Health Matrix: The Journal of Law-Medicine

Volume 33 | Issue 1 Article 8

May 2023

# Limits on Biomedical Research: Whether, Why, and How

Christine Grady

THE OLIVER C. SCHROEDER, JR. SCHOLAR-IN-RESIDENCE LECTURE

# LIMITS ON BIOMEDICAL RESEARCH: WHETHER, WHY, AND HOW[†]

*Dr. Christine Grady*[††]

Biomedical research aims to advance our understanding of health and identify ways to prevent, treat, or ameliorate diseases. Biomedical research findings can have a real impact on society. A few recent examples include treatments for HIV and childhood leukemia, statins, and COVID-19 vaccines. But is all biomedical research that promises progress in understanding health and illness justified; or should there be certain areas of study or certain topics that are off limits?

Dan Callahan, the founder of the Hastings Center, wrote about progress in a paper published posthumously.[1] "Progress has given society the ethical and social benefits of modern medicine, as well as the most aggravating ethical challenges". Bioethics seeks to balance the benefits and harms of progress. This includes

† Edits from the annual Oliver C. Schroeder, Jr. Scholar-in-Residence Lecture sponsored by the Law-Medicine Center on November 10, 2022, at Case Western Reserve University School of Law. This version has been edited for publishing purposes and does not contain the lecture in its entirety. The full transcript is on file with the editors of Health Matrix. Please direct all inquires to h-matrix@case.edu.

†† BS, Georgetown University; MSN, Boston College; PhD, Georgetown University. Dr. Grady served from 2010-2017 as a Commissioner on the President's Commission for the Study of Bioethical Issues. Her work is known internationally, and she has lectured widely on ethical issues in clinical research and clinical care, HIV disease, and nursing. She is an elected fellow of the Hastings Center and of the American Academy of Nursing, a senior research fellow at the Kennedy Institute of Ethics and an elected member of the National Academy of Medicine.

1. Daniel Callahan, *Bioethics and the Future: Can Progress Be Tamed?*, HARV. MED. SCH.: CTRS. FOR BIOETHICS (Jan. 1, 2020), https://bioethics.hms.harvard.edu/journal/bioethics-balancing-harms [https://perma.cc/7897-FVSD].

determining whether there should be any limits, and if so, whether they should be hard or soft limits.

I use the analogy of a traffic light with a red, yellow, and green lights. Hard limits would function like a red light, soft limits like a yellow light, and no limits like a green light. Academics have argued for all three of those approaches.

David Baltimore, Nobel-Prize-winning biologist, considered whether society should limit biological research when or because " . . . the outcome could be detrimental to established societal norms and relationships that characterize our contemporary society".[2] He concluded that society should not, and cannot, limit biomedical research. He reasoned that such limits are impractical, unfeasible, and disruptive to the social order. He posits that limiting science would pose a number of significant risks.

First, he notes, the "Error of Futurism," which is the idea that we don't know enough about the future.[3] Since we cannot predict the future, any decision we make that might impact the future could be based on erroneous assumptions about what is going to happen. Second, limiting biomedical research would disrupt the renewal process that furthers our understanding and choices, and thus could be detrimental.[4] Third, limiting biomedical research could lead to fear, mistrust, and unrest. Limits that could be politically or ideologically motivated and may be promoted by certain public figures, could cause the public to distrust the research endeavor in its entirety. Finally, it is impractical, if not impossible, to limit research.[5] Baltimore believes that we could limit the volume of research, but not the types of research that are done.

The Presidential Commission for the Study of Bioethical Issues (Commission) argued that democracies depend on intellectual freedom coupled with the responsibility of individuals and institutions to use their creative potential in morally responsible ways. Further, progress requires that we leave people free to pursue their scientific interests. Historically, a great deal of scientific discovery was the result of serendipity or individual scientists pursuing their interests. The committee concluded,

2. David Baltimore, *Limiting Science: A Biologist's Perspective*, 134 Daedalus 7, 11–12 (2005).

3. *Id.* at 12.

4. *Id.*

5. *Id.*

"[A]t the same time, responsible science should reject the technological imperative: the mere fact that something new can be done does not mean that it ought to be done."[6]

John Harris, a philosopher at Oxford, describes research as an ethical imperative. He said that biomedical research is so important that there's a positive moral obligation to pursue it and to participate in it.[7] He argues that we cannot neglect research and have to do it. But he does put some limits on research by saying that research is both permissible and mandatory where the importance of the objective is great compared to the risks to participants. Among those risks is the possibility of exploiting participants, which is unacceptable.

