Addressing the ethical challenges to informed consent for brain tissue donation

Afrontar los desafíos éticos del consentimiento informado para la donación de tejido cerebral

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https://doi.org/10.36105/mye.2024v35n3.05

Abstract

The tremendous medical promise of human organoids has led large research institutions and national agencies to create brain tissue banks. In response, regulatory agencies have created regulations that guide consent processes for collecting tissue samples from donors. These regulations are, in part, intended to ensure that donors' samples are not used in ways that conflict with their moral values, beliefs, and goals. While these regulations frequently serve this purpose well, we argue that they are insufficient in the case of brain tissue donation because of unique ethical concerns that arise from technologies and applications that use brain tissue samples. After considering the inadequacies, we

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Reception: 29/11/2023 Acceptance: 12/02/2024

suggest how consent policies can be improved. We focus on US policy specifically because some Caribbean and Latin American countries reference US regulatory frameworks in developing their own.

Keywords: brain organoids, tissue donation, informed consent, neural organoids, ethics.

1. Introduction

The tremendous medical promise of human organoids, three-dimensional aggregates of human cells, has led large research institutions and national agencies to create brain tissue banks. Current large organizations include US National Cancer Institute, Cancer Research UK, UK Wellcome Trust Sanger Institute, and the Foundation Hubrecht Organoid Technology, Netherlands: Human Cancer Model Initiative. Moreover, in Latin America there are over 220 tissue banks (1). In response to the growing number of tissue banks, regulatory agencies have created regulations that guide consent processes for collecting tissue samples from donors (2). These regulations are, in part, intended to ensure that donors' samples are not used in ways that conflict with their moral values, beliefs, and goals. While these regulations serve this goal well in most cases, we argue that they are insufficient in the case of brain tissue donation. A growing literature points to unique ethical concerns that arise from technologies and applications, most commonly brain organoids, that use brain tissue samples (3-5). In this paper we examine US guidelines (i.e., The Common Rule, Subpart A) for live donor tissue donation and suggest that they fail to adequately achieve the ethical purpose of informed consent for brain tissue donation. We focus on US guidelines because of the documented influence US regulatory tissue donation frameworks can have on Caribbean and Latin American counties' own regulations (6).

In Section I we provide an overview of the varieties of human organoid technology. In Section II we survey some of the moral

https://doi.org/10.36105/mye.2024v35n3.05

concerns that have been raised about organoid technology. In Section III we explore the challenges and possible responses to obtaining the informed consent of donors. In section IV we describe the current model of informed consent in the Common Rule and argue that it inadequately protects the moral interests of donors. Finally, in Section V we propose improvements to the Common Rule 2 for consenting donors for brain tissue donation.

2. Section I: overview of uses

Human neural organoids are three-dimensional aggregates of human neural cells grown in the laboratory from stem cells or patient derived healthy or tumor cells (5). They are the most recent technological development for representing and studying brain biology and functions. Neural organoids can be employed in a variety of ways to study brain biology. *Human neural transplants* (aka xenografts) further expand the scientific power of this new model. By transplanting human derived neural organoids into nonhuman animals, researchers may study human neurons, glia, and other brain cells in the context of a whole behaving organism (5). *Human neural chimeras* are a special kind of transplant in which stem cells are injected into a nonhuman host early in embryonic development (5). In blastocyst complementation, for example, the transplanted stem cells replace most of the host cells in a particular brain region. Blastocyst complementation has been employed in mice, rats, and pigs for a variety of organs (7). Current versions of this model have yet to transplant human stem cells but there is no in principle technological barrier to doing so in the future.

Researchers employ these new techniques and models in a variety of ways with a promise of tremendous potential scientific and medical benefit, especially in cancer research. Neural organoids are particularly useful for developing cancer drugs that specifically target tumor cells. Since organoids can be developed from both healthy

https://doi.org/10.36105/mye.2024v35n3.05

and tumor tissue, researchers can screen potential drugs that specifically target tumor cells while leaving healthy cells unharmed (8). Furthermore, this technique for screening drugs can be used to tailor treatment protocols to individual patients.

