, *Exchanging Information Without Intellectual Property*, 91 TEX. L. REV. 227, 236 (2012) ("Intellectual property . . . allows inventors or creators to charge supercompetitive prices during the period of exclusivity.").

273. *See* Rebecca E. Wolitz, *A Corporate Duty to Rescue: Biopharmaceutical Companies and Access to Medications*, 94 IND. L.J. (forthcoming 2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3186418 [https://perma.cc/G6T6-VBAG] (describing high drug prices as impinging on ethical duties).

274. *See* Michael Chernew et al., *Effects of Increased Patient Cost Sharing on Socioeconomic Disparities in Health Care*, 23 J. GEN. INTERNAL MED. 1131, 1131, 1135 (2008).

275. This is assuming, of course, that payers will be forced to cover these new technologies but be unable to concomitantly raise premiums. The historical basis for this set of assumptions was weak in the early 2000s when premiums rose faster than expenditures. *See* J.D. Kleinke, *The Price of Progress: Prescription Drugs in the Health Care Market*, 20 HEALTH AFF. 43, 48–49 (2001). But the recent development—and extraordinary cost—of new therapeutics may be beginning to change this analysis: payers feel increasingly unable to say "no" to even expensive genetic therapies, many of which are, after all, "cost effective." The sudden sharp spike in costs for many therapies also means that payers cannot, in many instances, raise premiums in parallel. *See* Scott Gottlieb, Comm'r., FDA, Remarks at the Leonard Davis Institute Symposium, Harnessing the Curative Potential of Genomic Technologies (Sept. 28, 2018), https://www.fda.gov/NewsEvents/Speeches/ucm621964.htm [https://perma.cc/ST87-UFVJ].

276. Michael Chernew, David M. Cutler & Patricia Seliger Keenan, *Increasing Health Insurance Costs and the Decline in Insurance Coverage*, 40 HEALTH SERVS. RES. 1021, 1022, 1034 (2005).

care rationing or severe strain on the public fisc—an even broader cataclysm of injustice.[277] This latter fear is substantial: given Medicaid's virtually mandatory coverage scheme, increased costs of even significant, life-saving therapies may dramatically fray public resources, forcing state Medicaid administrators to choose between advocating for a specific health-care intervention rather than, say, fully funding a year of kindergarten.[278]

To be fair, the vector pick-and-shovel play's contribution to this problem is the same as it is with patents, in general, for gene-editing therapies. But incompletely disclosed vector patents, as in the pick-and-shovel play, present some particular nuances to this calculus. First, as necessary equipment to therapeutic gene-editing technology, vector patents have the ability to raise prices on end products (gene-editing therapies) even without disclosing which aspects of the technology they are covering. This makes it difficult, if not impossible, to parcel out price assessments and figure out ways of saving money for gene therapies.[279] Second, this phenomenon of multiple patentees covering a single product is likely to contribute to price increases in the form of "royalty stacking," a well-studied, albeit controversial, aspect of product development.[280] Assuming, without concluding, that royalty

277. *See* GRACE MARSDEN ET AL., INST. FOR CLINICAL & ECON. REVIEW, GENE THERAPY: UNDERSTANDING THE SCIENCE, ASSESSING THE EVIDENCE, AND PAYING FOR VALUE 7–8 (2017), https://icer-review.org/wp-content/uploads/2017/03/ICER-Gene-Therapy-White-Paper-030317.pdf [https://perma.cc/JEA2-SX5M].

278. *See id.*; Symposium, The Cost of a Cure: Creating Sustainable Solutions for Gene and Cell Therapies, University of Pennsylvania Leonard Davis Institute of Health Economics (Sept. 28, 2018) (conference attended by JSS and held under Chatham House rules).

279. That is, assuming that some vector technologies are substitutable prior to a given therapy's design, gene-therapy developers would have the opportunity to price shop or negotiate among multiple, competing vector technologies—but only if there was transparency regarding the relationship between the vector license price and the technology implemented. Such transparency *could* be tied to disclosures of vector technologies in patents. But as detailed in this Article, such transparency doesn't readily exist.

