Ethical and Policy Considerations for A Pluripotent Stem Cell Resource Center 2011 Update

Summary of the April 29, 2011 Annual meeting of the CIRM Medical Accountability Standards Working Group

Los Angeles, California

June 28, 2011

www.CIRM.ca.gov

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Additional Resources:

Meeting notice and agenda: http://www.cirm.ca.gov/agenda_2011-04-29/standards-working-group

Meeting transcript: http://www.cirm.ca.gov/files/transcripts/pdf/2011/042911_SWG.pdf

WebCast: http://www.youtube.com/watch?v=KcLdRMVZ6pE

Standards Working Group: http://www.cirm.ca.gov/WorkingGroup_Standards

ETHICAL AND POLICY CONSIDERATIONS FOR A PLURIPOTENT STEM CELL RESOURCE CENTER 2011 UPDATE 1

Executive Summary

CIRM's mission is to advance stem cell research under the highest standard for the development of therapies and cures for chronic disease and injury. To advance this mission, the institute is sponsoring an initiative to support the development of induced pluripotent stem cell (iPSC) repositories. Repositories are designed to be resources where investigators – working collaboratively with academia, industry and patient advocacy foundations – can store and distribute iPSC lines for ongoing disease research and therapy development. Currently, CIRM envisions a two-step project:

Step One (NINDS Collaborative): Collaborate with National Institute of Neurological Disorders and Stroke of the National Institutes of Health and funded consortia to store, generate and distribute iPSCs for disease modeling and drug discovery in neurodegenerative diseases e.g., Huntington's Disease, Parkinson's Disease and Amyotrophic Lateral Sclerosis.

Step Two (CIRM-sponsored Repository): Fund an iPSC repository for disease modeling and drug discovery across additional disease areas to bank, and also generate, and distribute lines from California investigators.

In April 2011, the CIRM Standards Working Group (SWG) convened to discuss policy considerations related to the iPSC repositories project. Discussion centered around obligations to cell and tissue donors on three interrelated issues:

1. Informed consent for donation of cells and tissue,
2. Communication of research findings, and
3. Procedures for discontinuing participation and/or withdrawing

The SWG recognized that CIRM should continue to maintain policy harmonization with federal requirements and iPSC should not be subject to stricter standards than other types of comparable cell and tissue research.[1] Further, the existing policies adopted by CIRM, namely the federal Common Rule and associated guidance, provides a comprehensive framework for informed consent and withdrawal from research.

The SWG indicated that CIRM should utilize experience gained from the NINDS collaboration and initiate further research to develop optimal approaches for informed consent and communication of research findings in the context of cell and tissue repositories. Table 1 identifies considerations that should be taken in light of CIRM's current initiative.

[1] The SWG endorses certain special requirements, such as bans reproductive use of donor materials, consistent with the *The National Academies Guidelines for Human Embryonic Stem Cell Research*.

Table 1: Summary of Recommendations

SWG Recommendation	Step 1: CIRM NINDS Collaborative	Step 2: CIRM Sponsored Repository
Ensure comprehensive informed consent for donation of cells and tissue	Provide CIRM grantee institutions deriving iPSCs with details regarding partnership to support informed consent of donors. Consent protocols should reflect potential for deposit, long-term storage, and redistribution of lines.	Build on knowledge gained from step 1 to evaluate optimal language to obtain broad consent for future use consistent with established standards.
	Consider opportunities to survey prospective donors about (1) Informed consent for donation of cells and tissue, (2) communication of research findings, and (3) procedures for discontinuing participation and/or withdrawals.	Describe scientific aspects of research including (1) gene analysis, (2) any linkage to medical information, and (3) potential for re-contact. Indicate that donated materials may be utilized in studies not directly related to donors disease. Consider whether consent requirements for control samples may differ from donors with disease.
Encourage communication of research findings	Consider opportunities to document uses /publications involving deposited lines. For example, see International Stem Cell Registry.	Develop mechanisms for tracking use and aggregate results from scientific studies. Develop access mechanisms to support informed consent and to enable access to aggregate results by donors.
		Prospective donors should be informed of circumstances where re-contact would occur.
Develop clear procedures for discontinuing participation and/or withdrawing	Procedures should be consistent with the Common Rule and established NIH and OHRP guidance.	Develop withdrawal procedures consistent with Common Rule (see Table 2).
		Based on principle of "justified reliance" continued research use and distribution of transformed materials may be justified.
Ensure compliance with established CIRM policy requirements		Material transfer agreements should include provisions to require recipient to use materials consistent with CIRM's GAP / MES Regulations.