In basic research, organoids allow researchers to explore the link between infectious agents and cancer development (8). Even though ~20% of cancer cases have been linked to infectious agents, little is known about the causal pathway between pathogens and malignant transformation. Organoids facilitate co-culture systems with different types of pathogens to study the processes and identify which agents (e.g., bacteria and viruses) are risk factors.

Organoids also provide a means of investigating the mutational processes active during tissue homeostasis and tumorigenesis (8). By using CRISPER-Cas9 gene editing technology, researchers can knock out or insert specific genes from healthy genetically stable organoids and observe the effects. Hence, the genetic stability of healthy organoids allows researchers to identify causal relationship between specific mutational processes and mutation signatures. Conversely, the genetically heterogenous composition of tumor organoids models the dynamic genetic properties of tumors. This allows researchers to analyze how intratumor heterogeneity affects cancer progression and therapy resistance.

Given the promising scientific and medical potential of organoids, several national and institutional cancer research organizations have developed/plan to develop living biobanks for tumor organoids and their matching normal tissue-derived organoids. Current large organizations include US National Cancer Institute, Cancer Research UK, UK Wellcome Trust Sanger Institute, and the Foundation Hubrecht Organoid Technology, Netherlands: Human Cancer Model Initiative. These biobanks will support advances in both basic research and personalized medicine. For drug development, large biobanks increase the statistical power of samples in order to discover correlations between genetic markers with differences in drug sensitivity (8).

https://doi.org/10.36105/mye.2024v35n3.05

The development and creation of large living biobanks implies many donors. These donors are stakeholders in the ethical use and management their samples. Some of these stakeholders, however, will find aspects of future research morally or religiously objectionable. As we explain below, this is particularly true of human brain organoids. Moreover, the more robustly that human brain organoids model the functions and complexity of human brains, the greater the likelihood that they will trigger ethical quandaries (9). In fact, researchers and organizations such as the National Academy of Science, Engineering, and Medicine (NASEM) have identified several such ethical concerns already (5).

3. Areas of Ethical Concern

Several papers have investigated the ethical issues associated with organoid technology (3-5,10,11) In this section we outline a selection of these ethical concerns in order to establish that some potential donors will have non-trivial moral concerns about brain organoids and their uses. Of note, we exclude concerns involving consciousness or pain perception with central nervous system (CNS) tissue-derived organoids. The NASEM Report argues that no biological evidence suggests such concerns are warranted (5). Hence, for now we set aside distant hypotheticals and focus primarily on ethical concerns surrounding current and foreseeable brain organoid applications.

Concerns for animal welfare: Current animal disease models limit research on uniquely human brain diseases. Human neural organoid transplants and chimeras offer a promising method of overcoming these limitations. Despite this technological promise, some donor-stakeholders may have one or more deeply held ethical or religious objections to research models that adversely affect animal welfare. Recognizing this, current regulations and practices require researchers to minimize the number of animals used, substitute

https://doi.org/10.36105/mye.2024v35n3.05

other models when possible, alleviate and minimize pain and distress, and provide appropriate living conditions (12).

Nevertheless, members of some moral communities (social groups that organize around norms and values) may universally oppose any harmful animal research, especially when there is no benefit to the animal. For example, although organoids allow researchers to escape the limitations of *in vitro* models, "host animals are essentially used as bioreactors to generate new vasculature for organoids as a means of maintaining their growth and maturation¨(11 p. 466).

Concerns about the ethics of enhanced cognitive capacities: Human neural transplants and chimeras raise the possibility of cognitive enhancement. Along with the potential for cognitive enhancement come concomitant ethical concerns about expanded capacity for suffering. This possibility may trigger concerns similar to those above.

Concerns for nonhuman animal-human mixing: Members of some moral communities may object, on moral grounds, to the mixing of animal and human biology. In particular, some religious traditions may maintain that integrating animal neural cells with human neural cells blurs a fundamental distinction between these kinds of beings (5). When animal-human chimeras have the possibility of acquiring distinctively human qualities, such research can be construed as undermining the dignity and uniqueness of human beings (and other species) (2). Furthermore, human-animal brain organoid transplants raise potential ethical concerns since the capacities associated with humans' moral status are located in the brain (3).

