Induced pluripotent stem cell-based systems for personalising epilepsy treatment: Research ethics challenges and new insights for the ethics of personalised medicine

This paper examines potential ethical and legal issues arising during the research, development and clinical use of a proposed strategy in personalised medicine (PM): using human induced pluripotent stem cell (iPSC)-derived tissue cultures as predictive models of individual patients to inform treatment decisions. We focus on epilepsy treatment as a likely early application of this strategy, for which early-stage stage research is underway. In relation to the research process, we examine issues associated with biological samples; data; health; vulnerable populations; neural organoids; and what level of accuracy justifies using the iPSC-derived neural tissue system. In relation to clinical use, we examine potential uses in pre-natal screening, and effects on clinical decision-making. Although our focus is providing recommendations for researchers developing work in this area, we identify the novel issue of deciding on an acceptable accuracy level for the system. We also emphasise an issue thus far neglected in the ethics of PM: PM tends to represent treatment decisions as though they should be directed solely by biomedical information, but this in itself could be detrimental to best personalising treatment decisions in the clinic.

Keywords: research ethics, neurology, epilepsy, genetics, regulatory issues, stem cell research

When prescribing treatments for serious illnesses, doctors are often faced with several pharmaceutical options and no straightforward way of determining which will be best for the patient, other than trial and error. A new sort of tool, which uses induced pluripotent stem cells (iPSCs) from the individual patient, has been proposed to inform these decisions in the context of epilepsy. iPSCs can be used to grow neural tissue cultures that can serve as genetically accurate models of patients. Exposing the cultures to different treatments may

allow doctors to match individual patients to treatments better and more quickly (Du and Parent 2015; Antill-O'Brien et al 2019). This tool would be a novel technique for informing clinical decisions and a new strategy within personalised (or 'precision') medicine (PM). It would raise regulatory challenges, as it does not clearly fit into current regulatory schemes; and scientific challenges to develop fit-for-purpose culturing procedures and validation methods. This paper investigates ethical dimensions of this sort of tool. We separately discuss ethical issues that arise in the context of research and development of such as system, and ethical issues that will arise in its clinical use. We focus on epilepsy treatment because this is a likely early application of the strategy, and early-stage research is already underway (DOH 2020).

We first outline the iPSC-derived neural tissue system to clarify what it requires and how it is novel (section 1). In section 2 we forecast what stages the research and development process is likely to require, to identify research requirements that could raise ethical concerns.[1] Section 3 examines ethical issues in the research and development process, namely: risks and burdens associated with collection and use of biological samples, data, and health; research with vulnerable populations; possible use of neural organoids; and determining what level of predictive accuracy justifies using the iPSC-derived neural tissue system. Section 4 examines ethical issues of adoption of the system into clinical practice, including use in pre-natal screening, and effects on clinical decision-making and clinician-patient communication. We offer recommendations to address each ethical concern.

[1] We draw on Brey's (2012) anticipatory ethics methodology, but adapt it to include ethical issues in research as well upon adoption.

While we focus on providing recommendations surrounding the iPSC tool in the context of personalised epilepsy treatment, we also aim to contribute to developing understanding of ethical issues in PM more broadly. Some of the identified ethical issues are not new and we point to relevant developed techniques and protocols for addressing them. However, issues related to deciding what level of predictive accuracy will justify using the iPSC-derived neural tissue system is novel. Further, we argue that consideration of the limitations of such a system, and the need to supplement the biomedical information it provides with different sorts of personal patient information reveals an issue as yet neglected in the ethics of PM. PM literature tends to represent treatment decisions as though they are, or should be, directed solely by biomedical information. But non-biomedical factors can be relevant to treatment outcomes and so should play a role in treatment decisions. For instance, a patient with a high level of family commitments might be less able to comply with complex dosing schedules; a patient trying to start a family may find side effects on libido intolerable although other patients tolerate them well. Treatment decision-making should take such factors into account, as a vital part of 'personalising' treatment decisions in the clinic. The need to take such non-biomedical factors into account should be more fully recognised in PM literature.

1: Personalising epilepsy treatment with an iPSC-derived neural tissue system

Where patients have progressive disease and there is potential for trauma, it is important to identify the best treatment as soon as possible to reduce the time spent unmedicated and possible deterioration. Despite its potential in the context of epilepsy, the iPSC tool would fall in an ethical and regulatory gap, as it is neither a treatment modality nor diagnostic

device. An account of how the device works in the context of difficulties in treating this serious illness will help illustrate why.

There are over 20 anti-epileptic drugs (AEDs) available. However, around 30% of epilepsy patients are treatment refractory. Of the ~70% receiving clinical benefit, around a third continue to experience some seizures as well as side effects (Nadkarni et al 2005, Eadie 2012; Walker et al 2015). It can also be difficult to predict which treatment will be optimal for any specific patient. There are different types of epilepsy, but we lack full understanding of many subtypes, and it can be difficult to classify a specific patient into a subtype due to difficulties measuring seizure activity (Scheffer et al 2017; Sterlini et al 2020; Johnson et al 2011; Eadie 2012).

iPSC-derived tissue cultures share an individual's genetic profile and can be developed into neural cell types in culture. The iPSC-derived neural tissue system would involve growing multiple iPSC-derived neural cultures, inducing seizures, and subjecting cultures to different treatments with cell response observed.[2] If this system could predict what AED therapy will work best for particular patients, it might reduce time spent trialling ineffective or nonoptimal treatments. In addition, epilepsy patients may be reticent to experiment with different treatments if they experience some improvement, even when they still suffer seizures. The iPSC-derived neural tissue system could identify patients on suboptimal treatment regimes.