280. *See* Mark A. Lemley & Carl A. Shapiro, *Patent Holdup and Royalty Stacking*, 85 TEX. L. REV. 1991, 1993 (2007) (defining "royalty stacking" as "situations in which a single product potentially infringes on many patents, and thus may bear multiple royalty burdens . . . reflect[ing] the fact that, from the perspective of the firm making the product in question, all of the different claims for royalties must be added or 'stacked' together to determine the total royalty burden borne by the product"). With this said, it is difficult to overstate how controversial the concept of "royalty stacking" has been in the patent economics literature; many well-regarded economists have disclaimed that such a phenomenon even exists. *See, e.g.*, J. Gregory Sidak, *Holdup, Royalty Stacking, and the Presumption of Injunctive Relief for Patent Infringement: A Reply to Lemley and Shapiro*, 92 MINN. L. REV. 714, 718–19 (2008) (recounting that royalty stacking did not occur in the development of various wireless communications standards).

stacking is a true risk for vector patents in gene-therapy products, the pick-and-shovel play makes this harder to investigate even while it is unclear which layers of the stack they apply to.[281] Lastly, the increased costs likely to come in the vector space bring with it the ethical issue of price transparency to patients and practitioners.[282] While all patented therapeutics in the United States suffer from extreme price opacity, vector-implementing gene therapies arguably make the practice worse by adding an increased layer of *technical* opacity to an already dark field of business practice.[283] The vector pick-and-shovel play may not be qualitatively different from patented drug pricing generally. But it certainly does not improve things.

IV. PICKS, SHOVELS, AND PATENT DISCLOSURE

Gene editing, vectors, and patents seem to exist in a complicated interrelationship of advanced therapies, platform technology, disclosure, and secrecy. This may make it appear that the issues arising from gene-editing vector patents are limited if not unique. But in fact the case illuminates some broader issues about how patents work for cutting-edge and unpredictable technologies. First, the ethical problems centering on partial disclosure and secrecy suggest that there are other benefits to patent disclosure other than merely technical

Perhaps the most serious criticism, however, comes from Einer Elhauge, who provides both an empirical and a theoretical denial of royalty stacking as a common occurrence. *See generally* Einer Elhauge, *Do Patent Holdup and Royalty Stacking Lead to Systematically Excessive Royalties?*, 4 J. COMPETITION L. & ECON. 535 (2008). Elhauge's criticism specifically takes the Lemley-Shapiro model to task for discounting the following "realistic assumptions: (i) that firms negotiate a series of patents when they make a multi-component product, (ii) that firms using the patents have information about their operations that patent holders lack[,] or (iii) that demand is not constant." *Id.* at 537. Notably, for the purposes of vector patents and gene-editing developers, it appears that neither assumption (i) or (ii) applies and that assumption (iii)—given the extraordinary untapped demand for gene-editing therapies—may, in fact, cut the other way.

This is all to say: as controversial as royalty stacking *is* in the academic literature, the specific circumstances surrounding the vector patent pick-and-shovel play suggests that it *may* occur here. The degree to which it occurs and whether the ultimate prices for therapeutics using patented vector technology are "excessive" remain to be seen. The authors are neither clairvoyants nor economists; we don't know.

281. *See supra* note 275 (regarding pricing and transparency).

282. *See* Narcyz Ghinea, Wendy Lipworth & Ian Kerridge, *Propaganda or the Cost of Innovation? Challenging the High Price of New Drugs*, 352 BRIT. MED. J., no. i1284, Mar. 11, 2016, at 1, 2 (criticizing the link between high therapeutic costs and high development costs given that development costs are not transparent); Fintan R. Steele, *Big Pharma's Commedia*, 123 CELL 971, 972 (2005) (noting therapeutic developers' need for development cost transparency given drug prices).

283. *See supra* Section II.B.

ones—namely, that they serve as a form of consumer information. Second, it serves as a potentially instructive case study of factors that contribute to the cost of inventing around an operative but only partially disclosed and patented technology. Lastly, it suggests that poor disclosure in combination with commercialization may work as a form of standards lock-in—a channeling of inventive efforts around working with a widely adopted standard rather than developing better ones. Besides simply allowing others to "make and use" the underlying technology, the case of gene-editing vector patents may further teach us that there are a number of ancillary benefits to patent disclosure.

