Handle with Care:
The WHO Report on Human Genome Editing

by I. GLENN COHEN, JACOB S. SHERKOW, and ELI Y. ADASHI

On July 14, 2021, the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing of the World Health Organization released a much-anticipated report comprised of two separate documents, *Human Genome Editing: Recommendations* and *Human Genome Editing: A Framework for Governance*.[1] The committee also released a "position paper" on both.[2] These documents—collectively referred to as the WHO Report on Human Genome Editing—complement a recently issued report by the International Commission on the Clinical Use of Human Germline Genome Editing, a joint effort of the National Academy of Medicine, the National Academy of Sciences, and the Royal Society from September 2020.[3] Other significant reports were issued earlier by the Nuffield Council on Bioethics, the German Ethics Council, and a host of others.[4] The WHO report, therefore, stands alongside a long list—more than five dozen—of other, similar reports about the ethics of human germline genome editing.[5]

But the WHO report also stands out in several respects. It is far more synoptic in scope than its predecessors, recognizing the multidimensional (and multijurisdictional) nature of governing human genome editing. It also contains recommendations for governance mechanisms that are far more nuanced than those in prior attempts. These include using intellectual property licensing as a private governance tool, an instrument largely unexplored in earlier reports. In addition, the WHO report is among the first to explicitly contemplate a world in which human germline genome editing is readily available, and it identifies a list of governance questions that regulators, developers, and users of the technology should consider in the technology's implementation. Rather than adopting a mechanistic framework of color-coded permissibilities or prohibitions, the WHO report suggests that ethical assessments of human germline genome editing are deeply complex and surprisingly fragile, that the technology, rather than being accepted in some circumstances and banned in others, should be handled with care.

The WHO Report

The product of a carefully selected group of senior experts who worked for over two years, the WHO report is notably expansive with respect to its consideration of human genome editing technology, ethical issues, and mechanisms of oversight. Technologically, the report encompasses "somatic, germline and heritable human genome editing" even while narrowing its coverage to exclude, among other things, editing of a variety of animal genomes and gene drives.[6] This wide net captures a much broader swath of activities than its predecessor reports, which largely focused on individual iterations of genome editing technology, such as CRISPR, or specific applications in humans. The WHO report, by contrast, is notable for recognizing that governance mechanisms for genome editing technologies are likely to be similar across diverse applications.

The report's considerations of ethical issues pertaining to the genome editing are similarly more expansive than those of previous reports, extending beyond the immediate

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The report is notable for its willingness to directly engage with the complex interconnections among national and supranational law—a tenuous system even in less morally charged circumstances—on a number of levels.

ethical issues concerning the subject or patient on whom the technology is practiced. For example, the report offers nine recommendations for governance that are a step removed from prior reports' focus on genome-edited individuals. It calls, for example, for addressing equitable access and priority setting for somatic human genome editing research, as made through a statement from the WHO's director general; convening member states to discuss the feasibility of harmonizing law, international agreements, and equitable sharing of genome editing technologies; and improving the process and monitoring of human genome editing clinical trials through a WHO registry. In addition, the WHO expert advisory committee recommends that the WHO's director general "make a policy statement to the effect that somatic and germline human genome editing research should only take place in jurisdictions with domestic policy and oversight mechanisms" and take steps to discourage travel to less-regulated countries to pursue gene editing research or therapy in some instances.[7]

The report also recommends a host of oversight mechanisms laid out in far greater detail (and with more ambition) than what was presented in its predecessors. These include the confidential reporting of unregistered, unethical, unsafe, or illegal human genome editing research or related activities; capacity building in resource-constrained countries to foster the equitable access of human genome editing research; involving the World Intellectual Property Organization and the World Trade Organization in examining intellectual property initiatives like "ethical licensing" for patents;[8] promoting "inclusive, multidirectional, multistakeholder dialogue" on gene editing; and improving the inclusion of underrepresented groups therein.[9] These recommendations mirror, in a general sense, much of what was proposed in earlier reports, but those reports rarely considered formal mechanisms to implement their aims. The WHO report, by contrast, explicates a series of process-oriented recommendations, including that the WHO develop a "set of officially endorsed and clearly defined ethical values and principles for use by its expert committees" reviewed every three years.[10]

Overall, the WHO report is notable for its willingness to directly engage with the complex interconnections among national and supranational law—a tenuous system even in less morally charged circumstances—on a number of levels. Such a willingness, it seems, is neither naïve nor overly optimistic but, instead, a careful consideration of extant governance mechanisms and how to implement them, as they currently exist, to achieve the recommendations' ends. To that end, the committee's considerably longer governance framework is not narrowly directed to the WHO and its director general but more generally to "those tasked with strengthening oversight measures, regardless of whether this is at the institutional, national, regional or international level."[11] To assist these policy-makers, the framework provides, among other things, a list of values and principles that can be applied to human genome editing and a review of off-the-shelf governance tools that are likely to be available in many jurisdictions, including judicial rulings, ministerial decrees, research funding conditions, patents, and scientific self-regulation. The report also uses hypothetical future scenarios pertaining to future uses of genome editing of various kinds, replete with a list of illustrative questions that various decision-makers might use in thinking about governance in such settings.[12] The report thus goes beyond merely establishing ethical principles in the abstract; it makes the consideration of such principles concrete, workable, and usable by a diverse set of policy-makers in a variety of jurisdictions.