[2] We refer to the tool as an iPSC-derived neural tissue *system* to acknowledge that it is not only the neural tissue itself that needs examination from an ethical perspective, but the entire process from sample collection through to impacts on treatment decisions. As we show below, some of the ethical issues relate, not to the tissue itself, but from various processes involved in this system and its use in context.

This iPSC-derived neural tissue system would require development of standardised procedures for culturing and testing. There are numerous types of tissue cultures, and it is not yet clear what type would most accurately model patients' treatment responses (Walker et al 2019). The system might be limited to providing information on epilepsies with genetic causation. Complications may arise if patients' drug responses are modulated by connections to other physiological systems or the blood-brain barrier.

Given that the authors are familiar with one iPSC-based predictive model in development for epilepsy, this article focuses on such as system (understood as we have described it in this section) for the purpose of ethical analysis. Some considerations we discuss are specific to epilepsy, but others would generalise to other devices that incorporate a patient's own iPSCs to test drug responses to aid difficult and important treatment decisions.

2: Possible targets of ethical concern

As is often the case in ethical assessment of emerging technologies, the eventual form of this system is uncertain. However, anticipating ethical issues with emerging technologies is important to prevent or address technologically plausible problems. This is particularly important in epilepsy research, which has sometimes been prevented or delayed due to ethical concerns (Ferlazzo et al 2017, Perucca 2008). Our next task therefore is to forecast what research and clinical translation are likely to involve, in order to identify possible targets of ethical concern (Brey 2012). In 2.1 we consider possible ethical concerns in the research process and in 2.2, in clinical practice.

2.1: Research and development

Identifying ethical issues in research toward an iPSC-derived neural tissue system is complicated by the its novelty, which makes it unclear what the research and development track looks like. What sorts of studies will researchers undertake to develop the system, and show that it is safe and effective? We argue that the system should be validated using processes similar to clinical predictive models and draw on these to identify requirements for research studies that may raise ethical issues (table 1).[3]

To justify use in clinical practice, research should provide evidence that the iPSC-derived neural tissue system is safe and effective for its intended use. What is needed is a basis for believing it can accurately and reliably predict treatment responses; that each patient-specific model bears a relation of predictive accuracy to the specific patient, with regard to response to epilepsy medications. To establish that the models have such a relation, studies will need to compare the outputs of models against actual patient outcomes, across an appropriate study population. What this indicates is that the iPSC-derived neural tissue system is, epistemologically, similar to other clinical prediction models. Like statistical or computational models, it will match specific inputs and outputs, without

[3] Research and development of new therapeutics are usually impacted by surrounding law and regulation, but in relation to the iPSC-derived neural tissue system these are still developing and provide little guidance. In relation to law, the stem cell field is characterised by a thick web of patent rights, with a majority of patents covering technologies associated with production and differentiation (Roberts et al 2014). Initial patents are seemingly broad and there can be difficulty determining their reach (Roberts et al 2014; Zarceczny et al 2009). As research reaches a more applied phase, patents are becoming more disease-specific (Morita 2019), and there is uncertainty as to how these apply to other forms of research. No regulators have yet developed advice on iPSC-derived neural tissue systems. Such system have similarities to other PM products however, notably companion and complementary diagnostics -- tests that indicate whether a particular patient is likely to respond to a targeted pharmacogenomic treatment (Scheerens et al 2017). Our discussion below draws on ethical discussion of these and some other similar strategies in PM.

providing an explanation. Predictive models are 'black boxes' that allow us to identify treatment response without needing to understand the highly complex biological mechanisms between input and output.[4] As such, guidance on the research track can be found by looking at the validation process for predictive models.

Research for predictive models uses stages of development, calibration, and validation. Predictive models are typically statistical or computational, not physical, and are derived from analysis of a dataset. Patterns were traditionally found using techniques guided by background biomedical knowledge; more recently machine learning techniques have been used (Steyerberg 2019, 2). After initial development, models are calibrated, that is, tested against a dataset and adjusted to ensure best fit to data. Development and calibration are iterative stages in the process of developing a predictive model, ceasing when the desired level of accuracy is reached. After calibration, models are validated by testing their predictions against actual outcomes. Validation ideally uses a different dataset from that used in calibration (since the model will already be 'fitted' to the initial dataset) (Steyerberg 2019; Steyerberg et al 2010; Debray 2015; Vergouwe 2003).

How does this apply to the iPSC-derived neural tissue system? *Development* would involve establishing that some form of iPSC tissue culture can be suitable for making the desired prediction: that when exposed to treatments culture responses are informative about how the patient responds. What kind of culture, culturing techniques, and measurement procedures are best for this outcome would need to be identified and a standardizable, reproducible process defined. For these purposes, the development stage

[4] For a detailed version of this argument see Walker et al (2019).

would require biological samples from people with epilepsy, and clinical data about their responsiveness to different treatments, though the number of subjects might be small.

Calibration would require comparing the predictions of the system with further clinical data, and altering various aspects of the modelling and measurement procedure, to increase accuracy to a desired level. This would require larger sets of biological samples and clinical data, and deciding on what level of accuracy is sufficient to justify a validation study.

Validation aims to establish that the finalised system provides sufficiently accurate predictions to justify its use. It will be preferable to use a different dataset in validation and calibration, to avoid risks arising from re-use of the calibration dataset (known as 'overfitting'). Second, since epilepsy type may be relevant to models' predictive accuracy, there are reasons to focus initially on a particular type of epilepsy. Third, there are reasons to prefer prospective studies: difficulties measuring seizure severity and frequency mean that retrospective clinical data may be subject to recall bias, placebo effects, and other interpretation effects. Further, epilepsy can improve on its own, so there is possibility of regression to the mean. Validation will require further biological samples and clinical data from additional patients.