Fifty-years ago, the philosopher Hans Jonas talked about biomedical research as an optional goal,[8] i.e., that progress through research is optional. He wrote " . . . slower progress in curing a disease would not threaten society, grievous as it might be to those who have that disease. But society would indeed be threatened by the erosion of our morals through a ruthless pursuit of scientific progress. Such degradation would make the scientific community's dazzling triumphs not worth having." He says that progress through medical research is optional because even the noblest purposes cannot abrogate the obligations that we have to people. These obligations include promoting responsible and useful research that has scientific and social value; protecting research participants from unnecessary risks, burdens, and exploitation; and respecting individuals' rights and autonomy.

Research ethics seeks to ensure that we focus on promoting useful research while protecting research participants. With that goal in mind, there are a few reasons that we do limit biomedical research. The first is that some research is not important enough to justify the burdens placed on participants. As Benjamin

6. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies,* at 5 (2010), https://ethics.emory.edu/_includes/documents/sections/what-we-do/12-15-10-rev-exec-sum-embargoed.pdf [https://perma.cc/3CY6-3Q6T].

7. John Harris, *Scientific Research is a Moral Duty*, 31 J. MED. ETHICS 242, 246 (2005).

8. Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, 98 DAEDALUS 219, 245 (1969).

Friedman explains, research must have social value.[9] Indeed, research that lacks social value is unethical even if the participant agrees to it. Many "me-too" studies, those asking questions with no purpose, or those posing questions to which we already know the answer lack social value.

There is often debate over the social value of a particular study compared to the risks that it poses. This debate spiked during COVID-19 when human challenge studies were contemplated. In challenge studies, researchers would infect people with COVID and then test different interventions. Advocates believed that challenge studies would be invaluable because they would allow scientists to assess interventions and determine their efficacy much more quickly. But opponents did not believe this approach was justified given uncertainty about the pace of challenge studies and the potential risks to participants. At the time, we knew little about how people got infected with SARs CoV-2, how sick they could get, and how they could be treated.

Another related reason to limit biomedical research is when it poses unnecessary or excessive harms to participants. Harm is a concern for both human and non-human animal participants. There are a number of tragic historical examples, such as the Nazi experiments and the Guatemala sexually transmitted disease studies. In these studies, the harm imposed on the participants was egregious, and the studies would not be undertaken today. There are also other examples of studies that can inappropriately harm participants, for example by enrolling participants without their knowledge or consent or through coercion. For example, enrolling homeless people in a shelter into a phase-one drug development study could be exploitative.[10]

Research ethicists continue to debate how much social value is enough to justify certain risks. Should we allow research without consent if the social value is high enough? No clear balancing test has emerged, yet existing regulations protect against unnecessary or excessive harm and lack of social value.

9. Benjamin Freedman, *Scientific Value and Validity as Ethical Requirements for Research: A Proposed Explication*, 9 IRB: ETHICS & HUM. RSCH. 7, 7 (1987).

10. Carl Elliott & Roberto Abadie, *Exploiting a Research Underclass in Phase 1 Clinical Trials*, 358 N. ENG. J. MED. 2316–17 (2008).

Marchant and Pope refer to these as "incidental regulations."[11] Incidental regulations limit when and how scientists conduct research, but not the substantive questions the research is trying to address.

It is possible that some research could impact humanity as a whole or alter the way we think about humans "Growing powers to manipulate human bodies and minds, not merely to heal disease,"[12] raise additional questions about whether there should be limits on research. Leon Kass notes that the potential to enhance people or control deviant behavior creates urgent questions about " . . . whether and how to regulate . . . not merely to assure safety and efficacy, but also to safeguard our humanity". So a central question is whether there are kinds of knowledge that we should not pursue in the context of research because they could harm our communities, disrupt our societal norms, impact human dignity, or create significant public backlash that would interfere with trust in institutions and research.

One interest is possible harm to communities. A historic example are studies with the Havasupai Tribe in Arizona. Havasupai Tribe members were recruited because of the high prevalence of diabetes among them. Researchers at Arizona State University (ASU) sought to find a genetic link to diabetes through studying their blood samples. But ASU researchers also used the Havasupai samples without specific consent to study and publish papers about alcoholism, inbreeding, and the origin and migration of the Havasupai from Asia. Other historical examples of studies harmful to communities are those that sought to identify a link between race and violence or that focused on what some people would call deviant behaviors. So, the question is whether these studies are acceptable and legitimate under any circumstances and who decides.