Concerns about encroachment on divine roles: Some moral communities may object to humans "playing God" by creating chimeras that fall outside of categories of beings created by a deity (5). This is a familiar objection to biotech, generally. On this view, experiments involving neural organoids and chimeras fall outside of the domain proper to humans and infringe on activities reserved for deities.

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Objections to human enhancement. The same technologies that have therapeutic uses can also be used for enhancement. Several surveys of potential donors and the general public identify moral concerns about organoid research directed towards this use (4,10,13).

Objections to use by private profit-seeking enterprises: In surveys of public attitudes de Jongh *et al.* (3), Haselager *et al.* (4), Bollinger *et al.* (10), all found that respondents often had concerns with knowledge generated from donated tissue being used to benefit privately held entities rather than restricted to publicly funded research.

The above list of ethical concerns is not intended to be comprehensive but rather is intended to establish two points: First, for members of some moral communities, some current and near-future brain organoid research applications present non-trivial ethical concerns. Second, these ethical concerns are not unreasonable and follow from reasonable worldviews.

There are, therefore, ethical concerns with brain organoid research that are non-trivial and reasonable. Donors with non-trivial and reasonable ethical concerns will likely want to know whether their donated tissues will be used for such purposes. Given the large number of donors that will be involved in current and future tissue banks for brain organoid research, it's worth investigating whether research informed consent guidelines and regulations adequately address this concern.

4. Current practice

Very broadly, the informed consent process is grounded in respect for persons (or autonomy). The core idea is something like this: When we seek to involve others in our projects, they have the right to know the nature and purpose of that project, its potential risks and benefits, and how it will affect their respective interests so that they may freely decide for themselves whether to be involved. A

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critical element of the informed consent process, therefore, involves not only disclosing information about a project but discerning what information is and is not relevant to prospective participants. In the context of tissue banking, informed consent depends, in part, on disclosing to donors the future uses and applications of donors' tissue samples within the context of their known and anticipated ethical concerns.

Samples can be collected for a specific research project or for yet-unknown future uses (i.e., secondary uses). When samples are collected for a specific research project, challenges surrounding disclosure are attenuated since the specific project can be robustly described. In this section we describe two challenges to adequate disclosure in gathering informed consent for secondary brain tissue use. Then we briefly describe and evaluate three approaches to disclosing future uses and applications. Next, we evaluate the current informed consent standards in the US (Common Rule Subpart A). Finally, we propose a model of informed consent that improves both.

4.1. Overview of models for disclosing future uses of donated brain tissue

a perennial challenge in developing informed consent processes involves determining what constitutes adequate disclosure. When disclosures are too broad or general, they risk obscuring or excluding details that may be relevant to participants. When disclosures are highly detailed and technical, they risk burdening and confusing participants. Moreover, in determining what constitutes *adequate* disclosure, informed consent processes must balance a variety of *desiderta* for various stakeholders with heterogeneous values and goals. Here, we focus on two main challenges to adequate disclosure for brain tissue donation: The *open-endedness challenge* and *the infinite ontologies challenge*.

The open-endedness challenge: an obvious challenge to consenting to donating brain tissue for future research is the inability to foresee every possible research application. This is particularly true

https://doi.org/10.36105/mye.2024v35n3.05

when tissue samples can be transferred to second party researchers/collaborators. Brain organoid technology is still in its infancy and unimagined applications may develop long after donors have consented. As noted above, some of those future applications may be morally objectionable to some donors. It's not possible to develop consent forms that contain all possible future uses.

The infinite ontologies challenge: adequate consent requires that participants be informed of the categories of current and foreseeable research for which their samples may be used. There are, however, an infinite number of categorization schemes and degrees of resolution one could employ to describe the future uses of donated brain tissue. For example, one could categorize uses according to alphabetical order, technologies and techniques (e.g., molecular phenotyping, patent-derived xenograft), or according to purpose (e.g., therapeutic use, basic research, drug trials, education, etc.).

