REWRITING NATURE: THE CASE OF HERITABLE HUMAN GENOME EDITING[†]

DANA CARROLL[*]

Genome editing is a powerful technology that allows the modification of individual DNA sequences in essentially any organism. The advent of Clustered Regularly Interspaced Short Palindromic Repeats ("CRISPR") has simplified the procedures of genome editing, extending its range in research, medicine, and agriculture. While scientists are busy modifying genomes, discussions of how societies can find a path to derive the benefits of the technology and avoid its misuses are welcome and timely.

In *Rewriting Nature*, Dr. Paul Enríquez draws on his training in both biochemistry and the law.[1] As a partial solution to the existing gap, he advocates for "a jurisprudence of scientific empiricism," envisioning that incorporating reliable scientific evidence into deliberations in the legal and regulatory spheres will allow adoption of sensible uses of genome editing technologies while avoiding capitulation to extreme advocates or extreme detractors.[2]

There is at least one positive sign that the legal profession is aiming to grasp the basics of genome editing. In February of 2021, I participated in a workshop on Emerging Areas of Science, Engineering, and Medicine for the Courts in preparation for revision of the Reference Manual on Scientific Evidence, a document meant to assist judges in cases involving complex technical issues.[3] I discussed genome editing in this context, and I think there is reason to expect that the technology will be included in the next edition of the reference manual.

In the early part of his book, Dr. Enríquez compares the genome editing revolution to the equally paradigm-disrupting development of molecular cloning

[†] This Essay was submitted as part of the *Boston University Law Review Online*'s November 2022 symposium on *Rewriting Nature* by Dr. Paul Enríquez. Online Editors Erin Beaton and Kaitlin Ostling organized the symposium, and Professors Christopher Robertson and Kevin Outterson moderated.

[*] Distinguished Professor Department of Biochemistry, University of Utah School of Medicine.

[1] *See* PAUL ENRÍQUEZ, REWRITING NATURE: THE FUTURE OF GENOME EDITING AND HOW TO BRIDGE THE GAP BETWEEN LAW AND SCIENCE (2021).

[2] *Id.* at 10-15.

[3] *See* NAT'L ACADS. OF SCIS., ENG'G & MED., EMERGING AREAS OF SCIENCE, ENGINEERING, AND MEDICINE FOR THE COURTS: PROCEEDINGS OF A WORKSHOP (2021), https://doi.org/10.17226/26231 (panel on Emerging Issues in the Biological Sciences); *see also* NAT'L RSCH. COUNCIL, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (3d ed. 2011).

and ensuing methods for manipulating DNA in the 1970s.[4] This is an apt comparison, but there are significant differences that pertain to the law.

In 1975, I attended the Asilomar Conference on Recombinant DNA Molecules (the "Asilomar Conference") that was called to assess potential uses and hazards of our new capabilities for joining and propagating DNA segments from different organisms.[5] I was also present at both International Summits on Human Genome Editing (the "International Summits") in 2015 and 2018 that were called for similar purposes.[6] The key difference between the Asilomar Conference and the International Summits is that, in 1975, we were basically ignorant about practical uses of recombinant DNA and what mishaps might occur. By 2015, we had extensive knowledge of how genome editing could be used and, at least in outline, what might go wrong in various arenas.

As a result of the lack of experience with recombinant DNA in the 1970s, people began to envision horror scenarios, where modified hybrid organisms escaped the lab and wreaked havoc on people and environments. In 1976, the City of Cambridge, Massachusetts, instituted a ban on recombinant DNA within its borders—which was reversed six months later.[7] My sense is that the public reaction to genome editing has been more muted and more focused on potential medical benefits.

There are many issues in *Rewriting Nature* that deserve discussion, but I want to focus on emerging and potential uses of genome editing to prevent, cure, or mitigate the effects of human diseases. This is an area of intense research and significant promise.

Clinical trials involving somatic genome editing—i.e., modifying the genome of cells in an existing patient—have been going on for quite some time,[8] and

[4] ENRÍQUEZ, *supra* note 1, at 77-78, 113-14.

[5] *See generally* Paul Berg, David Baltimore, Sydney Brenner, Richard O. Roblin III & Maxine F. Singer, *Summary Statement of the Asilomar Conference on Recombinant DNA Molecules*, 72 PROC. NAT. ACAD. SCI. USA 1981 (1975) (summarizing conference called to discuss recombinant DNA molecules and potential biohazards).

