Stem cell research policy and iPS cells

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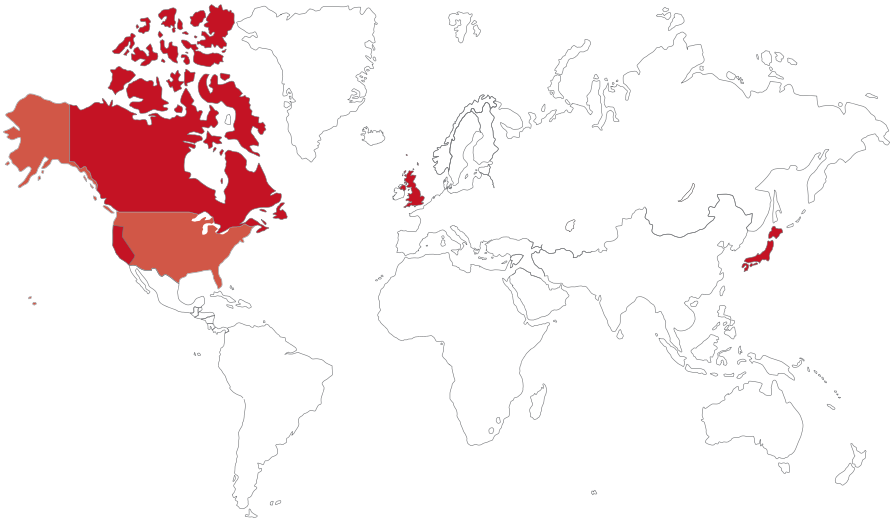
The field of induced pluripotent stem cells (iPSCs) will be subject to a wide range of laws and research ethics policies, many of which exist as a result of the controversies associated with research on human embryonic stem cells. Understanding this potentially complex regulatory environment will help iPSC research move forward and will inform future policy.

Few recent scientific advances have been met with as much enthusiasm as has the development of induced pluripotent stem cells (iPSCs). It was hailed as a breakthrough by both the scientific and policy communities—the former for the obvious scientific significance, and the latter due to the belief that iPSCs would make the ethical dilemmas that have previously dominated the field of stem cell research irrelevant.

There is no doubt that the development of iPSCs was a significant advance for science, and the research continues to progress rapidly[1]. However, it is a field that is emerging in the shadow of the deep, divisive and ongoing debates surrounding human embryonic stem cell (hESC) research. iPSC researchers will, to varying degrees, work in regulatory environments intended to address the moral controversies associated with embryo research and cloning technologies. The resulting challenges will inevitably be further coupled with the difficult task of navigating the often complex pathways of human tissue research, particularly for clinical uses. It can also be anticipated that jurisdictional differences in policy approaches and regulatory requirements will become increasingly important as researchers and cell lines move across national borders. These factors, among others, serve to create a potentially complex working environment for iPSC researchers and policymakers alike. For example, what existing regulations and ethics guidelines apply to iPSC work? Are there any significant differences in approaches between jurisdictions? How will existing differences affect interjurisdictional collaborations and sharing of materials? Given the speed at which the domain of iPSC research is growing (including the introduction of new researchers to the stem cell arena), focused consideration of these issues is timely and vital for the efficient and ethical development of the field.



Jurisdictions covered in the analysis.

In this paper we briefly review how iPSC research fits into current regulatory environments in Canada, California (as an example from the United States), the UK and Japan, and at the international level. We explore common themes and points of conflict and reflect on the broad diversity of approaches reflected in these jurisdictions. Our overall aim is to highlight current realities and challenges and to ground further work on future policy directions.