Once a categorization scheme is selected, one must still select the level of resolution. For example, "basic research" itself can be further divided into subcategories (e.g., research on proteins, the immune system, stem cells, microorganisms, biomarkers, etc.). The same applies to technological categories. The One True categorization scheme and level of resolution are not those that "cleave the world at its joints" but rather those that follow from normative and pragmatic choices. That is, the categorization schemes we choose will reflect the work we want them to perform.

Policymakers have responded to these two pragmatic challenges with a variety of models, some mutually exclusive and some compatible. Within the US context it will suffice to describe three that fall along a continuum:

Blanket consent: on this model, donors consent to their samples' *unrestricted* use in secondary research (3). The advantage of blanket consent is that, by presenting a binary all-or-nothing choice, it avoids the open-endedness and infinite ontologies challenges. The donor consents to all uses, present and future, or they do not.

https://doi.org/10.36105/mye.2024v35n3.05

There are, however, two major disadvantages: First, blanket consent may have the effect of reducing the pool of donors. Since a binary choice affords donors so little control in what happens to their samples, risk adverse donors may simply prefer to opt out. Second, blanket consent avoids the open-endedness and infinite ontologies challenges only by poorly achieving the ethical goal of informed consent.

Recall that a foundational ethical purpose of gathering consent is to ensure that participation conforms with (or at least doesn't conflict with) donors' goals and values. Blanket consent does not adequately describe or explain the myriad possible uses of donated tissue. Hence, participants cannot be said to adequately understand how and whether future possible uses conform with their goals and values. It is not *informed* consent in any meaningful ethical sense. So, even for those who provide consent, blanket consent risks violating the basic ethical purpose of the consent process. These criticisms are reflected in Haselanger *et al.* (4), Lensink *et al.* (13), and DeVries *et al.*'s (14) and findings that prospective donors and laypeople considered broad consent to be insufficient for addressing their values and concerns surrounding organoid research.

Specific consent and reconsent:[1] this model lies at the opposite end of the spectrum from blanket consent. Donors consent to the use of their tissue for *specific* research projects and reconsent for each new project. It handles the open-endedness and infinite ontologies challenges because by contacting and reconsenting donors for each specific use, it makes possible a robust description of the project. By doing so, this model better supports the ethical purpose of informed consent because it better ensures that each tissue use conforms with donor values and preferences.

The primary objection to the specific consent model is the time and resource burden it imposes on institutions and researchers (15).

[1] Sometimes called "dynamic consent." For example, see: Domaradzki and Pawlikowski (16).

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While attempts to recontact donors is relatively easy via email or text, these methods risk low response rates. Moreover, over time, contact information may become stale. This leaves a smaller pool of available samples and may affect the statistical power of some kinds of research. To be sure, current donor information could be tracked down in the same way social workers track down families of unaccompanied hospitalized patients. Nevertheless, such a process falls prey to the original concerns about the costliness of resource intensive processes.

A final challenge to the reconsent model involves concerns about data privacy. The ability to recontact to reconsent implies continued and relatively easy access to information linking a tissue sample (and accompanying genetic information) to a living donor. In cases where samples will be used by second party research institutions (public or private), data privacy becomes a non-trivial concern. Moreover, maintaining a database that stores this information will impose additional financial burdens on institutions.

Broad consent: this model occupies the middle ground between blanket and specific consent. It refers to "a process by which individuals donate their samples for a broad range of future studies, subject to specified restrictions" (15 p. 3) The precise nature of the specified restrictions is intentionally vague, and donors are not reconsented for each use of their sample. Broad consent is thought to balance the burden of reconsenting for every use with donors' desires to ensure their samples aren't used in ways that conflict with their goals and values.

One concern with broad consent involves the magnitude of economic costs and resources necessary to maintain an infrastructure that tracks which donors consented to which types of projects (3,15). Moreover, it's not clear that broad consent successfully avoids the open-endedness and infinite ontologies challenges since it is mute regarding the ontological categorie(s) according to which donors consent.