What about possible disruption of social norms? For example, research may seek to keep people alive well past 100 years old. Is that something we should do? What about creating chimeras? What about germline editing, which affects the next generation

11. Gary Marchant & Lynda Pope, *The Problems with Forbidding Science*, 15 SCI. ENG'G ETHICS 375, 375 (2009) (illustrating the kinds of limits Dr. Grady described).

12. Leon Kass, *Forbidding Science: Some Beginning Reflections*, 15 SCI. ENG'G ETHICS 271, 271 (2009).

of people? What about brain transplants? Some people believe creating embryos for research purposes is an affront to human dignity. Public backlash is also an important consideration for these questions.

An illustrative example that raises questions about disruption of social norms and possible harm to communities came from synthetic biology. The President's Commission was asked to report on the ethics of synthetic biology when Craig Venter, one of the people who mapped the human genome, created a synthetic bacterial cell. His research evoked concerns about playing God and whether humans can or should create life. There were also concerns about potential risks to the environment. At the same time, many recognized that synthetic biology had the potential to do a lot of good. Perhaps the example I remember best is that of Artemisinin (ART), a medication to treat Malaria. Malaria is a devastating disease that affects many people around the world. While there is a great need for ART, it is difficult to produce keeping quantities limited. Synthetic biology provided scientists a way to manufacture and produce large amounts of artemisinic acid in yeast cells because they proliferate rapidly.

Heritable genome editing is another example of a potentially valuable but controversial scientific pursuit. CRISPR-Cas9 ("CRISPR") is an exciting new tool for editing genes; the scientists who discovered it won a Nobel Prize in 2020. Many believe gene editing will be useful in curing serious illnesses such as sickle-cell disease.

But scientists can also use CRISPR to edit embryos. He Jiankui, a Chinese scientist, shocked the world in 2018 when he announced that he had edited two embryos using CRISPR to prevent the babies from being susceptible to HIV.[13] More specifically, he deleted, or at least attempted to delete, the CCR5 gene. A huge outcry from the scientific community followed his announcement as well as a call for a moratorium on heritable genome editing. This moratorium did not expand to somatic gene editing, such as in the Sickle Cell example, only heritable or germline editing that would be passed on to future generation, as

13. Dennis Normile, *Chinese Scientist who Produced Genetically Altered Babies Sentenced to 3 Years in Jail*, SCIENCE.ORG (Dec. 30, 2019), https://www.science.org/content/article/chinese-scientist-who-produced-genetically-altered-babies-sentenced-3-years-jail [https://perma.cc/MW2F-W638].

the potential harmful effects of such endeavors are currently unknown.

CRISPR is of particular interest in research ethics because it is easy to obtain. Indeed, you can buy a CRISPR kit on Amazon for less than $200. So, if you know enough to use it, you could buy a kit and edit genes in your garage. Concerns about the potential misuses of CRISPR began long before Jiankui's experiment. In 2015, the NIH issued a statement that it will not fund any gene editing in human embryos.[14] It cites several reasons: serious and unquantifiable risks or safety issues, ethical issues relating to consent, the violation of the next generation's rights, and a current lack of compelling medical applications. Indeed, the NIH noted it is "a line that should not be crossed." A recent paper analyzed laws and guidelines relating to heritable gene editing in 96 countries.[15] Of those 96 countries, almost all of them prohibit heritable genome editing.

Another area of emerging science that raises controversial questions is research on organoids and embryoids. Organoids are 3D structures that function like mini organs. They are made from pluripotent stem cells, and scientists believe they can eventually serve three functions. First, they could be used in fundamental research. When scientists are seeking to understand an organ but cannot access or manipulate it within a human body, they could use an organoid to study the physiology and pathophysiology of that organ. Second, organoids could be used in translational research; for example use of organoids could lessen the need for animal research because organoids could be used for drug testing. Third is regenerative medicine. Organoids could potentially be used to replace damaged organs in patients.

Despite these potential benefits, considering the ethical dilemmas presented by neural organoids, neural transplants, and neural chimeras is important. The brain is the essence of who we are, and many have concerns about artificial neural structures. The National Academy of Science, Engineering and Medicine recently published a report about the emerging field of human

14. NAT'L INST. HEALTH, *Statement on NIH Funding of Research Using Gene-Editing Technologies in Human Embryos* (Apr. 28, 2015), https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos [https://perma.cc/7P3T-BQNE].

