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## Translational Bioethical Decision-Making: Human Brain Organoids As a Case Study

### Abstract:

In an earlier essay I advocated that translational bioethics use the public's values, determined through social science, in its analysis of translational science technologies. It may be unclear what those values might be, and whether such a translational ethics would necessarily conclude that cutting edge technologies should not be developed. In this essay I show the public's values relevant to human brain organoids and argue that a translational bioethics analysis using these values would support continued organoid research.

One aspect of a translational bioethics is that it incorporates the public's values into its analysis. It is also not only about avoiding individual harms and promoting individual autonomy like standard research bioethics<sup>1</sup> but is also concerned with the social implications of the research.<sup>2</sup> In an earlier Ethics in Translational Research Essay in this journal<sup>3</sup> I outlined a method where translational bioethics could be built on the values of the public, with those values determined through social science investigation.

Like an IRB currently does with a more truncated set of values (or "principles"), a group of ethicists would weigh and balance the public's values for any research agenda in translational science. Note that the ethicists would not use any "alternative facts" the public may have, as we experienced in the COVID era. Translational bioethics should base its analysis on the values of the public because this is more consistent with democracy and if the public sees its own values reflected in science it will increase trust in science.

As Rothstein notes, translational science programs already engage with standard IRB ethics, which might result in everyone thinking that the only possible values that are relevant to science are the legally required IRB ones: autonomy, beneficence and justice. Therefore, readers of my previous essay may have had a hard time envisioning how my proposed system would be applied to a particular technology. So, my first goal in this short essay is to show the values of the public regarding a particular biotechnology.

My second goal is to show that using the public's values would not necessarily shut down innovative research, which may be a fear of some readers. In public communication, scientists report wanting to, in my terms, engage in one-way communication to the public instead of have the public give input on what science should be pursued.<sup>4</sup> While perhaps we should fear some of the public's facts, I want to show that using the public's values need not necessarily be feared.

In this essay I will interpret a recent study I conducted on the public's views of human brain organoids (HBOs) in terms of the values that could be maximized when considering HBO applications in translational science.<sup>5</sup> I will show that it is unlikely that a translational bioethics analysis using the public's values would shut down HBO research.

HBOs are a good example for me to use because this is the type of technology that has a high “yuk” factor for the public. An HBO is a 4-5mm piece of human brain tissue grown from stem cells obtained from skin and either kept in a dish or implanted in a laboratory animal. These emit electrical signals similar to that of a human fetus, and the signals change when they are stimulated with light. An HBO from one type of brain tissue can be connected to an HBO of another type of brain tissue to create an assembloid with increased complexity. At present these are mostly used to conduct basic research, such as whether certain compounds are toxic to brain cells. Work continues on facilitating the growth and increased complexity of HBOs.<sup>6</sup>

#### STANDARD BIOETHICAL ANALYSIS OF HUMAN BRAIN ORGANOIDS

IRBs are only concerned with harm to actual live humans, but HBOs are not humans or, to use the ethical term of art, “persons.” Therefore, the potential harm being considered in the IRB is whether the human who gave the cells gave permission for them to be used for HBO research. All broader social concerns about HBOs are not allowed to be considered in the American system of research ethics review<sup>7</sup> – hence the need for translational bioethics.

There is extensive debate among bioethicists about whether HBOs could achieve a high enough level of consciousness to be like other laboratory animals, and then be subject to the Institutional Animal Care and Use Committees that approve research using animals. Consciousness, and its correlates like ability to sense pain, is the absolute base capacity that concerns animal research ethics. There is also some ambiguity given that these are human tissues, so HBOs are not non-human animals. Avoiding harm is one of the bioethicists’ key values,<sup>8</sup> but it is only conscious entities that can be harmed. In some far-off future, an organoid with human-level consciousness might be subject to the IRB.<sup>9</sup> We can say that bioethicists value the relief of suffering (beneficence) that could come from HBO research while avoiding harm (non-maleficence) to animals and ultimately persons. These are essentially one-half of the values whose use has defined membership in the profession of bioethics since its origins.<sup>10</sup> Are these the two values that the public would use?