In terms of the cultures themselves, it is not yet clear what sort of tissue culture could best be used to model patients' responses to AEDs. Tissue cultures derived from iPSCs are often thought to avoid the most contentious ethical issues related to embryonic stem cell research (Caulfield et al 2010, Moradi et al 2019; though see Brown 2009). However, novel ethical concerns have been raised about neural organoids. Such concerns could be raised at all stages of research as well as upon adoption.

[Table 1 here]

2.2: Adoption in clinical practice

To identify potential ethical issues upon adoption in clinical practice, we reviewed bioethical literature surrounding PM, other forms of screening, and epilepsy treatment. We identified three sources of ethical concern. First, there are issues surrounding a possible use of the iPSC-derived neural tissue system in prenatal or preimplantation testing. Despite potential benefits of utilising the system to provide early treatment interventions for infants born with epilepsy, the fact that it may also identify genetic epilepsy risks in an embryo or foetus gives rise to different ethical considerations. Second, ethicists interested in PM have raised ethical issues related to stratification of the patient population, since identifying patient populations most likely to benefit from a treatment could in practice restrict access to treatment for those judged less likely to benefit (Prainsack 2017; Dickenson 2013; Fleck 2010; Chadwick 2014). As these judgements are probabilistic in nature, they can exclude people who would benefit from the system. The iPSC-derived neural tissue system differs from stratification as a personalising strategy – but could raise the same issue. Third, existing work on the ethics of PM indicates potential concerns related to effects of PM on clinical decision-making and clinician-patient communication, since PM strategies provide new, more fully biomedically-focused bases for clinical decisions (Savard 2013).

[Table 2 here]

3: Ethical analysis of the research and development process

The mapping of requirements in research and development helps identify risks and burdens likely to arise in the research and development process. These include risks and burdens

related to biological samples, data, and health; as well as issues related to vulnerable people in the research population; possible use of organoids; and the need to decide what level of accuracy justifies using the iPSC-derived neural tissue system. (Some of which may also occur in clinical practice). Below we examine each issue in turn, discuss considerations and provide recommendations.

3.1: Risks and burdens related to collection and use of biological samples

Biological samples for the iPSC-derived neural tissue system may be blood or skin samples, so collection need not be onerous or dangerous. Ethical concerns have been raised surrounding tissue sample donation where samples might be used for purposes other than those for which they were initially collected. In most jurisdictions human tissue cannot be sold, and donors retain some rights over how their tissues are used and consent to any uses (Boers et al 2016; Dickenson 2013). In the iPSC-derived neural tissue system, cultures may be destroyed during the process of exposure to different drugs. Unless there are specific reasons to keep some samples, there seem to be no ethical issues arising.

3.2: Risks related to data

The research will gather and generate clinical and biological information on individuals. Particularly at early stages there may be reasons for researchers to genetically sequence samples since research may intersect with other iPSC research to understand epilepsy. There are possibilities of harms to individuals if their biological data does not remain private, for example genetic discrimination if employers think epilepsy will impact on people's work (see e.g. Newson 2012, 130). There remain stigma and discrimination

surrounding epilepsy (Shostak and Ottman 2006), so it is possible data collected in this research could have such impacts.

Privacy concerns can be addressed by deidentification, consent, and protocols to ensure data security (Cohen et al 2014). Deidentification may be problematic in this research, since it will involve clinical data that could identify individuals even if other identifiers are removed, and there could be reasons to notify research participants of results of research relevant to their ongoing treatment (e.g., if the iPSC-derived neural tissue system is highly successful donors to early-stage research might benefit from knowing results of their modelling). Thus research protocols should ensure high standards of data security, and consent procedures should make clear risks associated with breaches.

If the iPSC-derived neural tissue system generates genetic data, it might result in increasing patients' knowledge of the cause of their epilepsy. Self-understanding in this regard can significantly change the experience of living with epilepsy, and interact with mechanisms of stigma and with family relations (Shostak and Ottman 2006). Neurologists using the iPSC-derived neural tissue system could consider referring patients to genetic counsellors or other social supports in cases where this may arise. Similarly, data might identify genetic risks relevant not only to the individuals in the study but to their family. This could raise issues as to whether this data should be revealed to family members or whether there is a 'right not to know' (Berkman and Hull 2014). Since individuals in studies would already know they are epileptic, families may already suspect some genetic disposition, so additional risks from participation do not appear high. However researchers might include protocols for revealing new genetic information to participants, perhaps including referrals to genetic counsellors where appropriate.

3.3: Health risks

Where research involves requesting participants to delay beginning or change treatment, it poses potentially significant health risks, arising from the risks of seizures. There are several ways to minimise these risks. Early studies for development and calibration of models could draw on retrospective clinical data about patients' responses to treatment regimens to which they have already been exposed. Use of retrospective data means the research will not require participants to alter their treatment. It also rules out the possibility of participants benefitting directly from the research participation. Participants should be carefully informed of this during the consent process to avoid therapeutic misconception (the mistaken view that research participation can have therapeutic effects; surprisingly difficult to clearly communicate to participants (Widz et al 2015)) and ensure consent is valid.

However, despite the risks there are reasons to use prospective clinical data, at least at later stages of research, to avoid biases. Prospective studies might randomise patients to treatment selection either via the iPSC-derived neural tissue system or through standard clinical procedures, so that the system is benchmarked against current practice. Potential study populations include three patient groups whose potential for risks from research participation will differ: those newly diagnosed, those who benefit from their current treatment but still experience seizures, and treatment refractory patients.[5] Patients on medication regimens of some benefit would risk worse health outcomes on the new regimen or could suffer from seizures while changing from one treatment regimen to another (which may involve delays for medication wash-out and onset). Newly diagnosed

[5] These groups may also be further broken down in particular studies, for example to reflect whether the cause of epilepsy is known, or where known, epilepsy type.

patients, if in the active arm of a randomised trial, would risk suffering from seizures while awaiting results of the iPSC-derived neural tissue system, as tissue cultures are grown and tested. The delay in beginning treatment could mean participants suffer seizures that might have been avoided, given many patients do benefit from first-line treatment.