[6] *See* NAT'L ACADS. OF SCIS., ENG'G & MED., INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: A GLOBAL DISCUSSION (2015), https://doi.org/10.17226/21913 [https://perma.cc/P6JA-TSCE]; NAT'L ACADS. OF SCIS., ENG'G & MED., SECOND INTERNATIONAL SUMMIT ON HUMAN GENOME EDITING: CONTINUING THE GLOBAL DISCUSSION (2018), https://doi.org/10.17226/25343 [https://perma.cc/UX2D-H4CZ].

[7] *See* The CRIMSON Staff & Anthony Y. Strike, *Council Extends DNA Experiment Ban; Wald, Meleson Debate Dene Research*, HARV. CRIMSON (Sept. 30, 1976), https://www.thecrimson.com/article/1976/9/30/council-extends-dna-experiment-ban-wald/ [https://perma.cc/53GP-ZNSE]; *Cambridge Council Allows Harvard DNA Research*, N.Y. TIMES, Feb. 8, 1977, at 16.

[8] *See* Pablo Tebas, David Stein, Winson W. Tang, Ian Frank, Shelley Q. Wang, Gary Lee, S. Kaye Spratt, Richard T. Surosky, Martin A. Giedlin, Geoff Nichol, Michael C. Holmes & Philip D. Gregory, *Gene Editing of* CCR5 *in Autologous CD4 T Cells of Persons Infected with* HIV, 370 NEW ENG. J. MED. 901 (2014) (investigating whether site-specific gene modification is safe).

recent ones based on CRISPR show promise.[9] Because the goals and technical approaches of such therapies closely resemble those of prior gene therapies, there is a solid legal and regulatory framework to deal with issues of safety and efficacy, as Dr. Enríquez and many others have concluded.

The same is not true for genome editing in the very earliest human embryos, where the goal is to ensure that the intended modification is carried in every cell in the child ultimately born. This is termed germline or heritable human genome editing ("HHGE"). Here, the issues are more concerning because we currently know less about potential adverse outcomes. The induced changes will be present in the germline—sperm or eggs—of the treated person and thus will be passed on to his or her offspring and beyond. Accordingly, the process fundamentally alters the inheritance of a human being.

There are easily envisioned potential benefits of HHGE: eliminating a mutation responsible for a devastating disease or reversing a predisposition to cancer, for example. Dr. Enríquez is quite optimistic about the future of HHGE and presents legal arguments for permitting it, including the right to procreate and the right to parental autonomy.[10] There is also an ethical argument for the right to benefit from publicly funded technology. There are, however, reasons to be very cautious.

HHGE is the method that led to the birth of the "CRISPR babies" in China in 2018.[11] Dr. He Jiankui made a relatively simple modification to a standard in vitro fertilization ("IVF") procedure with the intent of installing genomic protection against HIV infection.[12] When He and his team added sperm to the eggs, they injected CRISPR reagents into the egg to disable a gene called CCR5.[13] Dr. He was roundly criticized for doing this and was eventually fined and jailed.[14] Here are some of the reasons why the scientific community was so surprised and unsettled.

First, current heritable genome editing technologies have not been shown to be sufficiently safe and effective to warrant clinical use. With current tools, we cannot make only the genomic change we intend without inducing undesired

[9] *See* Haydar Frangoul, David Altshuler, M. Domenica Cappelline, Yi-Shan Chen, Jennifer Domm, Brenda K. Eustace, Juergen Goell, Josu de la Fuente, Stephan Grupp, Rupert Handgretinger, Tony W. Ho & Antonis Kattamis, *CRISPR-Cas9 Gene Editing for Sickle Cell Disease and* β*-Thalassemia*, 384 NEW ENG. J. MED. 252 (2021) (using CRISPR-Cas9-based gene editing to treat two cases of inherited diseases).

[10] ENRÍQUEZ, *supra* note 1, at 339-43.

[11] The He Lab, *About Lulu and Nana: Twin Girls Born Healthy After Gene Surgery As Single-Cell Embryos*, YOUTUBE (Nov. 25, 2018), https://www.youtube.com /watch?v=th0vnOmFltc [https://perma.cc/N3DA-VTJ6].

[12] *Id.*

[13] *Id.*

[14] Dennis Normile, *Chines Scientist Who Produced Genetically Altered Babies Sentenced to 3 Years in Jail*, SCIENCE (Dec. 30, 2019), https://www.science.org/content/article/chinese-scientist-who-produced-genetically-altered-babies-sentenced-3-years-jail [https://perma.cc/9WSN-XADZ].

changes, either at the intended target or at other sites in the genome. A recent report from an international commission, on which I served, sets out the procedural standards that would have to be met before initial clinical uses of HHGE should be contemplated.[15]

Second, it has not been demonstrated that either the editing process itself or the genomic changes it induces will not have consequences during embryonic, fetal and postnatal development. In this light, even the very first clinical uses should be restricted to cases of serious, monogenic diseases, for which a clear causative mutation is identified.[16]

Third, only in very rare situations would prospective parents not have alternative means of having a healthy, genetically related child, at least in principle. For example, couples can already use IVF with preimplantation genetic testing ("PGT") to detect potential offspring with some conditions before implantation. Only when couples are both homozygous for a serious recessive condition, like sickle cell disease, or when one parent is homozygous for a dominant condition, like Huntingtonss disease, would the couple not benefit from IVF with PGT. In such situations, the benefit of having a genetically related child could counterbalance the potential harms of HHGE, once safety and efficacy are demonstrated.