Introduction:

CIRM's mission is to advance stem cell research under the highest scientific and ethical standard for the development of therapies and cures for chronic disease and injury. To advance this mission, the institute is sponsoring an initiative to support the development of pluripotent stem cell (iPSC) repositories. Repositories are designed to be resources where investigators – working collaboratively with academia, industry and patient advocacy foundations – can store, generate new lines, and distribute iPSC lines for ongoing disease modeling and drug discovery research. The planning phase of this initiative included a series of workshops to evaluate scientific and ethics/policy considerations that should guide development efforts.

> *Ethical and Policy Considerations for A Pluripotent Stem Cell Resource Center* May 26, 2010: This report provides a preliminary assessment of ethics and policy issues related to the derivation and distribution of iPSC lines, and it serves to inform CIRM policy research.
>
> *Summary and Recommendations of the CIRM Human iPS Cell Banking Workshop* November, 17-18 2010: This report identifies two independent needs for cell repositories and provides consensus recommendations.

The Annual Meeting of the CIRM Medical Accountability Standards Working Group (SWG) was held on April 29, 2011. The SWG was asked to develop policy recommendations related to CIRM's proposal *iPSC Repository for Drug Development and Disease Modeling***.** This proposal outlines a two-step process for repository development.

> Step One (NINDS Collaborative): Collaborate with National Institute of Neurological Disorders and Stroke of the National Institutes of Health and funded consortia to store, generate new lines, and distribute iPSCs for disease modeling and drug discovery research in neurodegenerative diseases e.g., Huntington's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis.
>
> Step Two (CIRM-sponsored Repository): Fund an iPSC repository for disease modeling and drug discovery across additional disease areas to bank, generate new lines and distribute iPSCs from California investigators.

The Annual Meeting included a guest presentation titled *the Perspective of an iPS Donor Family Participating in Disease Research* followed by formal working group deliberations. The guest presentation served to illustrate ethics / policy issues that emerge in the operation of research repositories. The complete presentation may be viewed here:

http://www.youtube.com/watch?v=KcLdRMVZ6pE

Workshop deliberations focused on policy recommendations concerning three interrelated issues:

1. Informed consent for donation of cells and tissue,
2. Communication of research findings, and
3. Procedures for discontinuing participation and/or withdrawing

Informed Consent for Donation of Cells and Tissue:

The deliberations concerning informed consent assumed iPSC lines would first be derived at a collection site then deposited in a repository. Deposited lines would subsequently be distributed to researchers, as illustrated in figure 1.

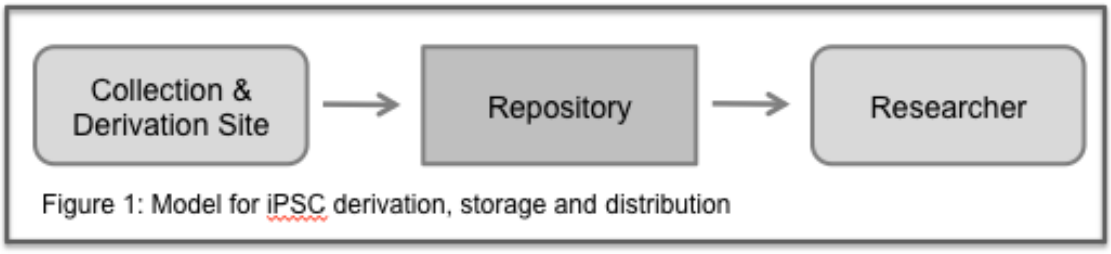

Figure 1: Model for iPSC derivation, storage and distribution

In order to segment deliberations concerning informed consent, working group members indicated it was helpful to distinguish between collection protocols involving one-time interactions with donors versus clinical studies or research requiring ongoing intervention with donors[2].