The policy context

Before reviewing the regulatory environment, it is appropriate to briefly consider some of the potential policy challenges associated with iPSC work. Though iPSCs have often been framed as being free of major ethical and policy issues, this is not necessarily

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the case. Some of the potential issues in iPSC work are similar to those associated with hESC research, whereas others mirror the ethics challenges in other research domains, such as genetics. For example, because an iPSC will necessarily contain the genetic information of the donor—and, as a result, information about potential disease predispositions—there may be privacy concerns[2]. Also, consent issues are likely to emerge. iPSC lines could be used for decades for innumerable different studies around the world, some of which may not even have been conceived when the cells were donated. What kind of consent is required to make this ongoing work ethically and legally sound[3]? The right to withdraw from participation in research is a hallmark of traditional research ethics norms[4]. How should this right operate in the context of iPSC research? Can donors of cells for iPSC research withdraw their consent to participate at anytime? If so, must the resultant cell line be destroyed? Of course, the pluripotent nature of iPSCs also raises challenges, the most notable arguably being the possible use of human iPSCs to create gametes[5], which raises several issues, including the creation and destruction of human embryos. These and other issues highlight the need for oversight and regulation of this area. However, as we will see below, a coherent approach has yet to emerge.

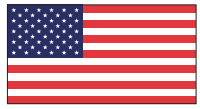
Canada

Canadian policy is dominated by the *Assisted Human Reproduction Act* (*AHRA*)[6]. In the context of stem cell research and cloning policy, the *AHRA* does two things: it criminally prohibits certain activities, including the creation of embryos for research purposes, somatic cell nuclear transfer, and germ line alterations, and it creates a regulatory framework along with an agency to administer the law.

As the *AHRA* is largely focused on "human reproductive material," it will probably not have much immediate relevance for researchers doing basic iPSC work. However, that status could change depending on the applications of the cells. If iPSCs are used to create germ cells, an embryo or a clone, then the *AHRA* would presumably apply. The last of those activities would be banned and the first two regulated by the agency. The *AHRA*'s prohibition of genetic manipulations that are capable of being passed on to descendants may also be relevant, depending, in part, on the method of iPSC derivation. Furthermore, the legislation's definition of "human reproductive material" is arguably impossibly broad. It covers "sperm, ovum or other human cell or a human gene, and includes a part of any of them." Could the agency use this definitional ambiguity to claim broader jurisdiction over all pluripotent cell lines? If so, the agency may have greater powers over iPSC research, and additional obligations under the *AHRA* could be imposed on all researchers in the field, not just those using iPSCs for the derivation of gametes.

In addition to federal law, there are national research ethics rules that are highly relevant to both current iPSC research, such as the creation of iPSC lines, and future areas of inquiry. Canadian iPSC researchers working in institutions that receive federal research funds (which includes most researchers in Canada) must comply with the national research ethics guidelines, including the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*[7] and the Canadian Institutes of Health Research (CIHR) *Updated Guidelines for Human Pluripotent Stem Cell Research*[8]. To obtain research approval, researchers must go through both a local research ethics board and, for some forms of research, the national Stem Cell Oversight Committee (SCOC). The CIHR guidelines cover all research involving human pluripotent stem cells—regardless of source. Therefore, Canadian iPSC researchers need to ensure they satisfy the enumerated consent requirements (namely, by obtaining consent from all sources and, for cadavers, some form of an advance directive containing the necessary consent to posthumous use of their tissue). In addition, when the work involves transplantation of iPSCs into humans or nonhuman animals, approval from the SCOC is required. The CIHR guidelines also, interestingly, contain an unambiguous requirement that all cell lines, other than autologous lines, must be anonymized. In addition, they state that clinical trials involving humans can only proceed if there "is overwhelming evidence from preclinical models for safety and efficacy," which will be relevant for any future clinical research.

United States (California)



iPSC researchers in the United States must contend with both national and state policy. There are significant state-by-state differences in US law. Therefore, by way of example, we describe the regulatory environment in California, a state that has been at the fore of stem cell policy and research, and that has a variety of regulations that are relevant to iPSC research. We note, however, that its approach is not necessarily representative of the situation in other US states.