Thus there are ethical reasons to favour trialling the system prospectively first among treatment refractory patients, who might also be more willing to accept the burdens of research participation. However, where potential participant populations are small, feasibility might be affected if studies are limited in such a way; and it is possible treatment refractory patients are not representative of the whole patient population. In addition, excluding other potential patient groups from research entirely might be considered paternalistic. We propose then that there is a presumption in favour of running first prospective studies with treatment refractory patients, but if this is not feasible that inclusion of patients in other categories is considered.

3.4: Vulnerable populations

Epilepsy is most commonly newly diagnosed in children and older adults (Epilepsy Society 2018). Research with children is often more ethically complex than with adults, since children cannot provide informed consent. There are jurisdictional differences in how these difficulties are navigated, but consent may be provided by a parent or guardian, and it may be appropriate to expect that children provide 'assent' (indication from someone unable to legally consent that they are willing to participate) (Spriggs and Gillam 2008).

Furthermore, among children with epilepsy, there are higher rates than in the general population of autism spectrum disorder and intellectual disabilities. Among older adults, epilepsy may be comorbid with dementia. These conditions have implications for

obtaining informed consent. If these populations are included in trials, researchers will need to consider jurisdictional requirements for research with vulnerable populations. Populations thought to be vulnerable should not be simply excluded from research for their own protection. Immediate exclusion is inappropriately paternalist, and can result in lack of research data on those populations, leading to worse health outcomes for its members in the longer term (Shivayogi 2013). However, protection measures have been developed, including protocols for assessing capacity to consent, authorising substitute decision makers where needed, reevaluating consent at several points during studies, and individual risk/benefit assessments for potential participants who are particularly vulnerable (Shivayogi 2013; NIH 2009).

3.5: iPSC-derived neural organoids

As noted above, ethical concerns have been raised about neural organoids and capacities for conscious experience or suffering (Farahany et al 2018; Sawai et al 2019, Koplin and Savulescu 2019; Lavazza and Massmini 2018, Munsie et al 2017). Even if unintentional, given neural organoids' ability to self-organise and that they recapitulate features of early foetal brain development, as technology develops neural organoids may develop capacities associated with conscious experience. Capacities for consciousness and for suffering are tied to having moral status – to being a subject to which other agents may have ethical obligations, rather than an object that may be treated as an instrument. If neural organoids were to develop the capacity to suffer or for higher cognitive functioning, their welfare would need to be taken into account. This concern is speculative; at present organoids do not have these capacities and their use should be regulated according to existing frameworks for stem cell and human biospecimens (Sawai et al 2019; Hyun et al 2020;

Koplin and Savulescu 2019). Nonetheless if organoid culturing progresses so that they may come to have such capacities, it might be problematic to develop and then destroy organoids for the purpose of guiding clinical decisions; additional procedures such as screening of neural organoids for consciousness may need to be employed (Koplin and Savulescu 2019) and new considerations related to donor consent would need to be taken into account (Lavazza 2018). An additional difficulty is identifying and determining the presence of consciousness in neural organoids (Lavazza and Massimini 2018; Shepherd 2018), prompting calls that a precautionary approach be taken with respect to the use of neural organoids (Koplin and Savulescu 2019; Sawai at al 2019). These considerations provide reasons to prefer use of other types of neural tissue culture, or organoids that do not have these capacities.

3.6: Setting an accuracy requirement

A more novel ethical issue is that a decision will need to be made about what level of predictive accuracy should be required to justify the risks of a prospective trial, and to justify using the iPSC-derived neural tissue system in clinical practice. Intuitively, we would require the iPSC-derived neural tissue system to do better than current practice at matching patients to a beneficial first treatment regimen. This intuition reflects the principle of beneficence, which requires that clinicians act in the best interests of the patient. However, there are several complicating factors. The first has to do with timing of delivery of an effective treatment for patients who are suffering from seizures and uncertainty. The second relates to the nature of the evidence comparing use of the system with current practice – this evidence will be general and statistical, rather than patient-centred. We discuss these two challenges below.

First, timing is a significant issue. While it is not unusual for patients to try several treatments before an effective regimen is found, many do respond to first-line treatment. For these patients, current practice provides a faster route to a satisfactory treatment regimen than waiting for test results from the iPSC system. A precise figure for responsiveness to first-line treatment is difficult because there is controversy over when to begin pharmacological treatment, and the definition of epilepsy was recently changed from having had at least two to having had one seizure (Scheffer et al 2017). One study reported that 49% of newly diagnosed patients became seizure-free on their first regimen (Brodie et al 2012) and an older study reports 47% (Kwan and Brodie 2000). These statistics suggest that the iPSC-derived neural tissue system should have at least a 50% level of accuracy.

In our view, however, a higher accuracy should be required to justify the additional risks and burdens of waiting for results from the iPSC-derived neural tissue system before starting a first treatment, as well as any privacy or consent risks associated with use of the system. This position is, moreover, supported by consideration of our second concern – the nature of the evidence likely to be generated by any clinical trial comparing treatment outcomes for patients under current practice with outcomes for patients using the iPSC-derived neural tissue system.

The underlying difficulty is that, although statistical comparison to standard practice might provide guidance, such comparisons fail to reflect the different preferences of individual patients. For some patients, delayed treatment might be a small burden that they are happy to put up with, whereas for others the delay might lead to anxiety or significant negative consequences in their personal and work lives. Identifying a general level of accuracy at which this would be adequately achieved will involve value judgements balancing the benefits to those who are assigned a more beneficial treatment or assigned to

treatment more quickly, against harms to those whose test results are inaccurate or who delay starting treatment. As such, we not only recommend that the system should be substantially more accurate than current practice, but that settling on an appropriate level of accuracy should involve consultation with patient groups as well as specialist clinicians and researchers, to ensure that patient concerns are fully represented and considered.

