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Great Expectations: Autism Spectrum Disorder and Induced Pluripotent Stem Cell Technologies

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Abstract New applications of iPSC technology to research on complex idiopathic conditions raise several important ethical and social considerations for potential research participants and their families. In this short review, we examine these issues through the lens of emerging research on autism spectrum disorder (ASD). We begin by describing the current state of iPSC technology in research on ASD. Then we discuss how the social history of and current controversies in autism research combined with the emergence of autism-specific iPSC biobanks indicate an urgent need for researchers to clearly communicate the limitations and possibilities of iPSC research to ensure research participants have the ability to provide fully informed, voluntary consent. We conclude by offering recommendations to bolster informed consent for research involving iPSC biobanks, both in the specific context of ASD and more broadly.

Keywords Induced pluripotent stem cells · Human embryonic stem cells · Autism spectrum disorder · Biobanks · Ethics · Informed consent · Patient autonomy

Introduction

Induced pluripotent stem cells (iPSCs) have attracted the attention of researchers, policymakers, and ethicists since Takahashi and Yamanaka first demonstrated that somatic cells could be reprogrammed to a pluripotent state via the induction of four genetic factors: Oct3/4, Sox2, c-Myc, and Klf4 [1]. In theory, these pluripotent cells have the ability to differentiate into all cells and tissues of the human body [2]. Unrestrained by some of the ethical and policy limitations of human embryonic stem cells (hESCs), iPSCs have the potential to become powerful multipurpose tools for disease modeling, drug discovery, and for research on conditions that lack a good animal model and for which a tissue sample cannot be obtained [2, 3]. The long-term advantage of this technique is that iPSC lines may eventually yield therapies that are an identical genetic match to the patient, fulfilling one important promise of personalized medicine. Though iPSC technology has so far been limited to studies of simple monogenic conditions, several recent successes have suggested a broader application to research on complex idiopathic conditions, most notably autism spectrum disorder (ASD).

Autism spectrum disorder, as defined in the DSM-5 [4], refers to four previously separate neurodevelopmental diagnoses including autism, Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS). Over the past two decades, ASD has gone from relative obscurity to becoming a focal point of political, media, and public attention. This change can be attributed in part to rising prevalence rates, with current CDC estimates showing 1 in 88 individuals affected by the condition [5]. Through the efforts of autism advocacy groups, ASD is now considered a national health priority in the United States, with government and private funding in excess of $400 million in 2010 [6]. Public interest, activism, and expectations for biomedical research on autism are at an all time high, underscoring the need for an effective informed consent process to ensure these expectations are in line with reality.

With respect to potential research participants who are autistic and their families, ASD research involving iPSCs raises several important ethical and social considerations. In

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this short review, we begin by describing the current state of iPSC technology in research on ASD. Then we discuss how the social history of and current controversies in autism research combined with the emergence of autism-specific iPSC biobanks indicate an urgent need for researchers to clearly communicate the limitations and possibilities of this line of research to ensure research participants have the complete ability to provide fully informed, voluntary consent. We conclude by offering recommendations to bolster informed consent both for ASD research involving iPSCs and for biomedical research utilizing this technology more broadly.

The State of iPSC Technology

Though the application of iPSC technology in biomedical research varies across studies, all iPSC research involves the following steps: (1) the introduction of reprogramming factors into somatic cells of patients to generate iPSCs and (2) the differentiation of patient-specific iPSCs into specialized cell and tissue types for later use in disease modeling, drug discovery and screening, etc. [7]. For iPSC-derived disease models to be effective, they must faithfully recapitulate disease-specific phenotypes, so it is essential there be a known phenotype for comparison to determine the validity of these models [8, 9]. Consequently, iPSC technology has thus far been limited to studies of conditions with known disease phenotypes, such as long-QT syndrome and spinal muscular atrophy [10, 11]. Though scientists acknowledge the theoretical appeal of applying iPSCs to work on genetically complex or idiopathic conditions like ASD, they have also expressed concern over the many and daunting practical challenges stemming from the lack of known disease signatures [9].