This is not to say that patents are the sole culprit—or solution—to better disclosure on the road to informed consent. Regulators like the FDA play an enormous if not primary role in the quantity and quality of information disclosed about manufacturing inputs like gene-editing vectors for clinical trials.[284] The FDA is, in many ways, an information disclosure agency; "today drug regulation guides the development of information that turns poisons, used advisedly, into drugs."[285] One can therefore certainly imagine a regime where the FDA is both statutorily authorized and administratively willing to mandate maximum disclosure regarding inputs for therapeutic manufacture. But that is purely imaginative. The FDA is both legally prohibited from requiring the disclosure of confidential business information from clinical trials and culturally unwilling to do so. This makes the role of disclosure for patents, however strong (or weak), all that much more important.

A. Expanded Audiences for Patent Disclosure

Patents have been classically described as a quid pro quo: the inventor receives exclusionary rights to the invention for the disclosure to the public of how the invention actually works.[286] Requiring such disclosure allows the public to make use of the technology not just after the patent expires but immediately once the patent application is published by the USPTO.[287] This allows others to test aspects of the invention, to attempt to build work-arounds to the patent, and to create

284. *See* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 380–84 (2007) (discussing FDA's role in information disclosure).

285. *Id.* at 347.

286. Sherkow, *Patent Law's Reproducibility Paradox*, *supra* note 31, at 865 n.128 (recounting the history of this phrase).

287. Eisenberg, *supra* note 35, at 1022; Seymore, *supra* note 35, at 624.

improvements.[288] According to Timothy R. Holbrook, "the public benefits from the disclosure of the invention because the public storehouse of knowledge is thus enhanced, allowing others to rely upon the teachings of the patent to generate even further follow-on innovation."[289]

Despite these paeans to "the public," the audience to which patent disclosures are directed tends to be limited. Most generously, patents are thought of as informing scientists and engineers in the technology's field.[290] This is implied by the statute, which requires patents' disclosures to inform "persons having ordinary skill in the art."[291] And there is, in fact, some empirical evidence suggesting that researchers, at least in some fields, "read" or are at least aware of patents.[292] More cynically, perhaps, disclosures only inform other patent professionals of patents in the field so they can either invent around or have their attorneys draft around them.[293]

But the pick-and-shovel case for gene-editing vectors suggests that patent disclosures may be important for others—namely, consumers of patented technology.[294] The lack of disclosure surrounding gene-editing vector patents, and the ethical issues this raises, teaches that clinicians, doctors, and patients may benefit from more robust disclosure paradigms, even if only indirectly. Better patent disclosure allows these consumers to make better choices about whether, when,

288. Fromer, *supra* note 35, at 548–49; Seymore, *supra* note 35, at 624.

289. Holbrook, *supra* note 35, at 131.

290. *See* Anderson, *supra* note 36, at 1590 ("Disclosure has always been focused around the PHOSITA: the person having ordinary skill in the art."); Lisa Larrimore Ouellette, *Do Patents Disclose Useful Information?*, 25 HARV. J.L. & TECH. 545, 550–54 (2012) (reviewing the existence of this "generous" view in the literature).

291. 35 U.S.C. § 112(a) (2012).

292. *See* Lisa Larrimore Ouellette, *Who Reads Patents?*, 35 NATURE BIOTECHNOLOGY 421, 421 (2017) (conducting, empirically, a survey assessment of scientists and engineers on whether and to what extent they derive useful information from patents); Ouellette, *supra* note 290, at 567–70 (surveying nanotechnology researchers).

293. Mark D. Janis & Timothy R. Holbrook, *Patent Law's Audience*, 97 MINN. L. REV. 72, 73–75, 86–88 (2012).

294. *Cf.* Anderson, *supra* note 36, at 1575 ("[A] patent can inform innovators, investors, and consumers about the value of an inventive idea."); Devlin, *supra* note 36, at 425 ("[Disclosures of patented] inventions are presumably of some worth to third parties as well, be they competitors, scientists, or consumers."); Ghosh, *supra* note 36, at 337–38 ("[Patent] disclosures for consumers can become more meaningful and provide guidance in how to respond to identified disease proclivities and risk."). To be clear, this refers to downstream, nontechnical users of the technology; it is not meant to refer to technical *users* of the patented technology stylized as consumers. *See, e.g.*, Fromer, *supra* note 35, at 599 ("[A]s each patentee is also a consumer of innovation literature, he benefits from others' better patent disclosures in his own research and development.").