Differences between the WHO Report and Its Predecessors

Aside from the WHO report's distinction of incorporating a kaleidoscope of practical mechanisms in its governance framework, it is also substantively different from its sister reports. Three substantive differences are especially notable: its refusal to focus on human heritable genome editing (HHGE), its consideration of intellectual property as a governance mechanism, and its willingness to engage with formal international law. While some of the recommendations pertaining to these differences—like those pertaining to international law—are less concrete than other areas of the report, the report seems to strike a different tone than previous reports do on similar topics.

Governing human heritable germline editing. The most notable difference between the WHO report and others is how little of it is prescriptive, especially as to HHGE. The report of the International Commission on the Clinical Use of Human Germline Genome Editing explains in great detail the category of use cases "for which a responsible translational pathway could currently be described" for HHGE (even while it rejects others),[13] whereas the WHO report

offers relatively little by way of recommendations on the subject. In its nine recommendations, there is only one elliptical reference to HHGE: "For heritable human genome editing, at a minimum, a statement should reiterate the earlier statement of July 2019."[14] That statement is itself only three paragraphs long, and its relevant part says only this: "WHO supports this interim recommendation and advises regulatory or ethics authorities to refrain from issuing approvals concerning requests for clinical applications for work that involves human germline genome editing."[15] The total foundation for such a recommendation was simply a gesture to the "unique and unprecedented ethical and technical challenges" posed by HHGE.[16] WHO Director General Tedros Adhanom Ghebreyesus's acceptance of these challenges was a terse approval: "I have accepted the interim recommendations of WHO's Expert Advisory Committee that regulatory authorities in all countries should not allow any further work in this area until its implications have been properly considered."[17]

The new framework instead contemplates the use of HHGE in a list of scenarios pertaining to *both* HHGE and nonheritable uses. In constructing a framework for considering such scenarios, the questions provided for policy-makers seem to apply to both heritable and nonheritable uses, as seen in these examples:

> Will transnational collaboration on preclinical and clinical research on heritable human genome editing be permitted when procedural and substantive standards differ in other countries?[18]
>
> If the existing oversight measures for research involving human reproduction are not adequate, is there a plan to create new oversight measures or to rely on regulatory review and approvals from an external body?[19]
>
> What capacity exists for long-term, possibly multigenerational follow-up on the health and safety of genetically modified offspring, and for monitoring possible effects on society as a whole?[20]
>
> How will distinctions be drawn between disease and disability prevention, and therapy?[21]

At the same time, the framework stresses that this listing of uses should not be read to "necessarily endorse any of the uses of human genome editing explored in the scenarios."[22] To the extent that this is a sea change from the WHO's July 2019 statement, perhaps all will be made clear by the director general at a later date. But it is striking that, contrary to many of the other leading documents, the WHO report does not seem to take a direct position on what is perhaps the most controversial of gene editing uses. Did this result from a lack of consensus among the report's authors, a recognition that the variation of use cases for HHGE makes taking any one position on the topic problematic, a sense of how the authors wanted the report to fit in to the ecosystem of other governmental and nongovernmental statements on the topic, or something else entirely? Without being a fly on the wall in the deliberations, we do not know, but this feature is certainly striking.

Intellectual property as a governance tool. Second, the WHO report distinguishes itself in how seriously it takes the issue of equitable access to—as opposed to universal restriction of—genome editing, especially in its discussion of intellectual property. In the early days of genome editing, scholars and licensors advocated that intellectual property holders of genome editing technologies wield their powers for good, that they use the threat of litigation to police "unethical" uses as a regulatory instrument.[23] These included threats of suit against those who would use patented genome editing technologies in the HHGE context, as well as in other controversial technologies, like gene drive, seed terminator technology, and tobacco research. The Broad Institute, for example, has famously imposed patent licensing restrictions on its technologies, even while interest in these applications has steadily grown.[24]