15. Françoise Baylis et al., *Human Germline and Heritable Genome Editing: The Global Policy Landscape,* CRISPR J. 365, 371 (2020).

neural organoids, transplants, and chimeras.[16] The report concluded that this kind of research is valuable and could teach us a great deal about the brain and nervous system. They noted that the science is at an early stage but is evolving very quickly. Despite concerns, there are many potential benefits to developing neural organoids, neural transplants, and neural chimeras. Brain disorders are difficult to study because of limitations on studying brains in humans or in animal models. Developing neural organoids or chimeras might address that problem.

One concern revolves around consciousness. Are neural organoids conscious or could they become conscious? It is possible that as these groups of neural cells evolve, they could develop awareness or sentience. Since we don't fully understand consciousness, we cannot reliably measure it. This also creates questions about oversight and regulation of organoid research.[17] Organoids are not humans, so they are not covered by human subject regulations. They also not animals, so they are not subject to the regulation of animal studies. Thus, there is a need for public engagement and debate about this ethical conundrum.

Other concerns have been raised about inserting human neural tissues into animals. Studies, for example, have been able to implant human brain cells into the brains of mice and rats.[18] In a recent study, the human cells not only assimilated into the rat brain, but continued to grow once assimilated.[19] Over a short period of time, about a third of the rat brain became human. This kind of study could blur the distinction between humans and animals, and potentially be distressing to animals. As bioethicist Alta Charo said, there is something discomforting about an animal stuck with a partially human brain.[20] This evokes a scene

16. NAT'L ACAD. OF SCI. ENG'G & MED., THE EMERGING FIELD OF HUMAN NEURAL ORGANOIDS, TRANSPLANTS, AND CHIMERAS: SCIENCE, ETHICS, AND GOVERNANCE (Nat'l Acad. Press 2021).

17. Dolly R. Haselager et al., *Breeding Brains? Patients' and Laymen's Perspectives on Cerebral Organoids*, 15 REGENERATIVE MED. 2351, 2352 (2020).

18. Omer Revah et al., *Maturation and Circuit Integration of Transplanted Human Cortical Organoids*, 610 NATURE 319, 319 (2022).

19. *Id.* at 323.

20. Kendall Powell, *Hybrid Brains: The Ethics of Transplanting Human Neurons into Animals*, NATURE (Aug. 3, 2022), https://www.nature.com/articles/d41586-022-02073-4

from the children's book, *Rats of NIMH,*[21] a story about rats made smarter in the lab. One rat says:

> We don't know where to go because we don't know what we are. Do you want us to go back to living in the sewer pipe and eating other people's garbage? Because that's what rats do. But the fact is we're not rats anymore. We're something Dr. Schultz has made, something new . . . our intelligence has increased more than one thousand percent. I suspect he's underestimated. We're probably as intelligent as he is, maybe more. We can read and with little practice we'll be able to write. I mean to do both. I think we can learn to do anything we want but where do we do it? Where does a group of civilized rats fits in?

Another kind of research that elicits calls for possible limits is dual-use research, which is any research that could be used for nefarious purposes. In 2017, the National Academy issued a report entitled *Dual Use Research of Concern in the Life Sciences*. They noted that "Policies governing dual-use research in the life sciences are fragmented and that most scientists have little awareness of issues related to biosecurity."[22] It identified a variety of mechanisms for the assessment and mitigation of risks in dual-use research of concern.

Dual use is not only a possibility in the life sciences. A paper by pharmacologic modelists using artificial intelligence notes that, "[t]he thought had never previously struck us. We were vaguely aware of security concerns around work with pathogens or toxic chemicals, but that didn't relate to us. We primarily work in a

[https://perma.cc/9UFV-MUDH] ("The neural combinations touch on what it is that makes us essentially humans — our minds, our memories, our sense of self").

21. ROBERT C. O'BRIEN, MRS. FRISBY AND THE RATS OF NIMH, at 137 (Aladdin 1971).

22. NAT'L ACAD. SCI. ENG'G & MED., *Policies Governing Dual-Use Research in the Life Sciences Are Fragmented; Most Scientists Have Little Awareness of Issues Related to Biosecurity* (Sep. 14, 2017), https://www.nationalacademies.org/news/2017/09/policies-governing-dual-use-research-in-the-life-sciences-are-fragmented-most-scientists-have-little-awareness-of-issues-related-to-biosecurity [https://perma.cc/86FD-MR5S].

virtual setting."[23] These scientists developed a commercial de novo molecule generator, guided by machine learning predictions of bioactivity, to process and select molecules with the least toxicity and the most targeted activity for certain human diseases. They experimented by inverting the logic, guiding it to reward toxicity and bioactivity instead. They were alarmed to find that in less than six hours, they generated more than 40,000 toxic molecules, some of which were known chemical warfare agents and others as or more toxic than some nerve agents.