Furthermore, idiopathic syndromes are difficult to model because they originate from not-yet-identified genetic causes or from environmental factors, such as pollution, age, or life style, which are difficult to recreate in a laboratory setting. The difficulty arises not only from attempting to model a specific cellular behavior but also because interactions of different cell types in a complex organ like the brain can lead to a tuning of the cellular responses and, therefore, to an acceleration or an attenuation of the symptoms. Current differentiation protocols tend to achieve high yields of one cell type only (the cell type that is known to be affected by the genetic mutations) but are defective in respect to the formation of more complex tissue-like or organ-like 3D structures. This further complicates the assumption that iPSCs could readily be used to model a large variety of clinical conditions, including ASD.

Moreover, iPSC technology is still in its infancy. Challenges in iPSC derivation and differentiation must be resolved before it can be effectively employed in research on complex conditions like ASD. For example, numerous publications point to the increased variability as well as the reduced efficiency of differentiation in iPSCs versus hESCs [12–17]. This increased variability results from defects in X-chromosome inactivation and genomic imprinting, aberrant epigenetic reprogramming, and the presence of point mutations and copy number variation differences [3]. Though recent advances promise to reduce variability and increase efficiency in iPSC differentiation, research involving iPSCs requires the use of key disease signatures to access the integrity of iPSC derived cells—a particularly problematic requirement for genetically complex or idiopathic disorders. Furthermore, any cellular therapy will need rigorous testing through an FDA-approved or equivalent clinical trial, a process that could take many years. As of this writing, only two FDA-approved trials using pluripotent cells are underway in the United States, both of which involve hESCs and both of which are still in the early phases of research [18]. The first and only clinical trial involving iPSCs was just approved by the Japanese health minister in July 2013 [18]. Such hurdles must be overcome before iPSC technology can be realized as treatments for conditions like ASD.

Given these concerns, hESCs, edited in their genome to carry the specific various mutations causing ASD, have been considered as a possible alternative. The rapid development of molecular tools that allow the precise editing of the hESC genome, such as TALENs-based gene editing, are emerging as valid approaches to model diseases (with the caveats mentioned above) and to dissect the role that different mutations have in the appearance of a specific disease [19]. But this approach carries inherent limitations. It is true that hESCs might be better and more reliable cell sources to dissect the molecular basis of genetic disease. However, it would be difficult to use hESCs to reproduce studies that would factor in the genetic background of individual patients, especially those that might capture the nuance of development in a case-by-case manner. Given these limitations, iPSC technologies thus become convenient paradigms on which to imagine a future of personalized medicine.

iPSC Research and ASD

Recent successes in research on cardiovascular and neuromuscular conditions have led to a broader application of iPSCs to research on clinical conditions with more variable phenotypes like ASD [10, 11, 20–22]. Because the use of iPSC technology in disease modeling requires a known disease phenotype for validation of the cellular model, autism research involving this technology consists primarily of studies on monogenic cases, such as Rhett Syndrome, Fragile X Syndrome, and Timothy Syndrome, which constitute only 15 % of all diagnosed cases [23–26]. Furthermore, due to the heterogeneity of both monogenic and idiopathic forms of autism, these studies are directed more towards beginning to identify relevant cellular

characteristics than towards drug development and testing [20–24, 26].

For example, Rhett Syndrome (RTT) is an X-linked monogenic ASD that results from de novo mutations within the gene encoding for the MeCP2 protein; it is widely accepted that RTT neurons display fewer action potentials, decreased action potential amplitude, and peak inward current [21, 23]. Thus, the validity of an iPSC differentiated neuron for RTT can be determined by the presence or absence of these key phenotypic signatures. Then, by comparing large populations of iPSCs for monogenic forms of ASD from biobanks, researchers can begin to identify other relevant cellular features, which promises to advance our biological understanding of these heretofore behaviorally defined conditions [27]. While the application of iPSCs to basic research on ASD may yield valuable information regarding the biological underpinnings of the condition, it is highly unlikely that this technology will result in drugs or therapeutics—cellular or otherwise—for ASD in the near future. Because current research is informed by only 15 % of diagnosed cases and given the heterogeneity of the condition, it is statistically improbable that findings relevant to one form of ASD will be relevant to all, slowing the development of broad-scale drugs and therapeutics [25].

Ethical Implications

Indeed, though iPSCs may not be encumbered by the same ethical restrictions as hESCs, their use in research is not without ethical concern [28]. Since 2009, tissue samples for the development of iPSC differentiated cell lines for ASD have been collected from affected individuals, including both individuals with idiopathic forms of the condition and those with monogenic forms, and their relatives for storage in iPSC biobanks [29]. Large-scale procurement of iPSCs raises questions about the privacy interests of donors, especially with the advent of large-scale genome-wide association studies [28]. These practices combined with the high expectations surrounding iPSC technology raise questions about how scientists communicate with autistic tissue donors and their families to ensure they understand and have realistic expectations for the research in exchange for undertaking these risks, a necessary step in order to provide fully informed consent.

