Check for updates

RESEARCH ARTICLE

# Too-Many-Oids: The paradox in constructing an organoid ethics framework

[version 1; peer review: 2 approved with reservations]

Andrew J. Barnhart, Kris Dierickx

Department of Public Health & Primary Care, Katholieke Universiteit Leuven, Leuven, Flanders, 3000, Belgium

**v1** **First published:** 25 May 2023, **2**:10 https://doi.org/10.12688/molpsychol.17552.1
**Latest published:** 25 May 2023, **2**:10 https://doi.org/10.12688/molpsychol.17552.1

## Abstract

**Background:** The field of organoid ethics is complex and multifaceted, and the need for flexibility and adaptability in the face of its moral complexity is of great importance. Certain kinds of organoids may be deemed morally controversial due to their intrinsic characteristics (*e.g.*, brain organoids, embryoids, or organoid intelligence models) and debates are underway over their possible moral standing. Furthermore, different domains of organoid applications, such as transplantation, precision medicine, or disease modeling have fundamentally different moral concerns.
**Methods:** In this paper, we argue that it is a mistake and near impossible to develop an overarching, all-in-one ethical framework that can sufficiently cover the myriad of organoid moral contexts. We first identify different ontological categories of organoid technologies along with morally problematic properties. We then present different moral contexts in which the organoid technologies are applied.
**Results:** Constructing an organoid ethics framework that can both consider all the relevant moral properties and contexts, and be a useful ethical lens for moral examination may lead to a paradox; the more relevant moral contexts the framework tries to incorporate, the more abstract and less useful the framework becomes.
**Conclusions:** It may be more useful for bioethicists to take on more collaborative and contextual approaches for organoids ethics.

## Keywords

Organoids, Ontology, Moral frameworks, Paradox, Contextual considerations

This article is included in the The Ethics of Brain Organoids collection.

**Open Peer Review**

**Approval Status** ? ?

| | 1 | 2 |
|---|---|---|
| **version 1** 25 May 2023 | ? view | ? view |

1. **Insoo Hyun**, Museum of Science, Boston, USA
2. **Tsutomu Sawai**, Hiroshima University, Higashi-Hiroshima, Japan
   Kyoto University, Kyoto, Japan
   National University of Singapore (Ringgold ID: 37580), Singapore, Singapore

Any reports and responses or comments on the article can be found at the end of the article.

**Corresponding author:** Andrew J. Barnhart (andrew.barnhart@kuleuven.be)

**Author roles: Barnhart AJ**: Conceptualization, Formal Analysis, Investigation, Methodology, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Dierickx K**: Conceptualization, Funding Acquisition, Methodology, Supervision, Validation, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** This project has received funding from the European Union's Horizon 2020 research and innovation programme, OrganoVIR, under the Marie Skłodowska-Curie grant agreement No. 812673.
*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*



**How to cite this article:** Barnhart AJ and Dierickx K. **Too-Many-Oids: The paradox in constructing an organoid ethics framework [version 1; peer review: 2 approved with reservations]** Molecular Psychology: Brain, Behavior, and Society 2023, **2**:10 https://doi.org/10.12688/molpsychol.17552.1

**First published:** 25 May 2023, **2**:10 https://doi.org/10.12688/molpsychol.17552.1

## Introduction

Organoid ethics is a field of study that deals with the philosophical, ethical, legal, and social implications of sourcing, creating, possessing, using, and distributing organoids—which are three-dimensional (3D) cellular structures that mimic the features and functions of *in vivo* organ counterparts[1]. The creation of organoids *in vitro* raises a number of ethical questions, such as the moral status of brain organoids, embryoids, and assembloids. In addition, organoids can now incorporate computer and silicon technology to create yet another class of organoid—organoids *cum silico*. The proposition and creation of Organoid Intelligence (OI) (brain organoids integrated with artificial intelligence [AI] computer systems) is only one example of this new organoid class[2,3]. It is unclear exactly what the moral standing of these new organoid-entities are. Furthermore, ethical considerations of organoids extends to their implications for animal and chimera models, appropriate consent models, and data privacy concerns to name a few[1,4–7].

Developing a comprehensive, overarching framework for addressing these questions is complex, as it requires taking into account a wide range of factors, including scientific, legal, and stakeholder perspectives. Additionally, the field of organoid research is rapidly advancing, which means that any ethical framework developed today will need to be updated when new information and organoid technologies emerge. Framework flexibility and contextual adaptability may initially be of use to certain classes of organoids or applications. However, these framework attributes can only extend so far. This paper first presents an overview of organoid categories, a number of their applications, and unique moral contexts found in each. Next, we argue that constructing an organoid ethics framework that can consider all the relevant moral contexts and be useful for moral examination may lead to a paradox; the more relevant moral contexts the framework tries to incorporate, the more abstract and less useful the framework becomes. It is a mistake and near impossible to develop an overarching, all-in-one ethical framework that can sufficiently cover the myriad of organoid moral contexts. Instead, it may be more useful for bioethicists to take on more collaborative and contextual approaches for organoid ethics.