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As we will see in the next section, the US regulatory scheme (Subpart A of the Common Rule) employs broad consent and implies technological categories for its consent ontology. However, in Sec. IV and V we argue that this choice can hinder the moral purpose of consent, and categories of moral concern may better serve this end.

5. Evaluating Subpart A of the Common Rule on Consenting for Tissue Donation

We now turn to Subpart A of the Common Rule (46.116(d)1-7) for the "storage, maintenance, and secondary use of identifiable specimens (collected for either research other than the proposed research or non-research purposes)." After evaluating this section of the Common Rule, we argue that it inadequately supports the moral purpose of gathering consent.

The first feature worth noting is that it explicitly employs a broad consent framework:

> *Broad consent* for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or non-research purposes) is permitted as an alternative to the informed consent requirements […] (italics added for emphasis).

Recall that broad consent (unlike blanket consent) restricts future uses to whatever *types* of research are identified in the consent. Hence, research institutions and tissue banks must provide:

> [a] general description of the *types* of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the

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> broad consent would permit the *types* of research conducted (italics added for emphasis);

Notably, there is no regulatory requirement to provide details about specific research studies. Instead, institutions and tissue banks may provide donors or their representatives:

> a statement that they will *not* be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, *including the purposes of the research*, and that they might have chosen not to consent to some of those specific research studies (5) (italics added for emphasis);

The broad consent framework that forms the regulatory standard functions as an ethical *minimum*. Whether we should accept this minimum depends, in part, on its ability to realize the ethical purpose of gathering consent.

5.1. Ethical Appraisal of Subpart A of the Common Rule (46.116(d)1-7)

A core purpose of gathering consent is to ensure that the projects in which participants engage conform with or do not conflict with their deeply held considered values, beliefs, and goals. Hence, part of the ethical ideal for brain tissue donor consent is that each use of a donated tissue conforms with —or at least does not conflict with— the donors' considered values and goals. While it is unrealistic to demand that regulatory policies conform perfectly with the ethical ideal, regulatory frameworks should aspire to continually close the gap between the actual and the ideal in the context of what is possible. In this section we argue that the Common Rule does not adequately ensure the ethical ideal because it poorly meets the ontological challenge: It employs a broad consent that conceives of use in terms of technological rather than moral categories. However, participants grant or withhold consent based on the moral dimensions of a use.

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Ontology of Types of Research and Degree of Resolution

If donors do not receive information relevant to their moral concerns, then the Common Rule does not adequately ensure the moral purpose of informed consent. As noted above, the Common Rule requires that researchers disclose the *types* of research that may be conducted with donated samples or personal information. Essentially, the Common Rule frames disclosure in terms of *technological* categories of research. However, fulfilling a fundamental purpose of informed consent requires that donors receive information relevant to *moral* categories of concern. Potential donors oppose kinds of technology because of the moral implications, purposes, or effects of those technologies, not because of some inherent dislike of a technology or technique *per se*. This mismatch between the categories that currently structure disclosure and the categories relevant to donors' moral concerns implies disclosure will not always be adequately support donors' needs.

The Common Rule's failure to adequately ensure informed consent follows from its failure to adequately address the infinite ontologies challenge. Recall that the infinite ontologies challenge holds that there are an infinite number of possible category schemes and degrees of resolution one could employ to categorize the uses of donated brain tissue. The Common Rule categorizes according to *types* of research, most naturally understood as *technological* types.

Moral categories, of course, can often be inferred from technological categories. For example, human neural chimeras are a type of research from which the morally relevant categories "research with stem cells" and "research on animals" may be inferred. However, there are other 'types' of research (in the technological sense) that use donated brain tissue from which there are no obvious (lay) inferences to morally relevant categories of concern. For example, some (technological) *types* of research may be used for a variety of *purposes* such as therapeutic and enhancement. Surveys of potential donors and laypeople reveal that some groups find the latter morally objectionable and therefore may need this information in order to give

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genuine consent (10,16). In short, technological categories do not reliably reveal moral categories.