Considerations Relating to Step 1 (NINDS Collaborative)

Candidate iPSCs for deposit in a NINDS-supported repository would likely be derived under a CIRM-compliant protocol involving one-time donor interaction. Consistent with the May 2010 workshop report, the SWG reiterated that the established CIRM framework requiring (1) IRB oversight and (2) consent for all donated cells and tissue was adequate for candidate iPSCs provided there are no restrictions imposed on the distribution of derived lines.

[2] The term “intervention” includes both physical interaction with the subject or utilization of medical information where the individual can be identified.

Guest Presentation: Perspective of an iPS Donor Family Participating in Disease Research

Chris Hempel discussed her family's experience with Niemann Pick Type C – a rare and fatal genetic cholesterol condition. The complete presentation may be found at this link: insert the link The family's twin daughters were diagnosed with Niemann Pick in 2007. After the diagnosis, the family learned there were few options for research and/or treatment. This prognosis compelled them to become directly involved in research and the scientific process. This involvement included:

- Working with the Mayo Clinic to identify the genetic basis for disease
- Submitting tissue for iPSC derivation and distribution through the Coriell Institute Biological Repository
- Raising money for research projects directed towards Niemann Pick disease
- Serving as a networking hub – are you talking about Chris, her family, her children, her foundation as the networking hub?? to "bridge the gap" between patient and researchers

In relation to iPSC repositories, Mrs. Hempel discussed her desire to learn about research involving her family's cells. She believes this knowledge is important for those interested in taking a personalized medicine approach to healthcare. However, she also acknowledged that some individuals, including members of her own family, are willing to participate but choose to remain anonymous and do not care to learn about research findings. Mrs. Hempel encouraged CIRM to:

- Play a leadership role in developing policies to support the needs of patients/donors
- Continue link patients and researchers to support information sharing to increase knowledge among participants
- Support training, collaborations and projects that improve patient education

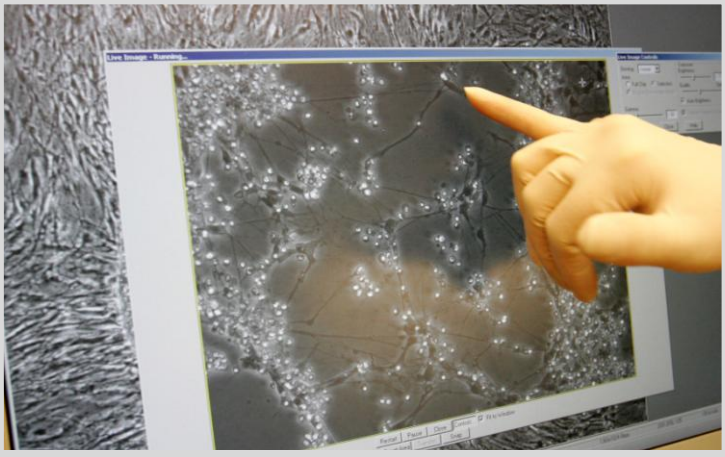

Image: Early development of neurons from family-donated iPSCs.

Source: Addi & Cassi Fund

The working group felt it was important that the donor be informed of the broad range of likely uses for derived lines. This concern was amplified for donors who may be approached because of a specific disease indication. SWG members cited past instances of hESC derivation and genetic studies where the consent process was deemed inadequate to support certain types of downstream research.[3],[4] Prospective donors should be informed that the use of lines might not be limited to their disease. Research indicates donors are overwhelmingly supportive of broad research use provided they are notified and asked in advance.[5] Further, because of the self-renewing capacity of pluripotent stem cells, broad distribution should not compromise specific disease research opportunities because stocks would not be depleted. Working group members also suggested that if: (1) there is comprehensive consent, (2) cell lines are not identifiable (in any form) and (3) they are used only in basic research, then there are no major ethical concerns.[6]

Conclusions and Recommendations for Step 1 (NINDS Collaborative)

- Existing iPSC lines derived in accordance with established CIRM standards should be eligible for deposit in the NINDS repository. Prior to deposit, the consent protocol should be reviewed for consistency with CIRM requirements[7] and any possible restriction on the distribution of derived lines.