In its report about synthetic biology, the President's Commission discussed the principle of "Intellectual Freedom and Responsibility."[24] The Commission noted that concerns about potentially malevolent uses are not typically sufficient to stop certain categories of research because of the potential loss of research benefits. Moreover, they and others worry if research limitations were established, whether they would be enforceable.

At the same time, I, among others, do not embrace the notion that there should be absolutely no boundaries or limits on research. Perhaps we should not limit wholesale categories of research, but we should ban certain studies under certain circumstances. And then we must parse through advantages and disadvantages of limiting the actual conduct of research, limiting the dissemination of research findings, and limiting the application of research findings.

Laws and regulations are potential guardrails in limiting certain research studies. But laws are blunt instruments and science can evolve quickly. Indeed, it is sometimes hard to create a law that isn't quickly outdated by scientific progress. Further, laws in one jurisdiction are not binding on others. As such, they are not effective in regulating the global scientific community. Even our own federal laws and regulations that protect human subjects only apply to some human subjects' research. As advised by the President's Commission, we should exercise regulatory parsimony, which would have us impose regulations where they work and not impose them where they are unhelpful.

Principles and guidance are other potential guardrails in limiting certain types of biomedical research. The President's

23. Fabio Urbina et al., *Dual Use of Artificial-Intelligence-Powered Drug Discovery*, 4 NATURE MACH. INTEL. 189 (2022).

24. *See* PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 6.

Commission drafted a list of principles relating to synthetic biology that could apply to any emerging technology. This list includes Public Beneficence, or the idea that research should be done in a way that maximizes the public good and minimizes public harm. Next is Responsible Stewardship, which is the idea that we are responsible not only for people now, but future people, future generations, and the environment. The Commission also identified principles of Intellectual Freedom and Responsibility, Democratic Deliberation, and Justice and Fairness. Compliance with these principles could hinder some otherwise potentially harmful research.

"Special scrutiny" by a designated body[25] is another possible tool for deciding research limits. Our current oversight structures lack an effective mechanism for considering the social and long-term effects of many research projects. Institutional review boards are not equipped to consider such effects and are instructed by regulations not to consider them. There have been advisory committees, and public commissions like the President's Commission and the National Bioethics Advisory Commission, that issued useful reports. But there is no national body that regularly, and independently, considers the long-term and social impact of different kinds of research.

Finally, and importantly, we should improve public engagement with science and research. Democratic deliberation was one of the President's Commission's principles and chief considerations. The Commission described it as, "an approach to collaborative decision making that embraces respectful debating of opposing views and active participation by citizens."[26] Democratic deliberation utilizes a very specific methodology, yet more general public engagement in various forms is also worth pursuing. As Leon Kass wrote, "oversight of these questions in our society belongs in principle to the Democratic polity at large. Not only because they're affected by these technologies but because the decisive issues for debate are matters of morals and politics, not of science or technical expertise."[27]

25. Alan Fleischman et al., *Dealing With the Long-Term Social Implications of Research*, 11 AM. J. BIOETHICS 5 (2011).

26. *See* PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 6.

27. *See* Kass, *supra* at note 12, at 276.

Despite the clear benefits of public engagement, it has become increasingly more difficult to accomplish. The scientific community must seek to engage the public; to engage them in discussion and deliberation about what types of research should and should not be done. To succeed in these efforts, we need to enhance scientific literacy, which is low in the United States and improve science education. Many people do not understand science on a meaningful level. To combat this, we must consider the future of science and the intersection of science and society.

It is not feasible, or advisable, to implement a wholesale prohibition of any category of research. In other words, we should not impose a categorical "red light." Nor can there be an unqualified "green light." It would be foolhardy for us to allow all research without evaluating the potential impact on our lives, safety, and the future. The optimal course is a yellow light. We must continue to do research to relieve the ills of the human condition without destroying our humanity. We must proceed, but proceed with caution. Regulations and laws have an important role in this, and guiding principles are key to a successful regulatory scheme. We need mechanisms for thinking about and applying these principles at a high level, a mechanism that can continuously review and anticipate research and its impact and make decisions accordingly. We have some mechanisms in place, but we need something more permanent. And perhaps most importantly, we need to better communicate and engage with the public. We must prioritize science education and bolster scientific literacy and engagement. We need to do all of this with a keen and open eye that recognizes the potential good and harms that science can generate and proceed with a strong dose of humility. We cannot anticipate every possibility, but we can make judgments, and revise those judgments, based on wisdom as we move forward in life and science.