Fourth, our understanding of human genetic interactions is lacking in many respects. Even in the case of monogenic conditions, the commission's recommendation is to limit the use of HHGE to restore a common, non-disease-causing sequence at the target site, because the creation of other, novel sequences could lead to unpredictable consequences.[17]

One example of the possibility for unanticipated interactions arises in the case of the "CRISPR babies." There are humans who naturally lack a functional CCR5 gene—the gene targeted by Dr. He—and are resistant to AIDS.[18] However, the responsible variant is found mostly in northern European genomes and is extremely rare in Asian genetic backgrounds.[19] CCR5 is a highly conserved gene and undoubtedly serves a critical function. It seems likely that there has been some sort of genomic adaptation to the loss of this function in Europeans—perhaps by the modification of other genes—that would not be

[15] *See* INT'L COMM'N ON THE CLINICAL USE OF HUM. GENOME EDITING, HERITABLE HUMAN GENOME EDITING 121-43 (2020), https://doi.org/10.17226/25665 [hereinafter HERITABLE HUMAN GENOME EDITING].

[16] *Id.* at 9-10. Monogenic diseases are caused by mutation of either one or both copies of a single gene. *Id.* at 39.

[17] *Id.* at 101-11.

[18] *Id.* at 22.

[19] *See* Corinne Capoulade-Métay, Liying Ma, Lien X Truong, Yasmine Dudoit, Pierre Versmisse, Ngai V. Nguyen, Marie Nguyen, Daniel Scott-Algara, Françoise Barré-Sinoussi, Patrice Debré, Gerges Bismuth, Gianfranco Pancino & Ioannis Thodorou, *New CCR5 Variants Associated with Reduced HIV Coreceptor Function in Southeast Asia*, 18 AIDS 2243, 2243 (2004) (observing that CCR5 "occurs frequently in Caucasians but is extremely rare in Asians or Africans").

present in Asian genomes. We have seen no reports on the status of the CRISPR babies since their birth. I hope they are healthy.

The case of polygenic conditions mediated by variants in multiple genes, like obesity, height, or intelligence, is even more challenging. Using whole genome association studies, people claim to have identified dozens or hundreds of genomic sites that are linked to intelligence, but each single one makes only a tiny contribution.[20] Changing one such target would have a negligible effect, and the effect of changing many at the same time would be unpredictable given the influence of genetic background. (This is to say nothing about how intelligence is measured in these studies.)