## Method: Argument overview

The overall structure of this argument is similar to a *reductio ad absurdum*. We argue that given the set of propositions relating the variety of organoids, applications, and moral contexts, it would be absurd to construct an overall ethical framework for entirety of organoid ethics. In order to do this, we first lay out a new way to ontologically classify organoids in addition highlighting often considered morally problematic properties. We chose specific and recent examples that highlight these ontological distinctions. Next, we point to the variety of applications of organoid models and highlight some of the more recent applications. The last stage of this paper brings the contradiction, as we show that constructing a moral framework for all organoid classifications and applications brings about a paradox of abstraction and rendering the framework useless. Thus, to avoid this absurdity and paradox, it may be argued bioethicists ought to take on more collaborative and contextual approaches for organoid ethics.

## Organoid ontology and morally problematic properties

To say there is a variety of organoids is an understatement. For nearly every single organ and biological structure, there exists an organoid model and with it, possible ranges of complexity[8–10]. This immense diversity of organoids has given rise to projects such as the Organoids Cell Atlas and attempts to standardize organoid nomenclature[11,12]. We propose that organoids be broadly classified into at least three ontological classes: organoids *in vitro*, organoids *cum silico*, and organoids *in vivo*. Figure 1 below presents a top-down tree diagram depicting the broad distinctions along with examples found within the classification. This ontological classification serves as a practical means for reflecting on morally problematic or controversial properties of specific organoid models and to showcase the immense diversity of organoids any overarching moral framework would have to consider.

The first ontological class of organoids *in vitro* retains the common definition of an organoid. It holds both "simple" organoids (*e.g.*, enteroids, liver organoids, and cardiac organoids) to the more "complex" organoids (*e.g.*, brain organoids, embryoids, and assembloids)[10,13]. Simple organoids may not be morally controversial in-and-of-themselves as they typically do not possess morally controversial properties. But this does not exclude them from moral consideration in other contexts, such as the stem cell sources or material needed to generate them (*e.g.*, adults, children, animals, or embryos). Complex organoids may be deemed more morally controversial either because of properties they possess (*e.g.*, human embryoid models possessing properties very similar to human embryos), or for the possibility to gain problematic properties (*e.g.*, the possibility of brain organoids developing a form of consciousness)[14,15].

Another classification of organoid models is organoids *cum silico*. This may be defined as organoids that are deeply integrated with computer or silicon technology. It is not enough for an organoid to grow within a Petri dish for it to be classified as an organoid *cum silico*; some other form of technology must be integrated into the entity itself. Researchers integrate computer or silicon technology with organoids for a variety of reasons such as mitigating necrosis of the organoid core, providing better organoid structure and homeostasis, better measurement methods for early-stage organoid development and modeling, or to use as a form of biocomputing[2,16,17]. One example of organoids *cum silico* is cyborg organoids, stretchable mesh nanoelectronics are integrated with human induced pluripotent stem cells (hiPSCs), cells then undergo differentiation, creating a 3D spherical structure with the nanoelectronic mesh[16]. This has been done with both cardiac organoids and human brain organoids[16,18].

Another recent example of organoids *cum silico* is the recent proposal for developing an OI system. OI is a novel field