[Table 3 here]

4: Ethical issues if adopted in clinical practice

In this section we examine issues related to the potential for the system to identify the cause of a case of epilepsy or be used in prenatal screening, and effects on clinical decision-making and clinician-patient communication. We argue that consideration of the iPSC-derived neural tissue system helps pinpoint a neglected issue in need of recognition in the ethics of PM: that whilst PM tends to represent treatment decisions as solely or ideally directed by biomedical information, treatment decision-making should take other facts about individuals into account. This issue is little noted as yet in the ethics of PM literature, and is likely to arise in other PM strategies and applications.

4.1: Prenatal screening

Since the system could be used on foetal tissue, a potential use is to screen foetuses for future risk of genetic epilepsy. If there is family history of epilepsy potential parents could request screening with a view to providing early intervention. This might also identify cases of future treatment refractory epilepsy, and result in parents terminating pregnancies. The

system might also be used to test embryonic material as a form of preimplantation testing associated with IVF, so that potential parents select away from implantation of foetuses with higher risks of treatment-refractory epilepsy. The iPSC-derived neural tissue system could thus raise issues of when such decisions about which future children exist are justifiable and whether states can or should intervene in parental decisions, which have been debated in relation to other forms of prenatal screening and preimplantation genetic diagnosis (PGD) (e.g., Mills 2011; Nelson 1998; Cameron 2003).

Many regard such screening for 'medical purposes' – to prevent births of people with serious diseases – to be acceptable (Robertson 2003). Controversy remains over their use for clearly non-medical reasons (such as sex-selection), and cases that may or may not be seen as 'medical' (such as preventing the birth of people with disabilities or intersex variations (Sparrow 2013)). Genetic epilepsies seem likely to be regarded as medical conditions by many. However, some advocates consider epilepsy a category of neurodiversity, and some epilepsy sufferers report positive aspects to their condition (such as feelings of euphoria associated with seizure (de Souza 2018)). The 'expressivist critique', that preventing birth of people with particular conditions could perpetuate discrimination and stigma surrounding a condition, may thus apply in the case of epilepsy.

We do not defend a particular position on this ethical issue given that the potential for prenatal testing is less immediate than other ethical issues discussed and given that ethical and regulatory debates relating to all forms of prenatal screening are at an early stage. These factors would make any position we take on the issue premature. In general, however, we support the inclusion of patient voices in the development of any policies, regulations, or ethical guidelines on prenatal screening for epilepsy. There is a need for further work on issues surrounding genetic testing and epilepsy more generally. While

guidelines have been developed by some epilepsy advocacy and professional organisations, we are not aware of any that consider prenatal or preimplantation testing issues specifically (Shostak and Ottman 2006; Poduri 2017). The need to develop these will increase as genetic knowledge about epilepsy increases, and as it becomes clearer whether such screening is likely as potential prenatal or preimplantation uses become a reality. And, notwithstanding any unique considerations identified by patient groups, we also support consistency in ethical approach and guidance across different forms of prenatal screening.

4.2: Effects on clinical decision-making

Treatment decision-making takes into account various factors other than biomedical information on the likely effectiveness of treatments. This can include practical factors, such as financial costs, or the difficulty of a treatment regimen and the patient's capacity to meet it; and clinical factors, such as side-effects or comorbidities. The iPSC-derived neural tissue system would provide only biomedical information about likely effectiveness and may not provide much information on potential side effects, but could affect treatment choices in several ways, not all of which are desirable. As we argue below, effort will be required to mitigate harmful forms of dependence or over-reliance on the iPSC-derived neural tissue system.

Many people are enthusiastic for technological solutions, and the limitations of the iPSC-derived neural tissue system may be difficult to communicate to patients. It is thus possible treatment decisions will over-rely on it, such that other factors are not given enough weight. Yet these other factors can be important for patients' overall health and wellbeing (e.g., if a patient cannot tolerate side-effects), and relevant to the effectiveness of the chosen therapy (e.g., if a patient cannot easily comply with a complex dosing schedule).

If the iPSC-derived neural tissue system came into common use, insurers or national health systems might come to depend on it in their reimbursement decisions. At the extreme end, they might refuse to pay for treatments the system does not indicate as highly probable to work for a patient (Smart et al 2004, 327). Thus, systemic uptake of the iPSC-derived neural tissue system might block access to some treatments – even in cases where those treatments might have had some benefit for a patient, or might even have been optimal for a patient in view of other clinical or practical factors such as side effects. Further, availability of the system might impact on how clinician responsibility for decisions is regarded (Van Delden et al 2004, 315). Clinicians who prescribe something different from the recommendations of the iPSC-derived neural tissue system might be vulnerable to being held liable for adverse events. Resulting fear of litigation could influence clinicians to follow the results of the iPSC-derived neural tissue system, even where good reasons exist, on balance, to choose other treatments. Overall, these considerations suggest that explicit acknowledgement of the type of information provided by the iPSC-derived neural tissue system must be included in guidance and regulations about its clinical use – that is, it must be clearly acknowledged to provide only biomedical data, to be used alongside patient-centred considerations including personal circumstances and acceptability of side-effects to make treatment decisions.

This raises a point more generally applicable to PM: it is often presented as though it will enable clear allocation of patients to most effective treatments based on detailed and sophisticated patient-specific biomedical information. However, treatment decisions should take into account other factors relating to individuals, including both medical and non-medical individual circumstances. In attempting to make medicine more personalised, we should keep in mind the importance of the kinds of 'personalisation' that already take place

in the clinic in considering non-biomedical factors, especially in view of the tendency to regard biomedical data as more objective and compelling.