At the national level, there are a variety of policies that have relevance for stem cell researchers[9,10]. From the perspective of iPSC work, the 2005 National Academy of Sciences (NAS) *Guidelines for Human Embryonic Stem Cell Research* have emerged as the most significant national research ethics policy. Indeed, they were amended in 2008 to specifically address human pluripotent lines from nonembryonic sources[11]. The report states that, in general, the derivation of iPSCs from nonembryonic sources does not raise policy concerns that are not already covered by the ethics rules used to govern the sampling of tissue from human subjects[12]. Basic iPSC work such as derivation of lines, therefore, requires no additional ethics oversight, which in the United States generally means no formal engagement with a stem cell research oversight committee (SCRO). However, the NAS report notes several controversial uses of iPSCs that do need additional regulation, such as the transplantation of the cells into human blastocysts or nonhuman primate embryos (prohibited), the transplantation of human iPSCs into nonhuman animals at any stage of development (requires additional ethics review) and *in vitro* experiments designed to yield human gametes (requires additional ethics review). In addition, investigators must apply the same informed consent standards for iPSCs that they would for hESC research, informing donors about how long the cells might be kept, if they will be used for human transplantation, and if the lines are to be made anonymous.

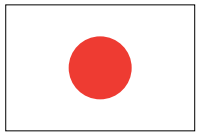
In addition to the NAS guidelines, iPSC researchers in California need to consider three overlapping sets of regulations: California Institute for Regenerative Medicine (CIRM) rules, state stem cell research guidelines and state law. First,

October 2009 amendments to the CIRM rules, which apply to researchers funded by CIRM, take a tiered approach to iPSC oversight[13]. If the researcher uses de-identified somatic cells or US National Institutes of Health (NIH) registry lines to create iPSCs, no additional SCRO oversight is required. Using identifiable somatic cells for iPSC work requires notification to a designated SCRO. But if the research involves clinical trials, introducing pluripotent lines into nonhuman animals at any stage, or the creation of human gametes, SCRO review is required for CIRM-funded research.

Second, the proposed amendments of the California Department of Public Health (CDPH) *Guidelines for Human Stem Cell Research*[14] address the oversight of stem cell research that is not fully funded through CIRM. Much harmonization exists among CDPH, CIRM and NAS guidelines on important issues such as donor consent and the research use of hESCs. In some respects, the CDPH guidelines are confusing in that they seem to expressly exclude iPSCs from their ambit but, at the same time, they also identify circumstances—such as when human pluripotent stem cells are introduced into nonhuman animals or into humans during clinical trials—in which research using iPSCs is prohibited or will require SCRO or institutional review board (IRB) committee review. Researchers should be sensitive to this apparent contradiction, which is likely an artifact of the fact that the authorizing law is aimed at hESCs.

Finally, investigators and regulators must grapple with the application of the state's statutory laws. The relevant legislation in California, Senate Bill No. 1260 (ref. 15), requires implementation of the CDPH guidelines and amends the *Health and Safety Code* to include oversight of "human embryonic stem cells, human embryonic germ cells, and human adult stem cells, including somatic cell nuclear transplantation." Though the statute references NAS and CIRM guidelines for hESC research, one of its consequences is that it adds the requirement of SCRO approval to some animal research and to clinical studies that previously only required IRB oversight. Further, subsequent changes to CIRM or CDPH rules have yet to find their way into law, though the amendments seem likely to go forward. Nevertheless, the regulatory field in California is in a state of flux at present, thus making it potentially confusing for iPSC researchers.

Japan



In Japan, a framework regulating stem cell research has been established over the past 10 years but does not at present apply to basic research using human iPSCs. The *Guidelines for Derivation and Utilization of Human ES Cells* were issued by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in 2001 (ref. 16). They allowed the use of frozen supernumerary embryos left over from fertility treatment, but required compliance with strict regulation, including a two-step review by institutional and governmental committees. In 2009, the guidelines were split into two: one part for the derivation and distribution of hESCs[17] and another for their use[18]. In the latter, the review system has been simplified so that only institutional review is required. For clinical research using stem cells, the *Guidelines for the Clinical Research using Human Stem Cells*[19] was brought into force in 2006 by the Ministry of Health, Labor and Welfare (MHLW) and at present deals only with clinical research using somatic stem cells.