and how to use the patented technology. This is true even if consumers do not read the patent themselves and the disclosed information is only conveyed to them by others, like commercial users.[295] In this way, patent disclosure can operate as an object of consumer efficiency akin to Clarisa Long's model of patents as "signals," giving consumers enough information about the underlying product to make informed choices about purchasing and use.[296] This is analogous, perhaps, to the operation of trademarks as minimizing consumers' search function with regard to quality, even if consumers know little about the guts of the mark-holders' manufacturing process.[297] Far from the technical notion of patent disclosure working simply to allow persons having ordinary skill in the art to replicate—that is, "make and use"—the technology, patent disclosure here informs consumers about the risks

295. *See* Anderson, *supra* note 36, at 1591 ("[T]here are numerous nonskilled audiences that a patent can reach. The dissemination of important information to a consumer may not allow the consumer to make the invention himself, but that is beside the point. The consumer may need to know other information before deciding to purchase a patented device: How much does the patented product cost? Does it work? Is it better than what came before? Is it technologically innovative? Very little of the information needed to make a purchasing decision will be contained in a patent. But the patent (even the very existence of the patent) may encourage a consumer to purchase, even though that information is not technical in nature.").

For this reason, one of the more typical solutions to information asymmetries—vertical integration—is unlikely to be effective. *See* Lee, *supra* note 159, at 1541–43 (discussing vertical integration arising from information asymmetries). To the contrary, vertical integration here is likely to exacerbate the problem of poor *consumer* disclosure. In such an instance, a firm—no longer required to demonstrate the novelty or significance of its technology to other businesses—could keep even more information secreted from downstream purchasers.

296. *See* Clarisa Long, *Patent Signals*, 69 U. CHI. L. REV. 625, 677 (2002) ("The social benefit of patent signaling is the increase in market efficiency because of the existence of more information about the firm. . . . Without patents to provide a window (however hazy) into the firm, investors might carry out inefficient searches in pursuit of better information. When the two types of inefficiencies are netted out, the firm's informational advantage may render excessive signaling by the firm preferable to excessive searches by investors.").

297. *See* Stacey L. Dogan & Mark A. Lemley, *A Search-Costs Theory of Limiting Doctrines in Trademark Law*, 97 TRADEMARK REP. 1223, 1225–27 (2007) (reviewing literature and cases supporting the notion that trademark law seeks to encourage "efficient resource allocation and bring consumers the highest quality products at the lowest prices"). At the same time, the search-costs theory of trademark has come under sustained attack. *See, e.g.*, Mark P. McKenna, *The Normative Foundations of Trademark Law*, 82 NOTRE DAME L. REV. 1839, 1840–41 (2007) (challenging the notion that diminished search costs and "improving the quality of information in the marketplace" are normatively appropriate moorings for trademark law). Whether search costs are *indeed* an appropriate touchstone for granting trademarks is an issue beyond the scope of this Article. At the same time, it may be interesting to think about the vector patent pick-and-shovel play as arising from an analogous connection between patent signals, poor patent disclosure, and shoddy marks.

and benefits of the technology they wish to use.[298] Simply put, patent disclosure may not only serve as a manual but also as a label.

B. Informing the Costs of Inventing Around

Patent disclosure provides another benefit: it allows others to "invent around" the patented technology.[299] By providing information about how the claimed technology actually works, users and commercial developers can assess how to adapt the technology to avoid infringement (and royalty payments).[300] Far from being a nefarious practice, this is a core function of peripheral claiming in patent law.[301]

At the same time, inventing around claimed technology may be more costly than simply obtaining a license to the sought-after technology.[302] Patent disclosure, therefore, allows users to assess not only *how* to invent around particular technology but also the *cost* of doing so. There exists economics and patent law literature noting that the costs of inventing around a particular claimed invention increase as disclosure decays; it is hard to figure out how much it costs to get around a patented technology if it is hard to figure out how the technology works.[303] But the inverse implication is likely true as well:

298. *Cf.* Sherkow, *Patent Law's Reproducibility Paradox*, *supra* note 31, at 899 (linking irreproducible patent disclosure of drugs to issues concerning patient safety among others).