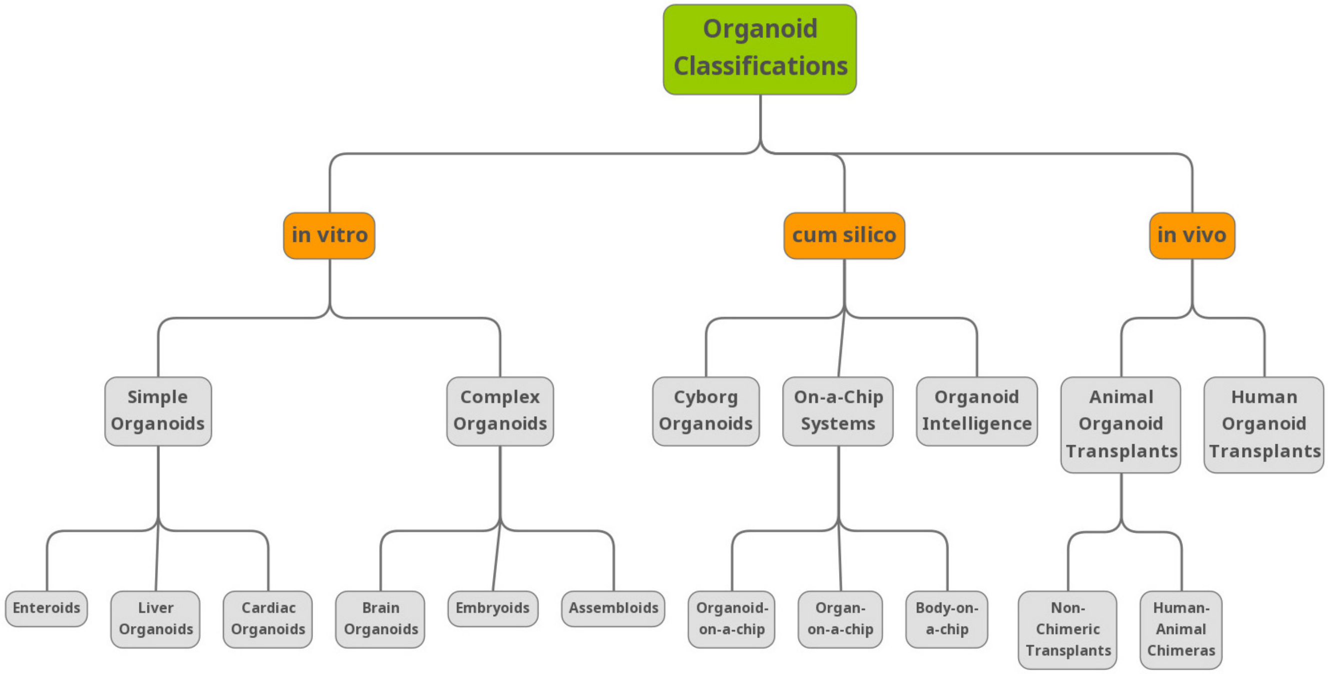


**Figure 1. A top-down tree diagram portraying broad ontological classifications of organoid models with examples found within each class.** The three ontological classifications explored are organoids *in vitro,* organoids *cum silico,* and organoids *in vivo.* Made with MindMup.

"aiming to expand the definition of biocomputing towards brain-directed OI computing"[2]. Researchers want to utilize brain organoids for biocomputing purposes by embedding them with microelectrode arrays connected to an AI computer system, allowing for certain informational inputs and outputs to the brain organoid. One experiment from Cortical Labs successfully trained an OI system to play the classic video game, Pong. By giving brain organoids input and output mechanisms, and thus the ability to control the Pong paddle in the game, the researchers who created DishBrain claim they made a sentient being[3]. Should this be the case, then the moral standing of such an entity is in question and requires examination as suggested by Smirnova *et al.*, and Kagan *et al.*, from Cortical Labs[2,3].

Finally, the ontological class of organoids *in vivo* contains organoid models that have been transplanted into other living entities such as animals and human beings. Organoids are transplanted into animal models for various reasons. For one, organoids have limitations as *in vitro* models. Their inner core lacks sufficient sources of nutrients, given their lack of vascularization, and thus often the organoid demonstrates necrosis at the core[19]. Evidence suggests that transplantation can aid in vascularization and nutrient delivery to the organoid[20–22]. Furthermore, there is hope that transplanting organoids into animal models could yield new treatments and techniques within clinical medicine[4,20,23]. The creation of chimeras *via* transplanting organoids of one species into a different species has given rise to some areas of moral discussion. Already comparisons and serious ethical thought is given to the lessons from the literary classic Frankenstein[24]. Ethicists are also giving consideration to risks and patient perspectives associated with transplanting organoids into human beings[25–27]. However, such issues are not related to the change in moral standing or morally problematic properties of a person or organoid. Rather, they relate more towards the ethical application of organoids, which is covered in more detail in the following section.

## Diverse applications and diverse contexts

To say there is a variety of organoid applications is also an understatement. Corrò *et al.*, identify an extensive list of biomedical domains in which organoid models could be implemented: toxicology, drug discovery, host-microbe interactions, gene editing, multiomic studies, phylogenetic studies, developmental biology, disease modeling, precision medicine, and regenerative medicine[9]. In addition, there are social applications for consideration such as commercialization[5,28]. Each domain of organoid application has unique ethical considerations and within each applicable domain of organoids is further diversity of moral contexts.