At the moment, basic research using human iPSCs is reviewed by general institutional ethics review committees for research involving human subjects. Any projects that involve genome analysis also need additional review that considers the *Ethical Guidelines for Research on the Human Genome and Gene Analysis*, which MEXT issued in 2001 and amended in 2004. For clinical research using iPSCs, a new committee has been constituted within MHLW to consider a modification of the 2006 *Guidelines for the Clinical Research using Human Stem Cells*, which it plans to finalize in 2010. The modification would incorporate hESCs and iPSCs and ideally will respond to the unique issues raised by these areas of research.

Among these potentially controversial issues, research that aims at the production of germ cells from iPSCs is one topic that has been examined by the government. In February 2008, the government imposed a moratorium on research involving germ cell production, stating that Article 45 of the *Guidelines for Derivation and Utilization of Human ES Cells*, which prohibits research for germ cell production from hESCs, should also apply to human iPSC research. Subsequently, a task force was set up within the MEXT Bioethics and Biosafety Commission. In December 2008, the task force concluded that research involving production of germ cells from pluripotent stem cells (including both hESCs and human iPSCs) should be allowed with strict oversight, according to guidelines that will be established in the future, but that fertilization using these derived gametes should be prohibited. Other potential issues relate to experiments that graft human iPSCs into animal embryos; these are allowed, but implantation of the embryos into an animal uterus is prohibited.

UK

The regulatory structure in the UK is particularly complex with regard to stem cell research. The *Human Fertilisation and Embryology Act 1990*, as amended by the 2008 act (*HFEA*), regulates hESC derivation[20]. As they are not derived from embryos, iPSCs do not fall under the ambit of the *HFEA*, nor are they required to be deposited in the UK Stem Cell Bank. Rather, they are broadly governed by the *Human Tissue Act* (*HTA*)[21], which applies to "the removal, storage and use of any human material (organs, tissues and cells) from a human body that consists of, or includes, human cells, with the exception of hair and nails from a living person, and gametes and embryos (these are separately regulated by the HFE Act (2008)). Established cell lines and any other human material created outside the human body are excluded from the act." The *HTA* came into force in 2006 and, after the introduction of the *European Union Tissue and Cells Directives* (EUTCD) into UK law on 5 July 2007, the *HTA*'s reach extended to cover the regulation of cell lines grown outside the human body for "human application."

Work with iPSCs also requires approval from local ethics review panels and from the national Research Ethics Service (nRES), which focuses on informed consent. Several other regulatory bodies are engaged when the research moves to transplantation into nonhuman animals or clinical trials. The Home Office regulates animal experimentation, and the Gene Therapy Advisory Committee (GTAC), working with several government agencies, has UK-wide responsibility for the ethical oversight of proposals to conduct clinical trials involving gene or stem cell therapies, while the Medicines and Healthcare products Regulatory Agency

(MHRA) has practical oversight of the latter. A UK Regulatory Route Map for Stem Cell Research and Manufacture has been designed as "a reference tool for those who wish to develop a programme of stem cell research and manufacture, ultimately leading to clinical application" (http://www.advisorybodies.doh.gov.uk/genetics/gtac/InterimUKSCroutemap120309.pdf). This map, much of which seems likely to apply to iPSC work, reveals the highly complex—and potentially burdensome—nature of the regulatory structure governing stem cell research and application, which requires approval from multiple regulators.

The issue of informed consent bears particular consideration with regard to the regulation of iPSC research, given the unique properties of iPSCs in comparison to other human tissue samples. For example, there are no restrictions regarding the *in vitro* derivation of gametes in the UK. Moreover, the *HFEA* permits (under license) the creation of embryos from such gametes, although they cannot be implanted or maintained for more than 14 days. However, the standard consent given for human tissue samples, including those that would be used for iPSC derivation, is for unrestricted use in research, despite the likelihood that some individuals might not appreciate the future possibility of their biopsy being used to derive gametes and make embryos. In addition, it is at present unclear how donor consent for iPSC research will be regulated for situations in which obtaining informed consent is difficult or impossible, such as from children or mentally incapacitated donors. The *HFEA* recognizes the importance of being able to derive hESCs from embryos created by somatic cell nuclear transfer (SCNT) using cells from such individuals, to enable valuable research on a set of important genetic diseases. It also allows the use of cells from established tissue banks where the donors are no longer alive or are otherwise untraceable. It is debatable at the moment whether the same conditions apply to obtaining consent for iPSC derivation. This issue may arise as a cause of concern for UK researchers, who fear delays in obtaining approval for their work.