299. *See supra* note 37 and accompanying text.

300. Dan L. Burk, *Perverse Innovation*, 58 WM. & MARY L. REV. 1, 24 (2016). *But see* Sichelman & Graham, *supra* note 37, at 135.

301. Burk, *supra* note 300, at 25 ("[F]ar from frustrating or eluding the intent of the patent, inventing around may be viewed as furthering important goals of the patent system.").

302. *See* U.S. DEP'T. OF JUSTICE & FED. TRADE COMM'N, ANTITRUST ENFORCEMENT AND INTELLECTUAL PROPERTY RIGHTS: PROMOTING INNOVATION AND COMPETITION 61 (2007), https://www.ftc.gov/sites/default/files/documents/reports/antitrust-enforcement-and-intellectual-property-rights-promoting-innovation-and-competition-report.s.department-justice-and-federal-trade-commission/p040101promotinginnovationandcompetitionrpt0704.pdf [https://perma.cc/WE9A-XDFK] (noting the tensions between licensing and design-around strategies); Christopher R. Leslie, *Antitrust and Patent Law as Component Parts of Innovation Policy*, 34 J. CORP. L. 1259, 1262 (2009) ("Professor Hovenkamp has explained that 'too much [intellectual property] protection can produce costly monopolies or exclusive rights that others must either license or innovate around.' This increases the costs of market entry and innovation, ultimately hurting both static and dynamic efficiency." (alteration in original) (quoting HERBERT HOVENKAMP, THE ANTITRUST ENTERPRISE: PRINCIPLE AND EXECUTION 249 (2005))); Glynn S. Lunney, Jr., *Patents and Growth: Empirical Evidence from the States*, 87 N.C. L. REV. 1467, 1490 (2009) ("[If] it is less expensive to license than to invent around[,] . . . taking a license is individually rational.").

303. *See, e.g.*, Anokhin & Wincent, *supra* note 10, at 441 ("As long as the strength of the patent protection regime is a known quantity—which is generally believed to be the case—the prospective entrepreneur may assign probabilities to the likelihood of a counterattack by the patent holder and/or estimate the chance of the endeavor['s] success and take those

robust patent disclosure improves cost assessments of inventing around claimed technology.[304]

Yet in some cases, even robust patent disclosure is not enough to induce users to invent around a particular technology—the relative costs are simply too high. In the case of gene-editing vectors, costs are high because there are other structural barriers to working around patented products—namely, FDA regulation and the highly experimental and uncertain nature of the technology itself.[305] If a commercial developer needs FDA approval to commercially use a vector created in-house, and if the developer has to run costly and highly uncertain experiments to obtain that approval, that may be substantially more costly than simply obtaining a license to the technology from a company like Spark Therapeutics. Couple this with the fact that currently approved vectors actually "work" in the regulatory sense of the phrase, and the relative cost of inventing around becomes insurmountably high.[306] Why spend money reinventing the wheel?

What poor disclosure of gene-editing vector patents teaches is that poor patent disclosure, in tandem with structural barriers to commercial development, can operate to discourage others from inventing around even a troublesome, patented, but otherwise useful technology.[307] Inventing and receiving approval for new vectors is

probabilities into account when considering whether or not to pursue the respective opportunity." (citation omitted)); Richard J. Gilbert, *Patents, Sleeping Patents, and Entry Deterrence*, 17 J. REPRINTS ANTITRUST L. & ECON. 205, 247 (1987) ("The patent grant does offer substantial protection when the cost of imitating the patented article is high. . . . In many cases the patent disclosure is grossly inadequate to enable firms to copy new technology."); Seymore, *supra* note 35, at 654 n.172 ("[A] competitor can attempt to design around the invention or find flaws in the disclosure to invalidate it.").

304. This is, to be clear, an intuition. There is little, if any, literature the authors could find assessing the merits of this argument. Empirical work—essentially, a survey asking firms that read patents whether disclosure has helped or hindered design-around efforts—would be helpful to assess whether this phenomenon exists in the real world.