At the same time, patents in this area run the risk of widening health disparities, especially where they are used to license only "profitable" diseases or increase the cost of medical products once they hit the market.[25] Leaning too heavily on patents as a governance instrument for such controversial technologies is potentially deeply antidemocratic; it would place much ethical decision-making about human genome editing largely in the hands of wealthy institutions and companies that are barely accountable to the public.[26] In some ways, patent governance runs counter to the deliberative, health-focused framework at the center of the WHO report. This risk was noticed by the WHO committee, which included in its discussion of intellectual property a call to "address equitable access to the benefits of research and priority setting (for example, sickle-cell disease as a priority)" and for WHO to foster capacity building in less developed countries.[27] This may include exploring licensing costs proportional to countries' research resources.[28]

Despite these earlier conversations among licensors and academics, it is striking how much of the text of the WHO's recommendations is devoted to discussing patents—both the idea that licensing terms may be used to restrict unethical possible uses and also concerns that licensing may give patent holders too much power and may interfere with the development of cost-effective gene editing. Such a recommendation comes against the background of a series of ongoing global patent disputes concerning one genome editing technology, CRISPR-Cas9.[29] While the importance of patent holders and licensing in governance is an area that has largely gone unexplored in HHGE principles documents, our hope is that the WHO recommendations will spur more discussion.

Nonetheless, the report does not immediately address concerns some have voiced about the propriety of patenting such technologies in the first instance.[30] Unlike the United

States, most European countries prohibit patents on ethically controversial technologies thought to violate the *ordre public*, or public order, including patents directed to human embryonic stem cell lines. Such rules seek to incorporate a moral valence to biotechnology patents, disallowing ownership over certain technologies that are thought to violate—or come close to violating—aspects of human dignity.

The practical effect of such bans, however, is likely to be counterproductive. Prohibiting patents on controversial technologies allows anyone in the relevant jurisdiction to use the technology without fear of a patent infringement suit or a responsibility to pay any relevant patent holder royalties for using the technology in question. This prohibition makes it is easier, cheaper, and simpler than using uncontroversial but heavily patented technologies. In addition, prohibiting patents for controversial biotechnologies disallows patent holders from using the threat of patent enforcement as a curb against unethical uses. If the WHO's recommendations about using intellectual property as a governance tool are to be implemented, public-order exceptions to patentability seem to stymie their best uses.[31]

International Law

Finally, there is the matter of international law for genome editing. While the report of the International Commission on the Clinical Use of Human Germline Genome Editing focused much more on national regulation, one might have expected the WHO report—coming as it does from a global health body—to recommend international law making.[32] But this is not central to the recommendations made. The document does not make a strong push for treaty making. Instead, the recommendations urge the WHO to convene member states to address "the feasibility of international agreements on regulatory approaches for human genome editing."[33] Such an approach—tempered with the word "feasibility"—seems to recognize the complexities of crafting new international agreements at a time when principle-based international regulations are, arguably, at their nadir. No better example can be found than in the difficulties surrounding international vaccine manufacturing and sharing during the pandemic, even with (or, perhaps, despite) the existence of consensus-based international regulatory bodies meant to smooth such disputes.[34] The WHO report should be commended for its blunt honesty.

To be sure, the governance framework does occasionally discuss treaty-making, especially in one of its scenarios on medical tourism for HHGE, where it rightly observes that the "consequences of human genome editing would be global, as is the fertility industry through which this practice would likely be introduced" and that those "[t]aking governance action should not assume that the action will be solely domestic, nor that it will necessarily move towards greater permissibility."[35] Nevertheless, by the end of the report, one feels that the international law elements, while carefully considered, are grounded in practical realities given the state of the world today. If the WHO does not push for an international treaty and instead makes other forms of international law on genome editing the body's priority, treaty making on human genome editing is likely to wither on the vine—assuming it was ever viable fruit.

From Theory to Governance

The WHO report could have begun where its predecessors stopped: with a suite of abstract ethical principles and a series of curated bans on the technology. Instead, it starts by broadly applying itself to a wide variety of technologies seen through a lens of both legal and practical realism. This may sound like harsh criticism (of both the WHO report and its predecessors); we think it is, rather, simply a description of a rapidly maturing field. If governance of human genome editing is itself thought of as an engineering project, with the canonical design-test-build sequence, then the WHO report seeks to build something after prior, important work to design and test broader concepts. The report also breaks new ground in that it gives policy-makers a rich toolkit for thinking about how to govern these technologies from a variety of legal sources, including balancing equitable access with a consideration of intellectual property.

And yet, unlike its sister reports, it is surprising for not seeking to move the ethical needle one way or the other on HHGE. Nor does it portend significant international lawmaking in the area. We have no specific insights into why the WHO—an agency of the United Nations—has chosen to largely ignore such a path to governance. But the report's major contribution—a suite of recommendations for concrete domestic policies that are likely to affect international governance—is a practical advance for both policy-makers and ethicists. The ultimate success of such advances will largely depend on realities beyond those over which the WHO has control and how well, or carefully, genome editing is soon handled.