Last, it is worth noting that, because the *HFEA* requires that no license for embryo research be granted unless "any proposed use of embryos ... is necessary for the purposes of the research," future iPSC lines could conceivably affect the availability of licenses for further hESC research.

International policies

Given the increasingly global nature of scientific research, it is worth considering international policy statements relevant to iPSC research. While national norms, such as the NAS, can have great international influence, the International Society for Stem Cell Research (ISSCR) has produced a document, the *Guidelines for the Conduct of Human Embryonic Stem Cell Research*[22], specifically designed to have global application. These guidelines do not specifically address iPSC research, but they do address the use of human body cells (including both somatic cells and gametes) for the derivation of pluripotent stem cell lines. Drafted before the advent of human iPSCs, these guidelines were meant to apply to forms of stem cell research that would use differentiated human cells—such as skin cells—for SCNT. As such, iPSCs could be brought within the ISSCR Guidelines under a more general research classification that interprets iPSC research as essentially involving somatic cell donation for the development of new pluripotent stem cell lines.

The issue of how informed consent is addressed is a particularly clear example of the regulatory complexities facing iPSC researchers, and this is true from the international perspective as well. According to the ISSCR Guidelines, all body cell donors or their legally authorized guardians must give their contemporaneous informed consent for the use of the donor's somatic tissues in stem cell research—which would, therefore, include tissues donated for iPSC work. There are a few notable exceptions that pertain to the use of stored tissue samples. The ISSCR Guidelines state that tissue samples may be used for research without informed consent only if researchers procure somatic cells from a tissue bank whose consent documents specifically note nuclear reprogramming methods as one of the possible uses of the donor's tissues. Only in extremely rare cases may the requirement for specified informed consent be waived. In these exceptional cases (for example, a rare disease), there must be no reasonable and adequate alternative source for the unique characteristics of the tissue donor's somatic cells, such that another donor could be found who might offer contemporaneous informed consent.

Discussion

Although all of the reviewed jurisdictions have policies that are relevant to iPSC research, there are no comprehensive policies that were designed specifically to address this area. Most of the applicable regulatory frameworks were crafted to address other forms of stem cell research, such as work involving embryos and SCNT. Canadian law is largely the result of issues associated with research involving human embryos, gametes and SCNT[23]. In Japan, a country that has been a scientific leader in the iPSC field, the research community has only recently begun formal discussions about the potentially controversial issues associated with iPSC work. Even in California, the US jurisdiction that has arguably done the most specific policy work on point, the relevant guidelines were grafted onto or made to work within existing stem cell research oversight frameworks—leading to potential uncertainty about the consistency of their application. As is true in other areas of stem cell research[24], there appears to be at least some degree of policy discord between jurisdictions in the realm of iPSCs.

Does iPSC research really belong under a regulatory umbrella that was the result of the profound controversies associated with earlier stem cell research methodologies? Does iPSC research justify heightened oversight? Is it sufficiently different from other forms of tissue research so as to require specialized treatment? On the one hand, it could be argued that because iPSC research does not require the use of human embryos, it is inappropriate to lump it with other methods that cause so much social controversy. On the other hand, given that iPSCs have the potential (at least theoretically) to differentiate into a wide range of tissues, including germ cells, it could also be argued that many of the issues associated with hESC research and SCNT do endure. Although the regulatory response is far from consistent in the reviewed jurisdictions, on the whole it seems that emerging policy is largely informed by the latter perspective. When compared to hESC research, the methods used to initially create iPSCs may not be as ethically problematic or socially controversial. However, some of the uses of iPSCs once they have been created almost certainly are, which may justify more specific regulatory oversight. It seems logical for regulatory responses to iPSCs to map this distinction of derivation versus use of the cells.