Perhaps the solution is to insist on highly detailed descriptions of the possible research for which a sample may be used. But even highly detailed descriptions of future research can fail to reveal some morally relevant information to donors. For example, surveys on public attitudes toward tissue donation find significant concern over whether the fruits of research on donated tissues will be for private profit or for the public good (10,16,17). Again, technological descriptions do not necessarily reveal information relevant to moral concerns.

The Common Rule employs "types of research" to address the infinite ontologies challenge. This choice, while useful, imperfectly aligns with the moral purpose of consent which ought to identify participants' moral categories of concern. It follows that informed consent practices should be modified to disclose information and gather consent about categories of known moral concerns in addition to potential technological types of research. These categories can be drawn from the burgeoning literature of surveys, reports, and philosophical work that investigate moral concerns associated with brain organoid research (see Sec. II).

Modifying consent practices to disclose and gather information about known categories of moral concern will help to close the gap between current consent processes and the ethical ideal. Moreover, it helps to address the open-endedness challenge since categories of moral concern remain fixed and will apply regardless of what types (techniques and technologies) of research are developed in the distant future. Admittedly, this modification does not fully overcome the open-endedness challenge since this would require anticipating every possible area of moral concern raised by distant future applications. Nevertheless, adding recognized moral categories of concern aligns the informed consent process more closely with the ethical ideal than does the current practice of disclosing only future uses, understood primarily in terms of types of technology.

https://doi.org/10.36105/mye.2024v35n3.05

Section V: Practical Guidance for Narrowing the Gap Between the Actual and Ideal Consent Practices

Developing a universal policy for disclosures in consent-gathering is challenging since biobanks can involve different contextual features such as demographics, geography, culture, and historical context. The larger the biobank (e.g., national biobanks), the more diverse the populations it will serve, the less likely there is to be a single consent-gathering policy that adequately addresses the unique needs of each. On the other hand, institutions and regulatory bodies require some level of standardization in order to avoid harms to donors.

To narrow the gap between the ethical ideal and current informed consent policy for secondary use, we suggest providing:

1. more morally robust descriptions of research categories,
2. options to opt out of known major moral categories of concern, and
3. the opportunity to request reconsents.

Broad consent is imperfect, but it is not without merit and is the general public's preferred model *if blanket consent and reconsent are the only other options* (14). Very often moral concerns can be reasonably inferred from descriptions of technological categories, especially when the purpose of the research is included. Broad consent itself can be improved by making explicit known morally relevant features, purposes, and implications of technological categories. Furthermore, consent forms can provide a checklist that allows donors to opt out of uses that involve known major areas of moral concern such as those identified in Sec. II.

Nevertheless, when dealing with nascent technology, not all moral concerns can be anticipated or inferred from the broad categories that researchers select for broad consent. While some donors may be indifferent to what happens to their tissue donation or find broad consent sufficient, others may not. To respect the latter group's concerns, donors should be able to opt in to having specific consents for

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each research project. Hence, informed consent should supplement broad consent with the opportunity for donors to be reconsented for each project.

Tradeoffs

Very few policies come without tradeoffs and our suggestions are no exception. Here we address two categories of burdens: Those borne by donors and those borne by researchers and research institutions. Regarding the latter, providing donors with the opportunity to selectively exclude their samples from future research because it violates one or more moral categories of concern requires a system for tracking preferences across time. Such systems must also track who wants to be reconsented and expend time seeking reconsents. All of this tracking and reconsenting requires time, resources, and money that might have otherwise been spent on research or other important activities.

Our proposals also impose potential risks on donors since reconsenting requires that personal information be linked to tissue samples. Systems that link donors' personal information, preferences, and contact information raise risks associated with data theft or discrimination. Institutions must therefore spend additional resources to ensure high levels of data security for donors who request reconsents.