Consider the application of brain organoids in the context of autism research for example. Such research often incorporates the medical model of disability (a concept of disability where disability originates within the individual and is a state of affairs that ought to be medically treated or cured) with the hope that precision medicines, treatments, and etiological understandings can be found[29]. This is in contrast with the ideas, values, and goals of disability found within the neurodiversity and neurodivergent movements. Such movements incorporate a social model of disability into their framework, and they consider autism as a form of human difference that is worthy of value and preservation, not treatment or cure[30]. Such value conflicts ought to be reconciled if brain organoid research on autism is to move forward. But the broader point here is that the moral context of this organoid *in vitro* application is one of a wide variety within brain organoids alone.

Organoids *cum silico* further compound ethical issues relating to use or application. OI systems have the added moral context of integrating brain organoids *cum silico* with artificial intelligence and machine learning systems. AI ethics is still a blooming field; the issues and concerns within it are far from settled. Ethical issues related to AI include transparency, data security and privacy, accountability, automation and job replacement, accessibility, the black box problem, algorithm discrimination, ownership, competition, inequality, democracy, and human rights and dignity[31,32]. There are also separate issues pertaining to the impacts that AI has on human psychology, the legal system, and on the environment and planet[32].

But in addition to these ethical issues associated with AI on its own, OI adds further ethical issues given its integration of brain organoids with AI systems. The diverse applications of brain organoids *in vitro* for biomedical purposes can also apply to OI systems. Many of the ethical issues associated with the application of OI and AI will overlap, nevertheless, the existing diversity of ethical contexts is already becoming too cumbersome to generate an overarching ethical framework that can act adequately to address all appropriate contexts.

## A paradox of plural moral contexts

Given the diversity in both morally problematic properties (*e.g.*, possible consciousness, sensations of pain, naturalness) and applications of organoid models (*e.g.*, commercialization, precision medicine, regenerative medicine), the challenge of making an overarching ethical framework that can cover all these relevant moral contexts becomes much more cumbersome. Attempts to generate an overarching moral framework may lead to a kind of paradox: the more relevant moral contexts the framework tries to incorporate, the more abstract and less useful the framework becomes. To use the recent OI proposal as an example, Smirnova *et al.*, identified a wide variety of domains where potential ethical issues can occur (*e.g.*, cell donation, bioculturing, organoid-machine interface, learning and computation, and applications)[2]. Within the "learning and computation" domain, Smirnova *et al.*, identified issues relating to AI algorithms, data sharing, sharing code and protocols, and the emergence of neurobiological features that contribute to human capacities as areas of concern. Constructing a novel ethical framework that can be applied to these potential issues would be challenging enough, given the current blooming of the AI ethics field in addition to a need for establishing a moral relevancy of neurobiological features correlating to human capacities. Should a novel framework genuinely overcome these challenges, it would then need to contend with other potential issues in the domains, as mentioned by Smirnova *et al.*

Certainly, advocates of pre-existing top-down frameworks (*e.g.*, consequentialists or deontologists) will continue to champion their application. To some extent, these top-down frameworks are already given some consideration within organoid ethics literature[33–37]. However, a possible drawback of using top-down heavy frameworks is that organoid ethics would be yet another battle ground for these theories, reducing deliberations and arguments among ethicists to principally over the philosophical strengths and weaknesses of the ethical frameworks. Ethicists may also find themselves trapped in long-standing, unsettled metaphysical debates. For example, some ethicists may want to begin with the task of either establishing or rejecting a moral status for organoid-entities with controversial moral properties. While this task is an important undertaking, the overall ethical deliberations may become too exclusively rooted in moral status, potentially overshadowing difficult moral contexts that need addressing (*e.g.*, brain organoids for autism research)[38].

Furthermore, a constructed top-down framework for an organoid *cum silico* like OI would have an intrinsic conceptual problem, in that it would not be applicable to other organoid-entities beyond its ontological category. Researchers with organoid *in vitro* and *in vivo* categories would not be able to make use of such a framework as relevant moral contexts would be ignored or missing. An OI framework with a heavy emphasis on AI contexts would certainly not be suitable for human-animal chimeric xenotransplantation experiments with organoids, nor would it be the most suitable for addressing concerns relating to gastruloid development. A further synthesis of these contexts into the framework could demand further abstraction of principles, values, or rules to such a degree that they may become useless moral truisms for researchers or regulators on the ground. Moreover, the novel framework could become like, or be an iteration of, existing top-down ethics frameworks (*e.g.*, consequentialism, deontology), at which point there would be no need to consider organoid ethical issues, specifically when constructing the framework itself.

Even when considering organoids *in vivo*, there are problems with cross application of a constructed moral framework. Organoids *in vivo* involve transplanting an organoid-entity into another living host-entity, but the host-entity may differ in terms of moral standing. The moral standing of mice is generally accepted to be less than that of human persons (though there is, of course, continued argument over the exact moral standing criteria). Transplanting human brain organoids into animal models will fundamentally require different ethical frameworks and analyses than transplantation into human beings.