A related concern is that, by moving treatment decision-making towards a more technologically-focussed model, there is a danger of reinforcing a predominantly biomedical picture of patients. Increasing use of technologies in medical practice can enforce a biomedical focus that can dehumanise patients, by encouraging clinicians to treat patients as physical objects with dysfunctioning parts, rather than as persons (Savard 2013; Vogt et al 2016; Van Delden et al 2004). While patients are indeed both, such a focus can alter how clinicians treat patients – such that trust, empathic engagement, and communication become more difficult. This is an ethical concern in itself, and can also lead to worse health outcomes. It may reduce quality of patient-clinician communication, so that clinicians are less likely to be aware of life situations that can impact on treatment decisions, and patients are less likely to have good understanding of their condition and treatment, lowering compliance (Hunter 1991). Since personalising treatment decisions actually *requires* attention to non-biomedical factors about individuals, it will be best supported by good clinician-patient relationships which enable information on such factors to be exchanged effectively in the clinical encounter. Yet, the PM literature tends to represent treatment decision-making as reliant only on biomedical information. This further underscores the importance of our recommendation that the iPSC-derived neural tissue system be considered indicative, not determinative of treatment. In addition, postmarket studies might assess overall alterations in patterns of treatment decisions and patient outcomes, compared with current methods of selecting treatments, and effects of using the iPSC-derived neural tissue system on clinical relationships and communication. If information the

system provides is outweighed by other factors in a significant proportion of cases, this might reduce its clinical usefulness.

5: Conclusion

iPSC-derived tissue cultures usable as patient-specific predictive models represent a novel method for informing clinical decision-making. Some of the issues faced by researchers are not new, and researchers will be able to draw on established protocols and procedures to deal with them. The novel issue of deciding on what level of accuracy justifies use of the system requires more research including engagement with the affected population. Issues related to prenatal screening or PGD are likely to overlap with existing work on such screening, but more attention to these in relation to epilepsy is needed. Further, consideration of this case helps identify an issue as yet little discussed in relation to the ethics of PM: that personalised medicine tends to represent treatment decisions as though they are (or should be) directed only by biomedical information, and this belief in itself could negatively affect clinician-patient communication and relationships. Treatment decision-making takes place in context and must take into account factors beyond biomedical indications if it wishes to best link individuals to specific treatments, indicating the need for robust clinical communication and relationships.

References

Antill-O'Brien N, Bourke J, O'Connell CD. 2019. Layer-by-layer: The case for 3D bioprinting neurons to create patient-specific epilepsy models. *Materials* 12:3218. doi:10.3390/ma12193218.

Berkman BE, Hull SC. 2014. The 'right not to know' in the genomic era: Time to break from tradition? *AJOB* 14(3):28-31.

Boers SN, van Delden JJM, Clevers H, Bredenoord AL. 2016. Organoid biobanking: Identifying the ethics. *EMBO Reports* 17(7):938-941.

Brey PAE. 2012. Anticipatory ethics for emerging technologies. *Nanoethics* 6:1-13.

Brodie MJ, et al. 2012. Patterns of treatment responses in newly diagnosed epilepsy. Neurology 78(20): 1548-1554.

Brown MT. 2009. Moral complicity in induced pluripotent stem cell research. *Kennedy Institute of Ethics Journal* 19(1):1-22.

Cameron C. 2003. Is there an ethical difference between preimplantation genetic diagnosis and abortion? *JME* 29(2):90-92.

Cartwright, Nancy. 1983. *How the laws of physics lie*. Oxford: Oxford University Press.

Caulfield T, Scott C, Hyun I, Lovell-Badge R, Kato K, Zarzeczny A. 2010. Stem cell research policy and iPS cells. *Nature Methods* 7(1):28-33.

Chadwick R. 2014. The ethics of personalized medicine: A philosopher's perspective. Personalized Medicine 11(1):5-6.

Cohen IG, et al. 2014. The legal and ethical concerns that arise from using complex predictive analytics in healthcare. *Health Affairs* 33(7):1139-1147.

Crook JM, Wallace GG, Tomaskovic-Crook E. 2015. The potential of induced pluripotent stem cells in models of neurological disorders: Implications on future therapy. *Expert Review of Neurotherapeutics* 15(3):295-304.

Debray TPA, Vergouwe Y, Koffijberg H, Nieboer D, Steyerberg EW, Moons KGM. 2015. A new framework to enhance the interpretation of external validation studies of clinical prediction models. *Journal of Clinical Epidemiology* 68:279-289.

De Souza SM. 2018. Too much of a good thing: Overtreatment in epilepsy. *Journal of Evaluation in Clinical Practice* 24:1049-1054.

Dent C. 2012. A Regulatory Approach to the Question: Should Genetic Inventions be Patentable? *Journal of Law, Information and Science* 22(1):16.

Dickenson D. 2013. Me medicine vs. we medicine. New York: Columbia University Press.

DOH (Australian Government Department of Health). 2020. Stem Cell Therapies Mission. https://www.health.gov.au/initiatives-and-programs/stem-cell-therapies-mission.

Du X, Parent JM. 2015. Using patient-derived induced pluripotent stem cells to model and treat epilepsies. *Current Neurology and Neuroscience Reports* 15:71.

Eadie MJ. 2012. Shortcomings in the current treatment of epilepsy. *Expert Review of Neurotherapeutics* 12(12):1419-1427.

Epilepsy Society (UK). 2018. Facts and Statistics. https://www.epilepsysociety.org.uk/facts-and-statistics#.XtUM3C-r2XU, accessed 1/6/2020.