Informed consent is a cornerstone of contemporary research ethics and is defined in the 45 CFR 46 [30] by three essential features: (1) disclosing to potential research subjects information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research. The numerous ethical issues of biobanking informed consent have been discussed extensively elsewhere. These include: whether to disclose incidental findings, when researchers unintentionally discover that the donor suffers from some kind of condition or predisposition to disease [31]; the risks and benefits associated with maintaining an active linkage between cell lines and the donor's medical information [32]; the advantages and disadvantages of reconsent, when donors are given the opportunity to reconsider their commitment to take part in research [33]; and the rights of cell and tissue donors to withdraw from participation in research at a later time [34]. On this last question, a donor's decision to withdraw his or her consent might be impractical and lead to a wholesale disruption of a research project [28]. As we discuss more fully below, there is the potential for immortalized iPSC lines to be used indefinitely for future research that is not yet contemplated, making it difficult to obtain truly informed consent by traditional standards.

But there is a deeper nuance of consent not previously addressed. In the case of autism research involving iPSCs, unchecked and pervasive public optimism may prevent research participants from fully understanding the limitations of current research and, thereby, rationally evaluating the possible risks and benefits of participation. This optimism is likely intensified by the media hype surrounding iPSCs. News headlines such as "Breakthrough with stem cells could 'end need for transplants" and "Stem cell study raises hopes that organs could be regenerated inside patients' own bodies" evoke the twin promises of personalized medicine and regenerative cell therapies [35, 36]. Others like "The pea-sized brains created from SKIN could lead to cures for disorders such as autism and schizophrenia" breathlessly portray groundbreaking stem cell discoveries as being applied in the near future even though iPSC technology is far from a therapeutic reality— especially for complex conditions like ASD [37]. As a result of this increased media attention, the public may incorrectly assume that expected research outcomes include therapeutics, or even a cure, for ASD. Consequently, potential research participants may have a skewed perception of the risks and benefits of research, jeopardizing their ability to provide proper informed consent.

This is all the more concerning given the history of stem cell tourism for ASD, which suggests that potential research participants—namely parents of autistic children—may overestimate the clinical value of iPSC technology out of a false sense of hope [38, 39]. Parents and their children have traveled great distances and at great expense for experimental stem cell treatments despite numerous warnings from physicians that these were unlikely to be effective [40, 41]. These and other instances demonstrate that parents tend to overestimate the benefits of stem cell technology while overlooking significant risks and may do so in the future with regards to emerging research involving iPSCs.

A skewed sense of the risk and benefits associated with clinical research may lead research participants to consent to this research where they otherwise would not [42, 43]. This is

especially true of desperate parents who seek immediate cures for their children with ASD. Moreover, in the specific case of autistic self-advocates and other proponents of the neurodiversity movement, this misunderstanding may actually prevent them from donating biological samples where they otherwise would. A newly emerged stakeholder group, these autistic self-advocates perceive ASD as resulting from natural variations in the human genome and seek to create a positive identity for autistic individuals. Their interests and aims conflict with the more traditional research goals prioritized by parent-advocates and researchers, which center on the treatment of autism and the elucidation of its causes [44–46]. Consequently, these individuals may opt out of donating tissues to iPSC biobanks from a misguided fear that their samples will be used primarily in research aimed at developing treatments for autism.

Conclusions and Recommendations

Together, these considerations underscore a need for researchers to be explicit and clear during the informed consent process. This is especially true as increasingly donors' samples are collected and stored in iPSC biobanks for future use rather than by individual researchers for specific studies [29]. As such, it is uncertain at the time of collection exactly what these samples will be used for as they can be applied to a myriad of research projects with difference procedures and aims [47]. Consequently, it is important that researchers do their utmost to ensure that potential research participants have a realistic understanding of the current state of research, including both its possibilities and limitations, so they can accurately evaluate the associated risks and benefits when providing informed consent.