## Multiple futures for organoid ethics

While constructing an organoid ethics framework that can cover all the varieties of organoids and their applications may be conceptually impossible or impractical, this does not mean that moral deliberations will, or ought to, cease. We do not claim that organoid ethics are a futile endeavor, or that it serves no practical use. Rather, what the diversity of organoids and their applications shows, and demands, is that the ethical approaches will also need to be diverse, adaptable, and grounded much more closely to relevant contexts. Indeed, the recent OI proposal intends to use an "embedded ethics" approach "whereby expert ethicists join and collaborate integrally with research and development teams to consider and address ethical issues *via* an iterative and continuous process as the research evolves"[2]. In addition, other bioethicists have presented similar approaches for organoid models that begin with a much more grounded and contextual orientation, such as collaborative ethics and ethics parallel research[39,40].

Furthermore, the current state of organoid ethics reflects the complex interrelations of different moral issues and contexts. For instance, donor consent is not only related to patients granting permission for generating organoid models for research but it is also entwined with commercialization[1,5,6,28]. However, bioethicists like Stoeklé *et al.*, may not necessarily agree with the idea that the state of organoid ethics is truly reflecting the subject's complexity. Rather it "may be a consequence of the history of bioethics, combined with theoretical and practical frameworks that are just as plural"[41].

Ultimately, there is no real need for an overarching ethical framework for organoids. Ethicists already have multiple tools and frameworks at their disposal for tackling organoid moral dilemmas. Embracing various ethical approaches allows for a more tailored response to the intricate ethical issues that organoid research and applications present. By accounting for the unique characteristics and contexts of each organoid model and application, ethicists can provide more relevant than informed guidance. This adaptability is of paramount importance as organoid development continues to advance, generating novel ethical questions and challenges. While pre-existing ethical frameworks, such as the six principles of animal ethics, the capabilities approach for justice, or virtue ethics for researchers are still relevant in specific moral contexts, the ethics of organoids ought to begin with a focus on a particular moral domain or context, rather than building a new overarching framework. The embedded ethics, collaborative ethics, and ethics parallel research approaches are examples of possible starting points for novel biotechnologies like the various categories of organoids[2,39,40].

## Conclusion: context matters

The extensive array of organoid models and their applications undeniably presents a formidable challenge when considering the ethical dimensions involved. Nevertheless, it remains imperative to thoroughly deliberate upon the ethical, legal, and social implications of these novel technologies. Embracing a diversity of adaptive, flexible, and context-specific ethical approaches, such as embedded ethics, collaborative ethics, and ethics in parallel research, ethicists can contribute to the responsible development and utilization of organoid technologies. This approach ensures that ethical considerations remain at the forefront of this rapidly advancing field while recognizing and addressing the unique moral contexts associated with organoid research and applications.

As the field progresses, it is crucial for ethicists, scientists, and relevant stakeholders to collaborate in the development of guidelines and frameworks that are both adaptable and context-specific, promoting the responsible and ethical advancement of organoid research. As new developments and innovations continue to emerge, collaborative and flexible approaches (rather than an all-encompassing framework) will be essential in navigating the multifaceted and diverse ethical landscape of organoid research and applications.

## Data availability

No data are associated with this article.

## References


1. Barnhart AJ, Dierickx K: **The Many Moral Matters of Organoid Models: A systematic review of reasons.** *Med Health Care Philos.* 2022; **25**(3): 545–560.
**PubMed Abstract** | **Publisher Full Text**
2. Smirnova L, Caffo BS, Gracias DH, *et al.:* **Organoid intelligence (OI): the new frontier in biocomputing and intelligence-in-a-dish.** *Front Sci.* 2023; **1**: 1017235.
**Publisher Full Text**
3. Kagan BJ, Kitchen AC, Tran NT, *et al.:* ***In vitro* neurons learn and exhibit sentience when embodied in a simulated game-world.** *Neuron.* 2022; **110**(23): 3952–3969.e8.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**
4. Barnhart AJ, Dierickx K: **A Tale of Two Chimeras: Applying the Six Principles to Human Brain Organoid Xenotransplantation.** *Camb Q Healthc Ethics.* 2023; 1–17.
**PubMed Abstract** | **Publisher Full Text**
5. Boers SN, Bredenoord AL: **Consent for governance in the ethical use of organoids.** *Nat Cell Biol.* 2018; **20**(6): 642–645.
**PubMed Abstract** | **Publisher Full Text**
6. Boers SN, van Delden JJ, Clevers H: **Organoid biobanking: identifying the ethics: Organoids revive old and raise new ethical challenges for basic research and therapeutic use.** *EMBO Rep.* 2016; **17**(7): 938–941.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**
7. Bredenoord AL, Clevers H, Knoblich JA: **Human tissues in a dish: the research and ethical implications of organoid technology.** *Science.* 2017; **355**(6322): eaaf9414.
**PubMed Abstract** | **Publisher Full Text**
8. Nguyen A, McAleavey K, Lyall K: **SnapShot: Advancing Organoid Technology.** *Cell Stem Cell.* 2019; **24**(6): 1008.
**PubMed Abstract** | **Publisher Full Text**
9. Corrò C, Novellasdemunt L, Li VSW: **A brief history of organoids.** *Am J Physiol*