- Notify existing CIRM grantees deriving iPSC lines eligible for deposit in the NINDS repository of the collaboration with CIRM. Grantees should ensure that consent protocols adequately reflect the potential for deposit, long-term storage, and redistribution of lines.

- Utilize existing iPSC derivation protocols to support empirical research on outstanding policy questions relating to (1) Informed consent for donation of cells and tissue, (2) communication of research findings, and (3) procedures for discontinuing participation and/or withdrawals.

[3] For example, based on consent language, the NIH limits the use of certain hESC lines to specific types of research see: http://grants.nih.gov/stem_cells/registry/current.htm?id=32

[4] Research involving samples donated by the Havasupai Indians was cited, see Mello, M and Wolf, L. The Havasupai Indian Tribe Case — Lessons for Research Involving Stored Biologic Samples. N Engl J Med 2010; 363:204-207, July 15, 2010.

[5] See Beskow LM, Dean E. Informed consent for biorepositories: assessing prospective participants' understanding and opinions. Cancer Epidemiol Biomarkers Prev. 2008 Jun;17(6):1440-51.

[6] Members contrasted basic research with non-identifiable cells to clinical research with patients or otherwise indefinable cell lines. They suggested studies with identifiable lines raise ethical challenges related to return of clinically significant findings.

[7] Code of California Regulations, Title 17, section 100100.

Considerations Relating to Step 2 (CIRM-sponsored Repository)

CIRM staff reported on cell sources and donor information envisioned in the CIRM-sponsored iPSC repository for disease modeling and drug discovery. Pertinent to the working group deliberations were the following points:

- Age, gender, race and HLA haplotype may be considerations for sample selection
- Whole genome genetic sequencing may be performed on donated tissue or transformed cells
- Retrospective and prospective medical history may be required to enhance scientific value
- It may be necessary to re-contact donors (e.g. maintain links to donors and derived iPSCs) to obtain information about family medical history or other medical factors.

Workshop participants noted that the issue of appropriate consent for studies involving genome sequencing is a topic of interest across funding agencies, and CIRM should track developments and incorporate practice guidelines. The SWG also directed CIRM staff to review additional studies regarding donation to biological repositories and disease research. The literature includes empirical analysis of issue addressed by the SWG. The following studies and results provided relevant information:

- Sparp et. al. 2011 suggested that a key factor in many patients' decisions to donate samples for genetic research is how those studies may impact identifiable racial and ethnic groups. Given Step 2 (iPSC repository for drug discovery and disease modeling) may involve group selection, patients' concerns about potential group benefits and harms in the study design should be ascertained and discussed in the consent process. Specific actions intended to mitigate the potential for harm should be communicated to donors. The objective is to encourage an appropriate distribution of diseases across a spectrum of the population.

- Murphy et. al. 2009 conducted 16 focus groups designed to evaluate public perspectives on informed consent for biological repositories. Focus groups probed participants on preferences ranging from broad/blanket research consent to specific study research consent. Some focus group members saw broad consent as a reasonable condition of enrollment that would optimize research opportunities. Some respondents wanted to be asked for their consent each time to allow them maximum control over use of their samples. One interesting finding is that some respondents indicated the process of re-consenting would keep them abreast of research development. This response suggests there may be value in

reporting on the types of studies performed (see Communication of Research Findings).

- Beskow and Dean 2008 surveyed prospective participants for a biological repository. The survey identified issues where participant's views may be divided. These issues included (1) development of commercial products, and (2) duration of sample storage. About a third of interviewees felt positive about commercial products and about one fifth responded negatively to the idea. More than half were confortable with unlimited use and distribution of samples. In addition, sixty percent of interviewees said they would agree to the use of their medical records to get updated information about their health.