Farahany, NA, et al. 2018. The ethics of experimenting with human brain tissue, *Nature* 556(7702):429-432.

Feist KM, et al. 2016. Prevalence and incidence of epilepsy. *Neurology* 88:296-303.

Ferlazzo E, Sueri C, Gasparini S, Russo E, Cianci V, Ascoli M, De Sarro G, Aguglia U. 2017. Methodological issues associated with clinical trials in epilepsy. *Expert Review of Clinical Pharmacology* 10(10):1103-1108.

Fleck LM. 2010. Personalized medicine's ragged edge. *Hastings Center Report* 40(5): 16–18.

Gibbons MC, Foley MA, O'Halloran Cardinal K. 2013. Thinking inside the box: keeping tissue engineered constructs in vitro for use in preclinical models. *Tissue Engineering Part B* 19(1):14-30.

Heller M, Eisenberg RS. 1998. Can patents deter innovation? The Anticommons in Biomedical Research. *Science* 280(5364): 698-701.

Hilgartner S. 2018. Foundational technologies and accountability. *American Journal of Bioethics* 18(2): 63-65.

Hyun I, Scharf-Deering JC, Lunshof JE. 2020. Ethical Issues Related to Brain Organoid Research. *Brain Research* 1732:146653. doi:10.1016/j.brainres.2020.14665.

Jeong S, Kim S, Buonocore J, Park CJ, Welsh J, Li J, Han A. 2018. A three-dimensional arrayed microfluidic blood–brain barrier model with integrated electrical sensor array. *IEEE Transactions on Biomedical Engineering* 65: 431–439.

Johnson MR, Tan NCK, Kwan P, Brodie MJ. 2011. Newly diagnosed epilepsy and pharmacogenomics research: A step in the right direction? *Epilepsy and behaviour* 22:3-8.

Koplin JJ, Savulescu J. 2019. Moral limits of brain organoid research. *Journal of Law, Medicine and Ethics* 47:760-767.

Kwan P, Brodie MJ. 2000. Early identification of refractory epilepsy. *NEJM* 342(5):314-319.

Kwan P, et al. 2010. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 51(6):1069-1077.

Lavazza A. 2018. What (or sometimes who) are organoids? And whose are they? *Journal of Medical Ethics*

Lavazza A, Massimini M. 2018. Cerebral organoids: ethical issues and consciousness assessment. *Journal of Medical Ethics* 44(9):606-610.

Hunter KH. 1991. Doctor's stories: The narrative structure of medical knowledge. New Jersey: Princeton University Press.

Mills C. 2011. *Futures of reproduction: Bioethics and biopolitics*. Dordrecht: Springer.

Moradi S, Mahdizadeh H, Saric T, Kim J, Harati J, Shahsavarani H, Greber B, Moore JB. 2019. Research and therapy with induced pluripotent stem cells (iPSCs): Social, legal, and ethical considerations. *Stem Cell Research and Therapy* 10:341.

Morita Y, Okura H, Matsuyama A. 2019. Patent application trends of induced pluripotent stem cell technologies in the United States, Japanese and European applications. *BioResearch Open Access* 8(1):45-58.

Munsie M, Hyun I, Sugarman J. 2017. Ethical issues in human organoid and gastruloid research. *Development* 144:942-945.

Nadkarni S, LaJoie J, Devinsky O. 2005. Current treatment of epilepsy. *Neurology* 64 (Suppl 3): S2-S11.

National Institutes of Health. 2009. Research involving individuals with questionable capacity to consent: Points to consider. Available at https://grants.nih.gov/grants/policy/questionablecapacity.htm, 1/6/2020.

Nelson JL. 1998. The meaning of the act: Reflections on the expressive force of reproductive decision-making and politics. *Kennedy Institute of Ethics Journal* 8(2):165-182.

Newson A. 2012. Population screening. In Public Health Ethics: Key Concepts and Issues in Policy and Practice, ed A Dawson: 118-142. Cambridge: Cambridge University Press.

Ottawa Rules. 2020. Available at http://www.theottawarules.ca/ankle_rules, 28/5/2020.

Parikh RB, Obermeyer Z, Navathe AS. 2019. Regulation of predictive analytics in medicine. *Science* 363(6429):810-812.

Perucca E. 2008. Designing clinical trials to assess antiepileptic drugs as monotherapy. *CNS Drugs* 22(11):917-938.

Poduri A. 2017. When should genetic testing be performed in epilepsy patients? *Epilepsy Currents* 17(1):16-22.

Prainsack B. 2017. Personalized medicine: Empowered Patients in the 21st century. New York: NYU Press.

Rao MS. 2013. LULL(ed) into complacency: a perspective on licenses and stem cell translational science. *Stem Cell Research & Therapy* 2013 4:98.

Roberts M, Wall IB, Bingham I, Icely D, Reeve B, Bure K, French A, Brindley DA. 2014. The global intellectual property landscape of induced pluripotent stem cell technologies. *Nature Biotechnology* 32(8):742-748.

Savard J. 2013. Personalised medicine: A critique on the future of health care. *Journal of Bioethical Inquiry* 10:197-203.

Sawai T, Sakaguchi H, Thomas E, Takahashi J, Fujita M. 2019. The ethics of cerebral organoid research: Being conscious of consciousness. *Stem Cell Reports* 13:440-447.

Scheffer IE, et al. 2017. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 58(4): 512-521.

Scheerens H, et al. 2017. Current status of companion and complementary diagnostics: strategic considerations for development and launch. *Clinical and Translational Science* 10(2): 84–92.

Shepherd J. 2018. Ethical (and epistemological) issues regarding consciousness in cerebral organoids. *Journal of Medical Ethics* 44(9):611-612.