*Cell Physiol.* 2020; **319**(1): C151–C165.
PubMed Abstract | Publisher Full Text | Free Full Text

10. Kim J, Koo BK, Knoblich JA: **Human organoids: model systems for human biology and medicine.** *Nat Rev Mol Cell Biol.* 2020; **21**(10): 571–584.
PubMed Abstract | Publisher Full Text | Free Full Text

11. Bock C, Boutros M, Camp JG, *et al.:* **The Organoid Cell Atlas.** *Nat Biotechnol.* 2021; **39**(1): 13–17.
PubMed Abstract | Publisher Full Text | Free Full Text

12. Paşca SP, Arlotta P, Bateup HS, *et al.:* **A nomenclature consensus for nervous system organoids and assembloids.** *Nature.* 2022; **609**(7929): 907–910.
PubMed Abstract | Publisher Full Text

13. Takebe T, Wells JM: **Organoids by design.** *Science.* 2019; **364**(6444): 956–959.
PubMed Abstract | Publisher Full Text | Free Full Text

14. Ankeny RA, Munsie MJ, Leach J: **Developing a Reflexive, Anticipatory, and Deliberative Approach to Unanticipated Discoveries: Ethical Lessons from iBlastoids.** *Am J Bioeth.* 2022; **22**: 36–45.
PubMed Abstract | Publisher Full Text

15. Koplin JJ, Savulescu J: **Moral limits of brain organoid research.** *J Law Med Ethics.* 2019; **47**(4): 760–767.
PubMed Abstract | Publisher Full Text | Free Full Text

16. Le Floch P, Li Q, Lin Z, *et al.:* **Stretchable Mesh Nanoelectronics for 3D Single-Cell Chronic Electrophysiology from Developing Brain Organoids.** *Adv Mater.* 2022; **34**(11): e2106829.
PubMed Abstract | Publisher Full Text | Free Full Text

17. Park SE, Georgescu A, Huh D: **Organoids-on-a-chip.** *Science.* 2019; **364**(6444): 960–965.
PubMed Abstract | Publisher Full Text | Free Full Text

18. Li Q, Nan K, Floch PL, *et al.:* **Cyborg Organoids: Implantation of Nanoelectronics via Organogenesis for Tissue-Wide Electrophysiology.** *Nano Lett.* 2019; **19**(8): 5781–5789.
PubMed Abstract | Publisher Full Text

19. Zhang S, Wan Z, Kamm RD: **Vascularized organoids on a chip: strategies for engineering organoids with functional vasculature.** *Lab Chip.* 2021; **21**(3): 473–488.
PubMed Abstract | Publisher Full Text | Free Full Text

20. Kitahara T, Sakaguchi H, Morizane A: **Axonal Extensions along Corticospinal Tracts from Transplanted Human Cerebral Organoids.** *Stem Cell Reports.* 2020; **15**(2): 467–481.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Daviaud N, Friedel RH, Zou H: **Vascularization and Engraftment of Transplanted Human Cerebral Organoids in Mouse Cortex.** *eNeuro.* 2018; **5**(6): ENEURO.0219-18.2018.
PubMed Abstract | Publisher Full Text | Free Full Text

22. Mansour AA, Gonçalves TJ, Bloyd CW, *et al.*: **An *in vivo* model of functional and vascularized human brain organoids.** *Nat Biotechnol.* 2018; **36**(5): 432–441.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Xu R, Brawner AT, Li S, *et al.*: **OLIG2 Drives Abnormal Neurodevelopmental Phenotypes in Human iPSC-Based Organoid and Chimeric Mouse Models of Down Syndrome.** *Cell Stem Cell.* 2019; **24**(6): 908–926.e8.
PubMed Abstract | Publisher Full Text | Free Full Text