We note that there is debate about how best to attain a "realistic understanding" of current research, especially when the research and its potential applications are rapidly changing. At the heart of the controversy is whether donors should be offered a list of choices of all the possible present and future scientific uses of their tissues (also called categorical or study-specific consent) or should instead agree to unspecified and general use of their materials for research. Established concepts of informed consent require participants to be informed about the specific details of each proposed research project [48]. Yet, because of the large number of research participants involved in iPSC banking studies and the many projects—known and unknown—that may use the cell lines in the future, getting specific consent from each and every donor is, from a practical perspective, nearly impossible.

We note that national and international research ethics policies are not uniform, and little agreement exists in the general public or among ethics and policy scholars about what form of consent is best for iPSC research. Existing recommendations for informed consent procedures for iPSC biobanks focus on alerting potential participants of the various research studies of what ways their samples could be used [47, 49]. The question is whether a broad consent can ever be truly informed and, therefore, satisfy well-established principles of consent. For some, providing detailed information about each project remains essential. Others suggest that because biobanks are for the public good, a generalized consent process can be justified [50].

With the above in mind, we offer three recommendations—centering on benefit, risk, and feedback—that would help realize the potential benefits of iPSC technology on ASD while safeguarding the ability of research participants to provide informed consent. First, when communicating the possible uses and hoped-for benefits of donating tissues, we suggest that researchers discuss the current state of iPSC technology and offer realistic scenarios about the future therapeutic applications for ASD with participants. We urge that researchers be clear about the probable, and not just possible, outcomes of research, so that participants can exercise their full autonomy in providing informed consent. It is especially important that researchers be clear about these with regards to the possibility of treatments for ASD arising from iPSC research, given the concerns expressed by parents of autistic individuals, autistic individuals, and autistic self-advocates. Given the fluid state of iPSC research and the uncertainty surrounding future therapeutic uses, a model of consent that explicates the planned research and the specific use of the tissues but is general about future research questions and possible cures and treatments seems prudent.

Second, we urge researchers to be clear about the potential risks and benefits associated with donating tissues. Besides including standard language about using cells and tissues for genetic research, provisions of confidentiality, and the ability to withdraw from the project at any time, consents should contain information specific to iPSC research and disease-based biobanking [51]. These include clear explanations of what samples or data can reasonably be withdrawn; that iPSC lines are immortal and may be stored for many years; that repositories holding the cells will distribute them to other researchers and medical professionals at universities, hospitals, research institutes, and companies around the world; and that because the lines are used to study disease, participants have the right to refuse future contact by investigators on matters of health or significant diagnostic findings. In additions, risks to participants arise if iPSC lines are distributed beyond the remit of the original research. Uncovering anomalies of potentially unknown clinical significance or identifying a disease state or predisposition can involve potential psychological risks and intrinsic harm, violating donor privacy. These risks cut both ways: participants should know that anonymous use of tissue or data means they will never know

specific information about findings related to their samples [50].

Third, we note that the iPSC biobank context creates deeper questions about designing proper informed consent. There is concern over the effectiveness of current consent mechanisms [52–54]. Biobanking experts feel that adding yet more information and rules to extant models of consents—such as requiring iPSC researchers to obtain new individual consent for each new use of a sample—would slow or obstruct the progress of research. They deliberate about whether consents are too burdensome, too complex, or whether withdrawal of consent will compromise the effectiveness of long-term studies [54]. We suggest that in the ASD context, a more productive approach would be to ask stakeholder groups, such as parents of autistic children and autistic self-advocates, what kinds of information they see as important to include in informed consent and what kind of control they would like over the use of long-lived lines of stem cells made from their cells and tissues. A rigorous sociological study that surveys stakeholders could go a long way to provide feedback to researchers and ethics professionals who struggle with ways to protect the autonomy of these research participants. Building tailored consents for ASD research participants with realistic calculations of benefit and risk might be one way to address this problem.

In sum, our recommendations can reach beyond the scope of autism research. It is time for the risks and benefits of iPSC biobanks to be properly communicated to donors of research materials. Stakeholders should be involved in deliberations regarding research aims, practices, and directions. These issues are pervasive within many disease advocacy communities. As such, we hope our recommendations will not only offer guidance to autism researchers utilizing iPSC technology but also provide a conceptual framework for iPSC research more broadly. Ethics must stay abreast with an ever shifting and rapidly advancing stem cell research landscape.

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Conflict of Interest The authors declare no potential conflicts of interest.

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