This review of policies highlights several common themes (**Table 1**). Most jurisdictions emphasize the need for comprehensive

Table 1 | Emerging themes in regulation of iPSC research

	Canada	California (US)	UK	Japan	International (ISSCR)
Consent	Requires free and informed consent, provided voluntarily and with full disclosure of all information relevant to the consent	Requires specific and informed consent	Requires free and informed consent, although standard consent allows for unrestricted use in research. Not clear if informed consent requirement can be waived when donors are unable to give consent	Requires free and informed consent	Voluntary, contemporaneous and informed consent required (with a few exceptions for stored tissue samples)
Identity	Requires anonymity (for nonautologous lines)	Using identifiable cells requires notification to a designated SCRO	Unclear, although importance of phenotype/genotype relationships, and therefore traceability, is recognized	Use of identifiable cells possible, but requires IRB approval	Use of identifiable cells requires additional and comprehensive review
Use: derivation of human germ cells	Permitted, subject to regulation, but cannot create an embryo for research purposes; will trigger application of *AHRA*	Requires additional ethics review	No restrictions on derivation; can create (but not implant) an embryo, with a license; limit of 14 days *in vitro*	Permitted, subject to strict oversight; fertilization prohibited	Unclear or not addressed
Use: transplantation into humans	Requires SCOC approval	Requires additional ethics review	Subject to oversight, GTAC and MHRA approval	Requires additional ethics review; updated guidelines expected in 2010	Requires additional and comprehensive review
Use: grafting into nonhuman animals	Requires SCOC approval	Requires additional ethics review	Requires local ethics review and Home Office license	Requires approval and oversight	Subject to review, approval and ongoing monitoring
Clinical trials with humans	Requires overwhelming evidence from preclinical models for safety and efficacy[a]	Requires approval and oversight	Requires approval and oversight and overwhelming evidence from preclinical models for safety and efficacy[a]	Requires approval and oversight; regulation under development	Requires additional and comprehensive review

The wording for each jurisdiction is not standardized but is instead meant to paraphrase the relevant regulation or guideline, in order to capture subtle variations.

[a]Could make autologous clinical trials a challenge.

informed consent, a heightened research ethics review process for certain activities (such as the transplantation of iPSCs into humans and nonhuman animals) and caution regarding the use of iPSCs to develop germ cells. However, the degree to which these results were intended, as opposed to being an unforeseen consequence of policy choices made for different reasons, remains somewhat unclear. Indeed, this is an area where further research would be useful, especially since the justification(s) underlying policy positions become increasingly important when considering policy development and harmonization efforts.

In addition, some subtle yet significant conflicts are emerging between different jurisdictions. For example, the Canadian policies specifically require that iPSCs be made anonymous. In contrast, California expressly recognizes the use of identifiable tissue. This anonymity requirement may prove problematic for Canadians—for instance, when the work moves to the clinic. In such situations, identifiability may be required to facilitate recontacting the donor before clinical use[25]. It may be necessary to track the continuing health status of the donor or to obtain additional consent for a different use of the tissue. Also, the requirement for anonymity might make it difficult for Canadian researchers to work with iPSCs from different jurisdictions. From a policy perspective, such conflicting positions raise questions about the underlying rationales, which have implications for the anticipated direction of future policy development. Variations regarding consent standards and requirements also deserve further scrutiny. As is true for hESC research, when different jurisdictions have different standards regarding how specific consent must be, such discrepancies can create issues for international collaborations and movement of cell lines across jurisdictions.

Ideally, iPSC research policy should be scientifically informed and based on a principled consideration of the relevant issues. It should also be consistent with existing policies and their underlying rationales; however, given the lack of clarity underlying the justifications for many existing stem cell research laws, this could be a challenge. Other key issues that will become increasingly important as iPSC research moves forward include harmonization efforts between jurisdictions (to facilitate interjurisdictional collaboration), assessing the impact of potential policy conflicts (both between and within jurisdictions) and addressing the unique ethical issues that surround some of the prospective uses of iPSC technology. This field unquestionably carries both scientific potential and therapeutic hope, but it is important that any regulatory frameworks that emerge balance the understandable excitement with the need to progress in an ethically sound manner[2,5].

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