#### THE PUBLIC’S VALUES RELEVANT TO HUMAN BRAIN ORGANOIDS

I conducted a national survey built from what is known about the public’s views of biotechnology. The respondents were shown a one paragraph description of an HBO that, critically, ended with “scientists want to experiment on these organoids to develop treatments for human brain disorders such as Parkinson’s or Alzheimer’s disease.” After the description they were asked to evaluate the statement: “research into human brain organoids should continue.” 4% strongly disagreed, and 5% somewhat disagreed, 42% somewhat agreed and 28% strongly agreed, with the rest selecting the neutral category.<sup>11</sup> Respondents had various “yuk” responses, as well as other concerns I will describe below, but still overwhelmingly supported the research. I think this is because HBOs were described, as they will be when people hear about them, as helping to relieve the suffering of disease. If the translational science agenda for HBOs did not include relieving disease, support would have been much lower. As for the bioethicists, relieving suffering (beneficence) is a value that the public clearly holds with regard to HBOs and in general.

Through various analyses I show that the public is not very concerned with the consciousness of HBOs. For example, differentially describing an HBO as obtaining no consciousness, the consciousness of an insect, the consciousness of a pig or the consciousness of a human fetus does not produce differences in how the respondent thinks the HBO should be treated.<sup>12</sup> This is consistent with other studies that show that the public's definition of a human does not include capacities like consciousness, but is either based on an old-fashioned biological account of "a human is that born from a human" or "a human is that which is made in the Image of God" or "a human is that which has socially interactive capacities like ability to show love and work on shared projects." This means that organoids are not going to be considered a human, or a person, no matter how complex they become. The definition of a human used by bioethicists, on the other hand, is that an entity that should be treated as human has certain cognitive capacities, with the absolute minimum capacity being consciousness.<sup>13</sup>

The second value the public is using will sound very strange to scientists. The public is concerned that the organoid would retain the essence of the human that donated the cells to create the HBO. I asked respondents to evaluate: "human brain organoids should be thought of as an extension of the person who donated the skin cells used to make it." Only 28% strongly or somewhat disagreed, 32% took the neutral position, while 41% somewhat or strongly agreed. I will call this value "respecting the essence of humans."

This idea that disembodied tissue retains a connection to the original human is actually a common finding in medical anthropology and medical sociology. The classic finding is that people who receive a transplanted organ think they have inherited the beliefs or behaviors of the donor, and even studies of blood donation show a portion of the public thinking that the blood retains "the essence" of the donor.<sup>14</sup>

The base reason for these beliefs is that members of the public are not materialists – they believe that it is not only matter that is real. The idea that there could be some non-physical connection between a body and its former connected part is not outlandish to people who believe in God, not to mention spirits, ghosts, luck and much else. For example, in a recent study, 83% of U.S. adults believed that people have a soul or spirit in addition to their physical body.<sup>15</sup> This belief in human essence sounds like the sort of "irrational" idea that, if listened to, would shut down organoid research. I suspect this is the kind of belief that worries many scientists about using the public's values.

## TRANSLATIONAL BIOETHICS ANALYSIS

If a translational bioethics commission was assigned the task of using beneficence and respecting the essence of humans as the values in deciding if HBO research should continue – what would they conclude? I think it is clear that they would recommend that HBO research for the purpose of relieving human disease should continue. First, analysis shows that the public overwhelmingly supports the value of reduction of suffering, so that is the most powerful value here. Second, respecting the essence of humans does not preclude HBO research. Pursuing this value does not imply that the HBO has the status of a human, but that it should have some modicum of respect.

For example, 73% agreed or were neutral on the idea that HBOs have some sort of connection with the donor of the cells, but 70% also agreed that HBO research should continue.

People can agree with both statements because they are not incompatible. The public does not think HBOs have human status and respect does not mean the entity cannot be sacrificed for a higher cause. Entities that have much more human essence are sacrificed for higher values. For example, the medical research system is premised on the idea that research subjects often risk harm to themselves to develop medical treatments for others. I think that most of the public I spoke with think that it would be respectful to sacrifice an HBO to relieve human suffering.

#### WHAT ELSE SHOULD BE DONE

Recall that one reason to use the public's values in translational bioethics is so the public sees its values in use by scientists and thus has increased trust. Mistrust in science is not about the public not believing in scientists' technical abilities but that they do not see their values as the same.<sup>16</sup> Now that we know the public's values on this issue, public trust could be enhanced, albeit very slightly, by talking about HBOs differently.