Maintaining links to the medical information, thus enabling the potential to continue to interact with individual donors, constitutes human subjects research as defined in 45 Code of Federal Regulations, Part 46. As SWG members indicated, this type of protocol requires extensive discussion with donors including consideration of reporting research results and options for withdrawing from participation. Given that a CIRM-funded iPSC repository involves recruiting new donors, providing this level of information and obtaining detailed consents addressing use, distribution and communication of results should be built into any future collections protocol.

The SWG also commented that unintended undue influence is a challenge when caregivers perform recruitment or request cell donation with their own patients. Mechanisms for avoiding undue influence– including involving "trusted intermediaries" – in the recruitment and consent stage should be considered.

Conclusions and Recommendations for Step 2 (CIRM-sponsored Repository)

- If donors are recruited on the basis of having a disease condition, the consent process should emphasize that donated biological materials may be utilized for research on other diseases.

- To the extent procurement strategies involve recruitment of groups or communities, strategies intended to mitigate the potential for group harm should be developed and communicated to prospective donors.

- Consistent with established CIRM consent requirements, the issues of commercialization and long-term storage plans should be clearly explained to prospective donors.

- Consistent with established CIRM regulations, researchers should be permitted to use materials from donors who agree to unrestricted uses consistent with the repositories' governance / release policies (see Other Issues - Governance).

- Although the primary purpose of the bank is to support therapeutic development activities such as disease modeling and drug screening (as opposed to develop cell lines for creating transplantation products application), scientific staff suggested development of cell-based therapies might not be ruled out. Given this possibility, opportunities for complying with FDA Human Cells, Tissues, and Cellular and Tissue-Based Products requirements should be considered and this potential should be discussed in the consent process.[8]

- Researchers should engage patient advocates and potential donor communities prior to initiating formal collection to gain their insights and perspectives as the consent process is developed. This evaluation should seek to differentiate the needs of donors with specific disease conditions from those acting as controls (healthy subjects versus someone affected with a disease). Mechanisms for avoiding undue influence in the consent process should be discussed.

- Choices, mechanisms and options for (1) communicating research findings and (2) discontinuing participation should be clearly described in the consent process.

One outstanding issue involves pediatric research and whether reconsent is needed when donors reach the age of majority. No specific recommendation was provided regarding reconsent. Any specific policy on reconsent should be disclosed in the consent process. It was acknowledged that reconsent may enhance donor autonomy, but there is also a potential for harm. For example, the minor may have been treated at a young age and is unaware of their previous disease status. In other instances, the minor may have a chronic disease to which they are aware, and would not be harmed by a reconsent. Absent the identification of specific disease targets for a CIRM-funded iPSC repository, it is difficult to evaluate the appropriateness of a reconsent standard.

Communication of Research Findings

During the SWG deliberations the value of offering “empowering choices” to prospective donors and research participants was a recurring theme. It was recognized that some individual donors, particularly those with disease, might value general information about research findings. Others may want to donate but choose to not be informed about findings. This range of viewpoints is supported by research cited below. The challenge is to develop a system that is responsive to participants’ expectations, conforms to existing regulations, and is ethically responsible.

[8] For example, should repository collect and archive additional biological specimens to support FDA (HCT/Ps) testing requirements.

CIRM staff performed a review of research regarding communication of results. The following studies provided useful information:

- Beskow and Dean 2008 surveyed prospective donors to a biological repository. The survey found nearly two thirds of interviewees were confortable with no expectation of receiving individual research results. The remaining third, however, was concerned about not getting results, especially if results related to a serious health condition. Nearly half thought it would be very important to receive generalized findings.

- Shalowitz and Miller, 2008 reviewed 28 studies regarding communication of clinical research results and concluded participants want aggregate and clinically significant individual study results. They indicated that investigators appeared to support communication of aggregate results but less is known about reporting individual results. They also suggested that fear of psychological harm should not be used as a reason not to offer results. They reached this conclusion based on the clinical and occupational health literature where individuals have been provided data about genetic testing, disease conditions and associated health risks. However, unlike these latter studies, individual results on research tests usually have unknown clinical significance.