24. Koplin J, Massie J: **Lessons from Frankenstein 200 years on: brain organoids, chimaeras and other 'monsters'.** *J Med Ethics.* 2021; **47**(8): 567–571.
PubMed Abstract | Publisher Full Text

25. Lensink MA, Boers SN, Jongsma KR, *et al.*: **Organoids for personalized treatment of Cystic Fibrosis: Professional perspectives on the ethics and governance of organoid biobanking.** *J Cyst Fibros.* 2021; **20**(3): 443–451.
PubMed Abstract | Publisher Full Text

26. Schneemann SA, Boers SN, van Delden JJM, *et al.*: **Ethical challenges for pediatric liver organoid transplantation.** *Sci Transl Med.* 2020; **12**(552): eaau8471.
PubMed Abstract | Publisher Full Text

27. Boers SN: **Chapter 9: Ethics of organoid transplantation: first-in-children?** In: *Organoid technology: an identification and evaluation of the ethical challenges*, (Utrecht University, 2019).

28. Choudhury D, Ashok A, Naing MW: **Commercialization of Organoids.** *Trends Mol Med.* 2020; **26**(3): 245–249.
PubMed Abstract | Publisher Full Text

29. Barnhart AJ, Dierickx K: **Cultures and cures: neurodiversity and brain organoids.** *BMC Med Ethics.* 2021; **22**(1): 61.
PubMed Abstract | Publisher Full Text | Free Full Text

30. Armstrong T: **The myth of the normal brain: embracing neurodiversity.** *AMA J Ethics.* 2015; **17**(4): 348–352.
PubMed Abstract | Publisher Full Text

31. Murphy K, Ruggiero ED, Upshur R, *et al.*: **Artificial intelligence for good health: a scoping review of the ethics literature.** *BMC Med Ethics.* 2021; **22**(1): 14.
PubMed Abstract | Publisher Full Text | Free Full Text

32. Huang C, Zhang Z, Mao B, *et al.*: **An Overview of Artificial Intelligence Ethics.** *IEEE Trans Artif Intell.* 2022; 1–21.
Publisher Full Text

33. Chen HI, Wolf JA, Blue R, *et al.*: **Transplantation of Human Brain Organoids: Revisiting the Science and Ethics of Brain Chimeras.** *Cell Stem Cell.* 2019; **25**(4): 462–472.
PubMed Abstract | Publisher Full Text | Free Full Text

34. Lavazza A: **Human cerebral organoids and consciousness: a double-edged sword.** *Monash Bioeth Rev.* 2020; **38**(2): 105–128.
PubMed Abstract | Publisher Full Text | Free Full Text

35. Lavazza A: **'Consciousnessoids': clues and insights from human cerebral organoids for the study of consciousness.** *Neurosci Conscious.* 2021; **7**(2): niab029.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Stoeklé HC, Ivasilevitch A, Marignac G, *et al.*: **Ethical Issues of Brain Organoids: Well Beyond "Consciousness"?** *AJOB Neurosci.* 2022; **13**(2): 109–111.
PubMed Abstract | Publisher Full Text

37. Sawai T, Hayashi Y, Niikawa T, *et al.*: **Mapping the Ethical Issues of Brain Organoid Research and Application.** *AJOB Neurosci.* 2022; **13**(2): 81–94.
PubMed Abstract | Publisher Full Text

38. Barnhart AJ, Dierickx K: **Moving beyond the moral status of organoid-entities.** *Bioethics.* 2023; **37**(2): 103–110.
PubMed Abstract | Publisher Full Text

39. Hyun I, Scharf-Deering JC, Sullivan S, *et al.*: **How collaboration between bioethicists and neuroscientists can advance research.** *Nat Neurosci.* 2022; **25**(11): 1399–1401.
PubMed Abstract | Publisher Full Text

40. Jongsma KR, Bredenoord AL: **Ethics parallel research: an approach for (early) ethical guidance of biomedical innovation.** *BMC Med Ethics.* 2020; **21**(1): 81.
PubMed Abstract | Publisher Full Text | Free Full Text

41. Stoeklé HC, Ivasilevitch A, Marignac G, *et al.*: **Creation and use of organoids in biomedical research and healthcare: the bioethical and metabioethical issues.** *Cell Adh Migr.* 2021; **15**(1): 285–294.
PubMed Abstract | Publisher Full Text | Free Full Text

# Open Peer Review

## Current Peer Review Status: ? ?

Version 1

Reviewer Report 19 January 2024

https://doi.org/10.21956/molpsychol.18827.r27377



?