Disclosure

I. Glenn Cohen is a member of the ethics advisory board for Illumina and the Bayer Bioethics Council.

1. WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: Recommendations* (Geneva: World Health Organization, July 2021), https://perma.cc/BX4L-2DHY; WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (Geneva: World Health Organization, July 2021), https://perma.cc/Q5G7-MN4A. In notes below, these two documents are cited, respectively, as WHO Expert Advisory Committee, *Recommendations* and WHO Expert Advisory Committee, *A Framework for Governance*.
2. WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, "Human Genome Editing: Position Paper," World Health Organization, July 2021, https://perma.cc/WK3S-M45Q.

3. National Academies of Science, Engineering, and Medicine and The Royal Society, *Heritable Human Genome Editing* (Washington, DC: National Academies Press, 2020), 2.
4. Nuffield Council on Bioethics, *Genome Editing and Human Reproduction* (London: Nuffield Council on Bioethics, 2018), https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction; Deutscher Ethikrat, *Intervening in the Human Germline* (Berlin: Deutscher Ethikrat, 2018), https://www.ethikrat.org/fileadmin/Publikationen/Stellungnahmen/englisch/opinion-intervening-in-the-human-germline-summary.pdf.
5. C. Brokowski, "Do CRISPR Germline Ethics Statements Cut It?," *CRISPR Journal* 1, no. 2 (2018): 115-25.
6. WHO Expert Advisory Committee, *A Framework for Governance*, v.
7. WHO Expert Advisory Committee, *Recommendations*, x.
8. Ibid., x.
9. Ibid., x.
10. Ibid., xi.
11. WHO Expert Advisory Committee, *A Framework for Governance*, x.
12. Ibid., 40-55.
13. National Academies of Science, Engineering, and Medicine and The Royal Society, *Heritable Human Genome Editing*, 2.
14. WHO Expert Advisory Committee, *Recommendations*, 5.
15. "Statement on Governance and Oversight of Human Genome Editing," World Health Organization, July 26, 2019, https://www.who.int/news/item/26-07-2019-statement-on-governance-and-oversight-of-human-genome-editing.
16. Ibid.
17. Ibid.
18. WHO Expert Advisory Committee, *A Framework for Governance*, 17.
19. Ibid., 24.
20. Ibid., 51.
21. Ibid., 51.
22. Ibid., 40.
23. C. J. Guerrini et al., "The Rise of the Ethical License," *Nature Biotechnology* 35, no. 1 (2017): 22-24.
24. Ibid.
25. J. S. Sherkow, "CRISPR, Patents, and the Public Health," *Yale Journal of Biology & Medicine* 90, no. 4 (2017): 667-72.
26 N. Scheinerman and J. S. Sherkow, "Governance Choices in Genome Editing Patents," *Frontiers in Political Science* 3 (2021): doi:10.3389/fpos.2021.745898.
27. WHO Expert Advisory Committee, *Recommendations*, 5.
28. Ibid., 5.
29. Scheinerman and Sherkow, "Governance Choices in Genome Editing Patents," 6.
30. J. S. Sherkow, E. Y. Adashi, and I. G. Cohen, "Governing Human Germline Editing through Patent Law," *Journal of the American Medical Association* 326 (2021): 1149-50.
31. Ibid.
32. I. G. Cohen and E. Y. Adashi, "Legal and Ethical Issues in the Report Heritable Human Genome Editing," *Hastings Center Report* 51, no. 3 (2021): 8-12.
33. WHO Expert Advisory Committee, *Recommendations*, 9.
34. N. Price et al., "What's Happening with Proposals for a WTO Waiver of COVID-Related IP?," *Written Description* (blog), July 30, 2021, https://writtendescription.blogspot.com/2021/07/whats-happening-with-proposals-for-wto.html.
35. WHO Expert Advisory Committee, *A Framework for Governance*, 53.

The Case for Ethical Efficiency: *A System That Has Run Out of Time*

by JOHN L. HAVLIK, MARK R. MERCURIO, AND SARAH C. HULL

It is no secret that physicians are busy. Many see dozens of patients a day and interpret an ever-increasing number of medical tests, delivering care that provides their affiliated hospitals an average of $2.4 million in revenue per physician annually in the United States.[1] Our medical system increasingly depends on physicians seeing as many patients as possible in as little time as possible, with the system too often conflating productivity with true clinical efficiency and prioritizing the former at the expense of the latter.

Productivity typically refers to the number of billable charges, or "relative value units" ("RVUs"), a physician generates in a given period. This calculation has nothing to do with quality or patient satisfaction, neither of which is captured in productivity metrics, and is therefore a flawed surrogate for clinical efficiency. Truly efficient care requires a more judicious allocation of time. Time should not be wasted, but patient throughput must not take precedence over patient care.

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