- Lemke et. al., 2010 performed a national survey of 208 human subjects protection professionals and concluded that this population was divided on key issues regarding the risks and benefits of genetics research. This study suggested the rapid technological innovation and the lack of clear guidelines presented challenges for human subjects protection generally.

- Helgesson et. al., 2007 suggested reporting research results back to sample donors can be problematic for several reasons. Most importantly, disclosing individual results of factors thought to imply risk may cause unjustified concern. This concern becomes amplified if no relevant treatment or prevention modality is yet available. Furthermore, reporting results back to donors who have not requested results was thought to beinappropriate.

Aggregate Results:

Developing systems to report general information about studies using iPSCs and aggregate findings can simultaneously support informed consent and results reporting. During the workshop, CIRM staff suggested a “real-time engagement” system could serve to inform participants. For example, active or passive systems could be used to provide research updates. Active systems could send notifications to participants and other interested parties on the types of research utilizing repository lines. Passive systems could include descriptions of the types of research performed with repository lines. Prospective donors and the public

could access systems, so they may be informed about actual uses for deposited iPSC lines. Newsletters and websites are examples of resources to provide ready public access to the aggregate study results.

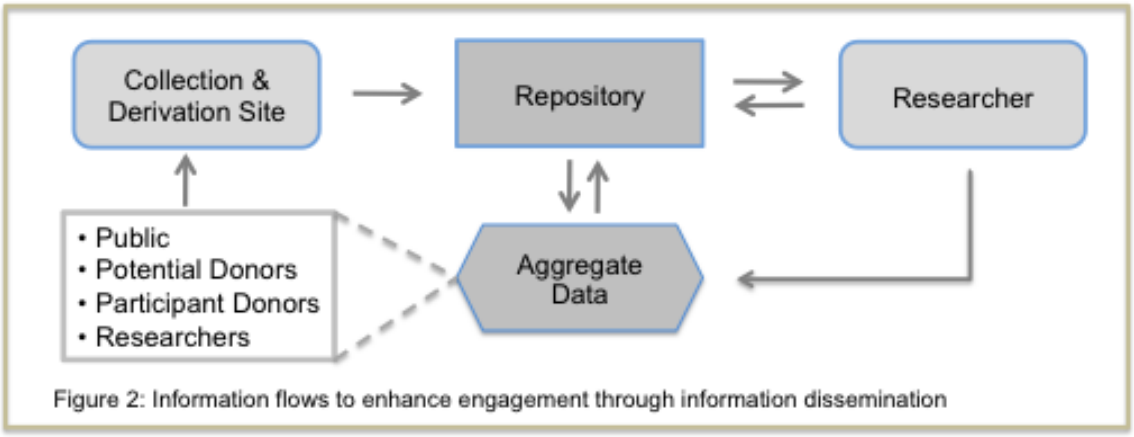

Figure 2: Information flows to enhance engagement through information dissemination

Donor Specific Results:

Consistent with Helgesson et. al., workshop participants representing research organizations emphasized the importance of understanding the (1) scientific analytic validity and (2) clinical utility of findings. Representatives indicated there are often pressures to act on information that has not been validated. For example, early research involving the identification of the BRCA1 gene was cited where there was pressure to act on unconfirmed findings. iPSC methods involve "reprogramming" of DNA; therefore, the issues of analytical validity and clinical application of research findings are likely to emerge because abnormalities may have been introduced during the reprogramming process.

If analytical validity and clinical utility issues are resolved, then there are recommended criteria for when results should be offered to participants. For example, in the context of genetic studies, the National Heart, Lung and Blood Institute Working Group recommends[9] offering individual research results when all of the following criteria are met:

1. The genetic finding has important health implications for the participant, and the associated risks are established and substantial.
2. The genetic finding can be acted upon clinically – there are established therapeutic or preventive interventions or other available actions that have the potential to change the clinical course of the disease.
3. The test is analytically valid, and the disclosure plan complies with all applicable laws.