305. NASEM, HUMAN GENOME EDITING, *supra* note 29, at 103–07 (reviewing FDA issues concerning gene editing); Shim et al., *supra* note 9, at 746 (cataloging FDA regulatory hurdles); *see also* Anokhin & Wincent, *supra* note 10, at 440 (describing the difficulties in becoming the first mover in highly regulated fields).

306. That is, inventing around may not be successful in the sense that the design-around vector may affect the therapeutic end product in such a way as to fail FDA approval. In that circumstance, the therapeutic developer is faced with bearing the cost of designing around the patented vector, but with no marketable product to show for its efforts. Such costs are almost certainly more than the cost of licensing a regulatorily "proven" technology.

307. *See, e.g.*, Gregory N. Mandel, *The Generic Biologics Debate: Industry's Unintended Admission that Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH. 1, 21–24 (2006) (describing this for biosimilars in the context of nonenablement).

fraught and expensive.[308] Whether this is enough to truly prevent those wishing to invent around the patent remains to be seen—it is an empirical question worthy of a separate investigation.[309] Poor patent disclosure, however, makes this assessment incredibly difficult. And without better information about how much inventing around actually costs, developers' appetite for inventing around patented vectors is likely to be diminished. The case with gene-editing vector patents teaches that another virtue of patent disclosure—even when there are commercial embodiments available—is a more accurate assessment of how much it would cost to avoid them.

C. Channeling Therapies and Platform Standardization

Generally, patent disclosure is an integral part of standard setting—an industry's agreement of common standards or components for a broader, complex technology.[310] For standard-setting organizations—the collective, often ad-hoc entities that oversee the standard-setting process—technical standards are adopted by users and downstream developers *en masse*.[311] Where certain developers own smaller pieces of the standard set to be adopted, patents serve as one instrument for each participant to disclose their particular contribution to the standard.[312] Because standards often prove sticky—it is difficult, for example, to require hardware manufacturers to remove USB ports from their wares after the USB standard has been adopted—patent holders often commit to contributing their intellectual property through fair, reasonable, and nondiscriminatory licensing.[313]

This well-worn process turns, however, on the robustness of patents' technical disclosure; with poor disclosure, it may be difficult, if not impossible, to determine whether patents committed to a standard actually practice it or not.[314] This is a routine if not common

308. *See, e.g.*, Ricki Lewis, *What Should Gene Therapy Cost?*, PLOS BLOGS (Oct. 26, 2017), https://blogs.plos.org/dnascience/2017/10/26/what-should-gene-therapy-cost/ [https://perma.cc/964T-VAU4] ("Luxturna was in clinical trials for 9 years, and that's expensive. Developing the vector alone can cost $500,000 to $1 million.").

309. *See supra* note 306.

310. Jorge L. Contreras, *Essentiality and Standards-Essential Patents*, *in* CAMBRIDGE HANDBOOK OF TECHNICAL STANDARDIZATION LAW: COMPETITION, ANTITRUST, AND PATENTS 209, 209–10 (Jorge L. Contreras ed., 2017).

311. *Id.*

312. *Id.*

313. Contreras, *Much Ado*, *supra* note 38, at 2.

314. *See, e.g.*, Anne Layne-Farrar, *Moving Past the SEP RAND Obsession: Some Thoughts on the Economic Implications of Unilateral Commitments and the Complexities of Patent Licensing*, 21 GEO. MASON L. REV. 1093, 1102 n.31 (2014) ("[E]ven after a standard

problem for electronics and software standards where more patents are frequently tied up in standards than readily necessary.[315] In those industries, however, technical operability of the underlying technology is rarely an issue; the role of standard-setting organizations is to ensure, among other things, that users can practice standard technologies even if the patents claimed to be covering them are indeterminate. But there are no such standard-setting organizations, at least to date, for gene-editing vectors. The gene-editing vector patent cases described here, therefore, begin to clarify what happens when a certain component technology becomes standard but only poorly discloses how it operates. Poor disclosure means that a standard may be adopted that is otherwise technically suboptimal, unsafe, or not universally applicable.[316]