**Tsutomu Sawai**
[1] Graduate School of Humanities and Social Sciences, Hiroshima University, Higashi-Hiroshima, Japan
[2] Institute for the Advanced Study of Human Biology, Kyoto University, Kyoto, Japan
[3] Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, National University of Singapore (Ringgold ID: 37580), Singapore, Singapore

I appreciate the opportunity to review "Too-Many-Oids: The Paradox in Constructing an Organoid Ethics Framework." The manuscript's critique of the overarching framework appears unclear. While I endorse the authors' preference for collaborative and contextual bioethics approaches, they need to define the organoid ethics framework more clearly, incorporating examples, particularly of embedded, collaborative, and parallel approaches. Additionally, the paper's numerous organoid examples do not sufficiently demonstrate the ineffectiveness of the criticized framework or their evaluation within the proposed framework. An in-depth analysis of 'organoid ethics' classifications and their implications for ontological classifications, as I have also explored in my paper (Sawai et al, 2022) [Ref 1]and depicted in Figure 1, would be beneficial.

The manuscript seems to undervalue traditional ethical frameworks like consequentialism and deontology in organoid ethics. A balanced discussion emphasizing their importance, along with specialized approaches, is crucial.

I recommend expanding the manuscript to thoroughly explore the feasibility and challenges of embedded, collaborative, and parallel ethical approaches in organoid ethics, even beyond the current scope. This expansion would significantly enhance the paper's contribution to the discourse on ethical complexities in organoid research. Addressing the potential straw man argument, as pointed out by Reviewer 1, is also necessary.

**References**

1. Sawai T, Hayashi Y, Niikawa T, Shepherd J, et al.: Mapping the Ethical Issues of Brain Organoid Research and Application.*AJOB Neurosci*. 2022; **13** (2): 81-94 PubMed Abstract | Publisher Full Text

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and does the work have academic merit?**
Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
Not applicable

**Are all the source data underlying the results available to ensure full reproducibility?**
No source data required

**Are the conclusions drawn adequately supported by the results?**
Partly

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** My expetise is in bioethics in general and stem cell ethics (including brain organoid ethics).

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 26 June 2023

https://doi.org/10.21956/molpsychol.18827.r26879



? **Insoo Hyun**
Center for Life Sciences and Public Learning, Museum of Science, Boston, MA, USA

This manuscript, “Too-Many-Oids,” argues that there are too many ontological classes of organoids to allow for an all-in-one ethical framework to handle the range of ethical issues generated from this new area of science. While I agree with the authors’ conclusion – namely, that other ethical approaches, such as embedded ethics, collaborative ethics, and ethics parallel research offer better starting points – I do not think the authors’ way of arguing for this conclusion is very persuasive.

First, is *anyone* actually arguing in favor of the position that all these varieties of organoids and their potential arrangements and uses *should* be captured under a single moral framework? I am not aware of anyone who actually commits themselves to this argument. This seems like a straw man to me. Of course, some have argued that the possibility of consciousness in brain organoids is of concern and have subsequently argued that organoids' moral status can be built upon this possibility. But this type of argument is not the same as saying that a single moral framework should capture the full range of organoid research ethical issues. Thus, I am not aware that the idea of encompassing all organoids and their applications under one moral roof is something to argue against (which the authors here devote the bulk of their manuscript to doing).

Second, this "too-many-organoids" argument should spend a bit more time explaining what "ontology" means at the beginning, since (most?) readers of this journal may not have a philosophical understanding of this term of art.

Third, I find the ontological view of organoids a bit confusing because each one could be very different due to method of derivation and cultivation, and the often one-off nature of organoids. Also, some organoids are disease-specific and others are healthy controls. Aren't these different ontological states?

Fourth, on the bottom of page 5, the authors state, "Transplanting human brain organoids into animal models will fundamentally require different ethical frameworks and analyses than transplantation into human beings." That is true, but isn't there already a fundamentally different ethical framework in place for the former – namely animal research ethics and animal welfare?

Fifth, on page 6 the authors claim that "The embedded ethics, collaborative ethics, and ethics parallel research approaches are examples of possible starting points for novel biotechnologies like the various categories of organoids." Can the authors explain why these are not themselves broad frameworks? Are these envisioned as processes or approaches to moral decision making? If so, then what is the difference between a framework and a process (at least a process that is informed by some moral principles or guiding considerations)?

If the authors could address the straw man concern and clean up some of their distinctions, particularly around the difference between ethical frameworks and the type of approaches they seem to recommend, this manuscript would be much improved.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and does the work have academic merit?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Not applicable

**Are all the source data underlying the results available to ensure full reproducibility?**

No source data required

**Are the conclusions drawn adequately supported by the results?**
Partly

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** Bioethics; human brain organoids; bioengineering ethics; regulation and science policy.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**