Smart A, Martin P, Parker M. 2004. Tailored medicine: Whom will it fit? The ethics of patient and disease stratification. *Bioethics* 18(4):322-343.

Sparrow R. 2013. Gender eugenics? The ethics of PGD for intersex conditions. *AJOB* 13(10):29-38.

Spriggs MP, Gillam LH. 2008. Consent in paediatric research: an evaluation of the guidance provided in the 2007 NHMRC National statement on ethical conduct in human research. *Medical Journal of Australia* 188(6):360-362**.**

Sterlini B, Fruscione F, Baldasarri S, Benfenati F, Zara F, Corradi A. 2020. *International Journal of Molecular Sciences* 21:482.

Steyerberg EW. 2019. *Clinical prediction models: A practical approach to development, validation, and updating, 2nd Edition*. Dordrecht: Springer.

Steyerberg EW, et al. 2010. Assessing the performance of prediction models: A framework for some traditional and novel measures. *Epidemiology* 21(1):128-138.

Trusheim MR, Berndt ER. 2015. The clinical benefits, ethics, and economics of stratified medicine and companion diagnostics. Drug Discovery Today 20(12):1439-1450.

Van Delden J, Bolt I, Kalis A, Derijks J, Leufkens H. 2004. Tailor-made pharmacotherapy: Future developments and ethical challenges in the field of pharmacogenomics. *Bioethics* 18(4):303-321.

Vergouwe, Yvonne. 2003. *Validation of clinical prediction models: Theory and applications in testicular germ cell cancer*. Rotterdam: Erasmus University.

Vogt H, Hofmann B, Getz L. 2016. Personalized medicine: Evidence of normativity in its quantitative definition of health. *Theoretical Medicine and Bioethics* 37: 401–416.

Walker LE, Mirza N, Yip VLM, Marson AG, Pirmohamed M. 2015. Personalized Medicine Approaches in Epilepsy. *Journal of Internal Medicine* 277(2):218-234.

Walker MJ, Bourke JL, Hutchison K. 2019. Evidence for personalised medicine: Mechanisms, correlation and new kinds of black box. *Theoretical Medicine and Bioethics* 40(2): 103-121.

Widz CW, et al. 2015. Why is therapeutic misconception so prevalent? *Cambridge Quarterly of Healthcare Ethics* 24(2):231-41.

World Health Organization. 2019. *Epilepsy: A public health imperative*. Geneva, World Health Organization.

Zarzeczny A, et al. 2009. iPS Cells: Mapping the Policy Issues. *Cell* 139(6):1032-1037.

Stage of research and development	Requirements potentially raising ethical issues
Development stage	• Biological samples • Clinical data (small sample) • Possible use of neural organoids
Calibration stage	• Biological samples • Clinical data (larger sample) • Decision as to what level of predictive accuracy is acceptable
Validation stage	• Biological samples • Clinical data (larger, preferably distinct sample) • Preference for prospective data and to limit to specific epilepsy type (if feasible)

Table 1. Requirements of research and development process raising potential ethical issues

Possibilities	Targets of ethical concern
iPSC-derived neural tissue system provides probabilistic information on patients' reactions to different treatments	• Possible restricted access to treatments
iPSC-derived neural tissue system is used in prenatal/ preimplantation screening	• Issues of decisions about future children, parental autonomy, and potential to increase stigma or discrimination
iPSC-derived neural tissue system effects more biomedically-focused clinical decision-making	• Reduced clinical attention to non-biomedical factors in the clinic • Effects on clinician-patient communication

Table 2. Potential ethical issues of the iPSC-derived neural tissue system adopted into practice

Ethical issues	Suggestions and considerations
Risks and burdens relating to collection and use of biological samples	• Avoid retaining any biological samples, or if there is reason to do so ensure this is explained in consent procedures

Risks related to data	• Ensure high standards for data security • Consent procedures should include information on risks associated with data security breaches • Include protocols for revealing any new genetic information generated to patients
Health risks	• Use retrospective study designs at early (development and calibration) stages • Ensure participants are made aware they cannot benefit directly from the research within retrospective studies • Prospective trials could preference treatment refractory patients, or consider including newly diagnosed patients or patients gaining some benefit from current medication regimens if excluding these groups impacts on feasibility or patients consider exclusion paternalist • If newly diagnosed/currently treated patients are included, robust consent procedures to ensure patients understand risks
Vulnerable populations	• If studies include children, study designs could include protocols for parent/guardian consent and participant assent • If studies include members of vulnerable populations (e.g. people with autism spectrum disorder or dementia) protection measures should be adopted, e.g. proxy consent protocols; protocols for assessing participant consent; consent reevaluation during trial; and risk/benefit assessments for individual participants
Possible use of organoids	• Continue to assess need for ethical restrictions on research use of organoids as organoid technology develops • Prioritise development of the iPSC-derived neural tissue system that uses other types of tissue culture or organoids that do not have capacities for consciousness or suffering
Setting accuracy requirements	• Consideration of accuracy in determining a beneficial treatment in current practice and (for prospective studies) clinical equipoise • Researchers to consult with the affected population and specialist clinicians/researchers in making decisions about desired accuracy levels

Table 3. Ethical issues arising during research and development

Ethical issues	**Recommendations and considerations**
Application of the system in identifying aetiology or pre-natal screening	• Recognise the impact on patients of new information about epilepsy cause, and utilise referrals to genetic counsellors or other supports • Develop guidelines surrounding the use of the iPSC-derived neural tissue system (along with genetic tests

	for epilepsy) for prenatal or preimplantation diagnosis if/as such testing becomes available
Effects on clinical decision-making and clinician-patient communication	• Treat results of the models as indicative rather than determinative in clinical decisions • Postmarket studies to assess impacts on clinical decision-making and overall health outcomes

Table 4. Ethical issues if the system is adopted in practice