In addition, the gene-editing vector patents suggest that standardization in the shadow of poor patent disclosure may result in what we call "channeling": the continued development of downstream technology using a previously adopted standard simply because it's available.[317] In the gene-editing patent context, this means the selection of certain gene-editing therapies for development not because they have the strongest health impact but because they work with off-the-shelf vectors.[318] This risks exacerbating some of the potential inequities already brewing for gene therapy: that the therapies developed will largely be directed to genetic disorders afflicting wealthy, developed countries and sold for high prices.[319] In other cases, there is the risk that treatment for some diseases may lag behind because the underlying vector technology—vectors' picks and shovels—has not been robustly investigated.

has been defined, it can be a subjective judgment as to whether a particular patent's claims match the technical specifications of a standard.").

315. *See, e.g.*, Princo Corp. v. Int'l Trade Comm'n, 616 F.3d 1318, 1323–24, 1326 (Fed. Cir. 2010) (concluding that tying standards operative patent licenses to licenses for patents that did not practice a standard is not patent misuse).

316. A point of terminology is probably in order. In the context of standard-essential patents, patent *disclosure* frequently refers to the act of standard-setting participants disclosing *which* patents they own or license that they believe would be required by a technical standard. This is not what we mean here. We mean patent disclosure in the classic sense: the *technical* disclosure of information within a given patent.

317. *Cf.* Barnett, *supra* note 38, at 1865 (describing platform developers' attempt to give away expensively developed platforms, in order to encourage their adoption as a solution to the "host's dilemma").

318. *See supra* text accompanying note 39.

319. Sherkow, *Public Health*, *supra* note 33, at 669.

To be fair, in some instances channeling is less problematic. There are few issues with channeling in the information technology space, and indeed there are some instances in that industry where channeling has actually produced resounding successes.[320] But for gene editing and other advanced therapies, channeling gives cause for concern. Choosing diseases for therapeutic development has public health concerns that extend beyond mere market efficiencies. Better patent disclosure—knowing vectors' manufacturing and applicability details—would go a long way. The tail shouldn't wag the dog.

CONCLUSION

If gene editing is a modern-day gold rush, there's still a lot of money to be made in picks and shovels—the vectors used to get gene editors' molecular equipment into cells. Companies like uniQure, MaxCyte, and Spark Therapeutics are beginning to market vector "platforms" to more high-profile gene-editing companies. And in doing so, these vector companies have relied on both patents and secrecy: patents covering their technologies that fail to entirely disclose how they work. Just like the pick-and-shovel business during the 1848 Gold Rush, this is a form of informational arbitrage: if everyone knew exactly how the patented vectors worked, they would develop their own.

And yet, this strategy—good for oil and gas storage, bulk chemicals, or cloud computing services—raises some difficult bioethical issues when applied to experimental and potentially unsafe therapies. It makes uncertain the risk of experimental therapies using the vectors, lulling patients and clinical research subjects into a false sense of security. This is exacerbated by the scant patent disclosures made by vector developers that are often rooted in insufficient preclinical evidence. Patient autonomy is also impeded because secrecy, when combined with gene editing's hype, makes true informed consent difficult to obtain. And patents covering vectors, even when only partially disclosed, are likely to contribute to the already astronomical costs of gene therapies. Selling picks and shovels in a gold rush may be good business strategy, but when the miners are the ill and the desperate, it may simply be predation.

At the same time, the issues surrounding gene-editing vector patents also serve as a case study for patent policymakers on why

320. *See, e.g.*, Barnett, *supra* note 38, at 1865 (describing channeling, at least in beneficial contexts for "free" platforms, as resulting from the "host's dilemma").

robust patent disclosure is important. Patent disclosure informs not just users and technical developers of the technology but also consumers. It also clues in downstream developers—like gene-editing companies—on the costs of inventing around a technology, if needed. And lastly, patent disclosure polices against uncharacterized technologies becoming standardized—the "channeling" of future development around nuts and bolts that are not well understood. Just like the Gold Rush of 1848, more information about where to find good picks and shovels checks against the hype then displayed by Sam Brannan in that May in San Francisco:

> *"GOLD! GOLD! GOLD! From the American River!"*[321]

321. Watson, *supra* note 13, at 301.