A widely read book about research with human subjects and its consequences is *The Immortal Life of Henrietta Lacks*. Lacks was a poor African American woman whose cancerous cells were taken without her consent during surgery at Johns Hopkins Hospital, subsequently immortalized, and sold by commercial entities as the HeLa cell line used in biomedical research. The main message in the book is the racism of medical research practices, but it also includes a powerful account of Lacks' children seeing the essence of their mother to the cell lines. To take but one example, when one of her daughters looks at the cells through a microscope she says, implicitly starting with the value of medical knowledge: "John Hopkin is a school for learning and that's important." She then turns to balance this with human essence, continuing: "this is my mother. Nobody seem to get that."<sup>17</sup> Would the distrust generated by this episode in the history of medical research be lessened if scientists had acknowledged what the cells mean to the family?

Let's consider an analogy. More than 90% of allopathic medical schools in the U.S. have funeral- like memorial ceremonies for the cadavers that the students use to learn anatomy. A sociologist who analyzed this practice writes that the memorial ceremony "reifies the sacrality of the bequeathed bodies and re-humanizes anatomical specimens." She continues that:

The case of donor memorial ceremonies is interesting and unexpected because of a presumed distinction between the sacred and science, which leads [people] to assume that sacred practices are not necessary for and are nonexistent in the intensely scientific medical field. However, . . . managing the profanity of dissection is an urgent need experienced by medical students and faculty alike. It is important, even necessary, to everyone involved to show that the current practice of whole-body donation is honorable in all regards, and that studying anatomy through whole-body dissection is done for the higher purpose of saving the lives of future patients.<sup>18</sup>

I am not advocating having funeral services for HBOs because, again, no one in the public would think of them as full-blown humans (unlike the cadavers, who are, from the public's view, still human, albeit now dead). Medical schools have decided that these ceremonies are useful for the people involved, and perhaps talking about HBOs not as objects but as respected entities that many consider to have a human's essence might engender support for HBO science and science in general.

A translational bioethics should be based on the values of the public, and I have shown in this essay that those values are often somewhat different from those used in standard IRB ethics. That does not mean that using these public values results in rejection of research and I have offered an example of how the public's values on human brain organoids might lead to support for this research. I also argued that acknowledging the values used by the public may well forward the public acceptance of science. A translational bioethics may not only better represent the public than standard IRB ethics, but may result in more support from that same public.

ENDNOTES

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- <sup>6</sup> Committee on Ethical, Legal, and Regulatory Issues Associated with Neural Chimeras and Organoids et al., *The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance* (Washington, D.C.: National Academies Press, 2021), <https://doi.org/10.17226/26078>.
- <sup>7</sup> Code of Federal Regulations, 45 CFR 46.111 -- Criteria for IRB approval of research., accessed March 15, 2024.
- <sup>8</sup> John H. Evans, *The History and Future of Bioethics: A Sociological View* (New York: Oxford University Press, 2012), Ch. 2.
- <sup>9</sup> Henry T. Greely, “Human Brain Surrogates Research: The Onrushing Ethical Dilemma,” *The American Journal of Bioethics* 21, no. 1 (2021): 34–45, <https://doi.org/10.1080/15265161.2020.1845853>.
- <sup>10</sup> Evans, *The History and Future of Bioethics*, 43–64.
- <sup>11</sup> Evans, *Disembodied Brains: Understanding Our Intuitions on Neuro-Chimeras and Human-Brain Organoids*, 61.
- <sup>12</sup> Evans, 83.
- <sup>13</sup> John H. Evans, *What Is a Human? What the Answers Mean for Human Rights* (New York, NY: Oxford University Press, 2016).
- <sup>14</sup> Gill Haddow, *Embodiment and Everyday Cyborgs: Technologies That Alter Subjectivity* (Manchester: Manchester University Press, 2021), Chapter 1.
- <sup>15</sup> Becka A Alper et al., “Spirituality Among Americans,” *Pew Research Center*, n.d., 7.
- <sup>16</sup> Evans, *Disembodied Brains: Understanding Our Intuitions on Neuro-Chimeras and Human-Brain Organoids*, 124–25; John H. Evans and Cynthia E. Schairer, “Scientism, Trust, Value Alignment, Views of Nature, and U.S. Public Opinion about Gene Drive Mosquitos,” *Public Understanding of Science*, Forthcoming.
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- <sup>18</sup> Amy Patricia Lawton, *Dissertation: Donor Bodies, Medical Schools, and the Scientific Sacred* (Storrs, CT: University of Connecticut, 2022), 1.