[9] See: http://circgenetics.ahajournals.org/content/3/6/574.long

4. During the informed consent process or after, the study participant has opted to receive his or her individual genetic results.

Workshop participants also noted that notification protocols may create regulatory and logistical challenges for the repository. For example, some tests are regulated under Clinical Laboratory Improvement Amendments (CLIA). Results emerging from basic research would not originate from CLIA-compliant laboratories, so reporting may not be appropriate without retesting. Further, individual researchers typically cannot identify individuals associated with biological specimens. Repositories typically do not want to have access to identifiers because of the increased regulatory burden. Logistically, the management of individually identifiable data is costly and needs to be considered in the funding proposal.

Conclusions and Recommendations

- Step 1, the CIRM collaboration with NINDS and funded consortia collaborative, involves creating new as well as existing iPSCs for disease modeling and drug discovery. We anticipate there is no explicit consent or notification for returning individual results, so direct communication with donors would not be appropriate.

- Step 2 contemplates the recruitment of new donors with disease indication and ongoing interaction directly or indirectly (e.g. review of medical information). The SWG encourages the development of mechanisms to provide aggregate results. The collection protocol should describe under what conditions, if any, donors could be re-contacted to offer to provide individual results. These conditions should be clearly described to prospective donors.

- The SWG recognizes there are serious scientific issues concerning clinical significance and validity, logistical issues of tracking specimens, regulatory issues related to testing protocols, and ethical issues relating to the availability of efficacious interventions and the varying preferences of donors. Given the range of scientific, logistical and ethical issues, researchers should not be obligated to return individual results.

Discontinuing Participation

Research participants – human subjects – have the fundamental right to withdraw from research. An individual is considered a human subject when a researcher is (1) interacting directly with the individual or (2) in possession of identifiable private information (e.g. medical records, test results). If a participant decides to withdraw from all components of a research study, the investigator must discontinue all of the following research activities:

- Interacting or intervening with the subject in order to obtain data about him or her for the research study;

- Obtaining additional identifiable private information about the subject for the research study by collecting or receiving such information from any source (e.g., medical records).

Note, for research not subject to regulation and review by FDA, investigators may choose to destroy the subject's data or specimens or exclude the subject's data from any analysis if requested by the participant, as we next discuss.

A subject may withdraw from the interventional component of a study, but may allow the investigator to continue other research activities described in the IRB-approved protocol and informed consent document, such as accessing medical records. When a subject's withdrawal request is limited to discontinuation of the direct interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue.

OHRP interprets the Common Rule as allowing investigators to retain and analyze already collected data relating to any subject who chooses to withdraw from a research study, provided such analysis falls within the scope of the IRB-approved protocol. This is the case even if that data includes identifiable private information about the subject, and the study protocol undergoes continuing IRB review. In addition, the continued use of collected specimens is not addressed.

Workshop participants indicated it was common practice to stop distribution of banked specimens of untransformed (primary) cells and tissues after the donor withdrew consent for further use of the specimen. In the case of CIRM iPSC repository, the primary goal is to derive new lines from primary cells and tissue. Existing federal regulations do not address the status of derivatives with regard to subject withdrawal. Some workshop participants suggested derivatives should be considered distinct and further distribution and use (consistent with original consent) continue.

Independent of the regulatory status of primary tissue and transformed samples, the principle of justified reliance was evoked as rationale for continuing to utilize

transformed iPS cells. Justified reliance is a result of the researchers and repository making a good faith investment to produce a common resource (e.g. the iPSC line). If the research community invests further to develop this resource and generate knowledge, then science and society could incur harm from no further access. Members of the SWG suggested limiting the ability of a donor to request the withdrawal of transformed samples from further distribution may be justified provided this limitation was clearly disclosed at time of consent.