[20] *See, e.g.*, Jeanne E. Savage, Philip R. Jansen, Sven Stringer, Kyoko Watanabe, Julien Bryois, Christiaan A. de Leeuw, Mats Nagel, Swapnil Awasthi, Peter B. Barr, Jonathan R. I. Coleman, Katrina L. Grasby, Anke R. Hammerschlag, Jakob A. Kaminski, Robert Karlsson, Eva Krapohl, Max Lam, Marianne Nygaard, Chandra A. Reynolds, Joey W. Trampush, Hannah Young, Delilah Zabaneh, Sara Hägg, Narelle K. Hansell, Ida K. Karlsson, Sten Linnarsson, Grant W. Montgomery, Ana B. Muñoz-Manchado, Erin B. Quinlan, Gunter Schumann, Nathan G. Skene, Bradley T. Webb, Tonya White, Dan E. Arking, Dimitrios Avramopoulos, Robert M. Bilder, Panos Bitsios, Katherine E. Burdick, Tyrone D. Cannon, Ornit Chiba-Falek, Andrea Christoforou, Elizabeth T. Cirulli, Eliza Congdon, Aiden Corvin, Gail Davies, Ian J. Deary, Pamela DeRosse, Dwight Dickinson, Srdjan Djurovic, Gary Donohoe, Emily Drabant Conley, Johan G. Eriksson, Thomas Espeseth, Nelson A. Freimer, Stella Giakoumaki, Ina Giegling, Michael Gill, David C. Glahn, Ahmad R. Hariri, Alex Hatzimanolis, Matthew C. Keller, Emma Knowles, Deborah Koltai, Bettina Konte, Jari Lahti, Stephanie Le Hellard, Todd Lencz, David C. Liewald, Edythe London, Astri J. Lundervold, Anil K. Malhotra, Ingrid Melle, Derek Morris, Anna C. Need, William Ollier, Aarno Palotie, Antony Payton, Neil Pendleton, Russell A. Poldrack, Katri Räikkönen, Ivar Reinvang, Panos Roussos, Dan Rujescu, Fred W. Sabb, Matthew A. Scult, Olav B. Smeland, Nikolaos Smyrnis, John M. Starr, Vidar M. Steen, Nikos C. Stefanis, Richard E. Straub, Kjetil Sundet, Henning Tiemeier, Aristotle N. Voineskos, Daniel R. Weinberger, Elisabeth Widen, Jin Yu, Goncalo Abecasis, Ole A. Andreassen, Gerome Breen, Lene Christiansen, Birgit Debrabant, Danielle M. Dick, Andreas Heinz , Jens Hjerling-Leffler, M. Arfan Ikram, Kenneth S. Kendler, Nicholas G. Martin, Sarah E. Medland, Nancy L. Pedersen, Robert Plomin, Tinca J. C. Polderman, Stephan Ripke, Sophie van der Sluis, Patrick F. Sullivan, Scott I. Vrieze, Margaret J. Wright & Danielle Posthuma, *Genome-Wide Association Meta-Analysis in 269,867 Individuals Identifies New Genetic and Function Links to Intelligence*, 50 NATURE GENETICS 912 (2018) (identifying 205 associated genomic loci and 1,016 genes linked to variation in intelligence); G Davies, A Tenesa, A Payton , J Yang, SE Harris, D Liewald, X Ke, S Le Hellard, A Christoforou, M Luciano, K McGhee, L Lopez, AJ Gow, J Corley, P Redmond, HC Fox, P Haggarty, LJ Whalley, G McNeill, ME Goddard, T Espeseth, AJ Lundervold, I Reinvang, A Pickles, VM Steen, W Ollier, DJ Porteous, M Horan, JM Starr, N Pendleton, PM Visscher & IJ Deary, *Genome-Wide Association Studies Establish That Human Intelligence Is Highly Heritable and Polygenic*, 16 MOLECULAR PSYCHIATRY 996 (2011) ("[R]esults unequivocally confirm that a substantial proportion of individual differences in human intelligence is due to genetic variation, and are consistent with many genes of small effects underlying the additive genetic influences on intelligence.").

Like Dr. Enríquez, the commission outlined categories of potential uses of HHGE,[21] but ours were based more on an outcomes analysis—i.e., comparing the potential harms to the potential benefits. From this perspective, it is difficult to understand why Dr. Enríquez rates the treatment of some disabilities as less permissible than cosmetic enhancements.[22] It is good to be sensitive to people with disabilities, but the benefits of cosmetic enhancements are quite dubious and the results are still likely to increase discrimination.

The adoption of genome editing for clinical purposes, whether somatic or heritable, will inevitably exacerbate current inequities in medical treatments. The procedures are technically complex, require specialized facilities, and if experience is anything to go by, will be enormously expensive. Scientists should be working on methods that sharply reduce costs,[23] and it will be up to social and political institutions to devise approaches that equalize access. A World Health Organization committee took up the latter topics in a recent report.[24]

With additional research, HHGE may be shown to be safe for clinical use with appropriate precautions, or adequate safety and efficacy may prove difficult to attain. My view is that HHGE is going to happen, but until the science has progressed, it important to suppress unauthorized uses by rogue actors. This is certainly an area where regulation and enforcement have a role to play. Since HHGE is currently not permitted in the United States and many other countries, in agreement with Dr. Enríquez, I see no reason to adopt new laws governing its use until we have a clearer view of its real hazards and benefits.

While heritable human genome editing may yield benefits in the future, there are significant hurdles to navigate before we get there.

---

[21] HERITABLE HUMAN GENOME EDITING, *supra* note 15, at 101-11.

[22] ENRÍQUEZ, *supra* note 1, at 367-71.

[23] *See* Ross C. Wilson & Dana Carroll, *The Daunting Economics of Therapeutic Genome Editing*, 2 CRISPR J. 280 (2019).

[24] *See* WHO EXPERT ADVISORY COMM. ON DEVELOPING GLOB. STANDARDS FOR GOVERNANCE & OVERSIGHT OF HUM. GENOME EDITING, HUMAN GENOME EDITING: A FRAMEWORK FOR GOVERNANCE (2021), https://www.who.int/publications/i/item/9789240030060 [https://perma.cc/9VX7-MUFB].