The heightened data security risks to these donors can be addressed by disclosing them. That is, donors who select the option to be reconsented or to opt out of certain moral kinds of research must be informed of the additional data security risk they incur. No amount of security technology can overcome the fact that maintaining a link between a donor's personal information and a tissue sample creates a greater security risk than if there were no link at all. The institution's data security precautions should be explained in a way intelligible to a layperson with the caveat that data security is never 100% risk-free. Prospective donors can then choose for themselves

https://doi.org/10.36105/mye.2024v35n3.05

whether the security risks outweigh whatever benefits they derive from restricting uses or whether they even want to donate at all. The essential point with respect to the tradeoffs surrounding data security risk is that it is the (informed) donor who gets to make them based on their own values and concerns.

The more difficult problem surrounds additional costs borne by researchers and their institutions. One mitigating factor is that there is uncertainty surrounding what proportion donors will want restrictions on secondary uses or specific consent. For example, in a large survey offering US respondents choice between blanket, variations of broad consent, and specific consent, 45% replied that specific consent was the worst system of consent. 35% of respondents said broad consent was still unacceptable (but not the worst option), although it was the most favored.14 Domaradzki and Pawlikowski16 reviewed 61 other surveys and also found diverse attitudes towards the various consent schemes. However, they consistently found across all surveys that only a small minority favor the reconsent model. Since reconsenting is likely to be the costliest proposal to implement, the survey findings should allay concerns that research on brain tissues will be unduly hampered by a need to reconsent for each sample before each new use. Robust evidence suggests that few donors will likely select this option.

Finally, we must address the cost of a system that tracks the moral categories that some research donors want to opt out of. The cost is partly an empirical matter. Data bases already link genetic and demographic information to brain tissue samples (anonymized or not). It's likely that, without too much extra cost, such data bases could be modified to also hold information about a sample's use restrictions.

The other aspect of the tradeoff is normative. Certainly, we cannot expect our commitment to robust donor consent to be cost-free. We must weigh the value of gathering and maintaining genuine informed consent against the cost of doing so. Institutions engage in consent processes because, among other pragmatic reasons, it is a

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required part of conducting research. So, if fulfilling consent processes imposes prohibitive costs on research, then we must rethink our approach to consent. Fortunately, there is no evidence to suggest that this is the case. The burden of proof falls on whoever claims that the cost of modifying existing databases to hold additional information categories will be so great as to render research on brain tissue financially prohibitive.

6. Conclusion

We do not believe our suggestions are radical. If anything, they harmonize consent processes for brain tissue donation with existing policies elsewhere in the Common Rule. Consider, for example, consent policies for human pluripotent stem cell (iPSC) and human embryonic stem cell (hESC) donation. The Common Rule recognizes that members of some moral communities will have deep moral commitments about how these cells are used. Hence, in order to ensure that donors' moral concerns are respected, the Common Rule requires extensive disclosure of potential uses in terms of known categories of moral concern (45 CFR Part 46, Subpart A). For example, researchers must provide a statement that the hESC or iPSC and/or cell lines might be used in research involving genetic manipulation of the cells or the mixing of human and nonhuman cells in animal models. The morally fraught nature of research on brain organoids requires extending the same logic to the case brain cell donation.

In this paper we have argued that current informed consent guidelines in the Common Rule inadequately support the primary moral purpose of obtaining consent. Consent practices in medical research developed to ensure that subjects' participation conforms with or doesn't conflict with their considered values, beliefs, and goals. Prospective brain tissue donors' decisions to genuinely consent will depend on their normative commitments, and so consent

https://doi.org/10.36105/mye.2024v35n3.05

depends on how explicitly normative aspects of possible future research are disclosed and communicated.

The Common Rule employs a broad consent model and implies secondary research types should be disclosed in terms of types of technology. However, technological categories do not always obviously imply moral categories of concern. Furthermore, since moral categories are a primary factor determining whether a prospective donor will consent, these moral categories of use must be made explicit in order to ensure genuine informed consent.

To achieve this end, we have suggested that informed consent process for obtaining brain tissues provide more morally robust descriptions of research categories, options to opt out of known major moral categories of concern, and the opportunity to request reconsents.

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