Further, it must be emphasized during the consent process that it is impossible to control the use of de-identified specimens that have been distributed to researchers. The U.K. Biobank, profiled in our May 2010 report, is frequently cited as a model for allowing donors to withdraw and request the destruction of their stored samples. The Biobank acknowledges, "it may not be possible to trace all distributed sample remnants."[10] The U.K. Biobank recognizes that a promise of control over future uses cannot be functionally fulfilled after creating and distributing immortalized cell lines (since it may be impossible to retrieve all such material), or after transforming somatic cells into pluripotent cells or their progeny (since the original donated material has been modified or transformed). In fact, it is impossible to retrieve materials that have been completely anonymized to protect donor privacy. Similarly, the recent U.S. NCI Best Practices for Biospecimen Resources recommended informed consent documents "highlight the human subject's ability to discontinue participation," but stated that distributed samples "need not be withdrawn."[11]

Conclusions and Recommendations:

- Repository withdrawal policies should be consistent with OHRP guidance.[12]
- Table 2 provides additional recommendations for use of collected specimens and transformed iPSCs.
- The consent process for donation of specimens for derivation of iPSCs should discuss what will occur if the donor later decides to withdraw from the research project.

[10] see http://www.ukbiobank.ac.uk/docs/Informationleaflet130608.pdf
[11] National Cancer Institute. (2007) National Cancer Institute best practices for biospecimen resources.
[12] http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html

Table 2: Required and Recommended Actions for Participant Withdrawal

Withdrawal Option	OHRP Guidance	Required and Recommended Action
(1) No further contact by repository	Interaction or intervention with subject to obtain data must be discontinued.	**Required**: Right of participant to withdraw from further contact. Participant may allow access to medical information.
(2) No further contact and no further collection of donor medical information	Obtaining additional identifiable information about the subject must be discontinued.	**Required**: Right of participant to withdraw from further contact and from further collection of medical information.
(3) Withdrawal of "human subject" status (e.g. identifiers removed)	Retention and analysis of already collected data permitted, provided such analysis falls within the scope of the IRB-approved protocol. Continued use of collected specimens / derivatives not addressed.	**Required**: Participant must be allowed to complete withdrawal of human subjects status. **Recommend**: request consent to use/transform primary cells and tissue with identifiers removed. Use of primary untransformed specimens should only continue with consent and subsequent use should be consistent with original protocol.
(4) Withdrawal of primary (untransformed) tissue samples		**Recommend**: Discontinue further use/transformation of primary untransformed tissue but retain reference sample. Transformed samples may be used consistent with approval protocol.
(5) No further distribution of transformed materials	OHRP silent on use of transformed materials.	**Recommend**: Allow distribution and use of transformed iPSCs, provided this was clearly disclosed in consent process. IRB should review if donor claims continued distribution would constitute harm.

Other Issues

Repository Governance

Numerous authors suggest repository governance and the related issue of ongoing participant and public engagement impacts trust and can influence the overall efficacy of repository development.[13],[14],[15] This literature suggest there are a number of factors, consistent with CIRM's governance and oversight policies, that can serve to improve participant and/or public confidence. Established CIRM by-laws and regulations incorporate the following elements into Institute governance:

- Including patient / patient advocates in program decision making;
- Maintaining transparency and public engagement in policy development;
- Requiring independent oversight of research activities;
- Supporting public benefit from commercial development (e.g. CIRM's IP polices)

Any governance policy should also include standards for acceptable research. For example, materials transfer agreements between the repository and researcher should stipulate activities that are not eligible for CIRM funding are prohibited. Such restrictions serve to assure donors that their samples will be used for ethically responsible research.

The intended purpose of the repository is for research bank, but one may want to consider a collection protocol that would allow for development of clinical products. This potential should be addressed in the consent process. This would likely require archiving blood and other tissue required for FDA HCTP testing requirements.

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[13] Meslin EM. The value of using top-down and bottom-up approaches for building trust and transparency in biobanking. *Public Health Genomics*. 2010;13(4):207-14.
[14] O'Doherty KC, Hawkins A. Structuring public engagement for effective input in policy development on human tissue biobanking. *Public Health Genomics*. 2010; 13(4): 197–206.
[15] Cambon-Thomsen A, Rial-Sebbag E, Knoppers BM. Trends in ethical and legal frameworks for the use of human biobanks. *ERJ* August 1, 2007 vol. 30 no. 2 373-382.