Deriving iPS Cells from Previously Collected Research Biospecimens: The DISCUSS Workshop Report

July 2014

Deriving Induced Stem Cells Using Stored Specimens (DISCUSS): Points to Consider for Biobanking

1. Introduction

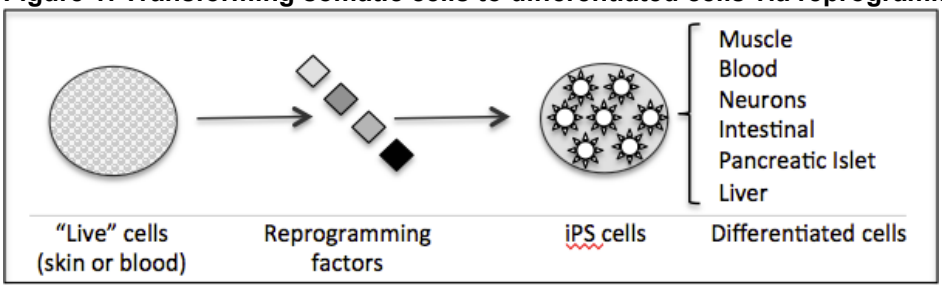
1.1 DISCUSS Goals

The DISCUSS Project was initiated to facilitate the advancement of biomedical research involving the use of cellular reprogramming methods. Cellular reprogramming has emerged as a leading technology for accelerating stem cell science and clinical translation. Scientists commonly use reprogramming techniques to transform somatic cells into pluripotent, multi-potent and differentiated cells (figure 1). The resulting cells can subsequently be expanded and maintained in repositories for a variety of biomedical research purposes.

Internationally, there are numerous initiatives underway to derive and to bank libraries of induced pluripotent stem cell (iPSC) lines that represent a range of human diseases. These libraries have significant potential to impact our understanding of disease mechanisms and improve treatment options through use in disease modeling, target discovery and drug development.

Some banking initiatives involve the collection of new biological specimens from human donors (referred to henceforth as "specimens"). This prospective collection enables the application of informed consent processes specifically tailored to iPSC derivation, research and banking. The DISCUSS Project team initially developed and applied model informed consent procedures for the prospective collection of blood and other somatic cells for iPSC research and banking.[1,2]

Figure 1: Transforming somatic cells to differentiated cells via reprogramming

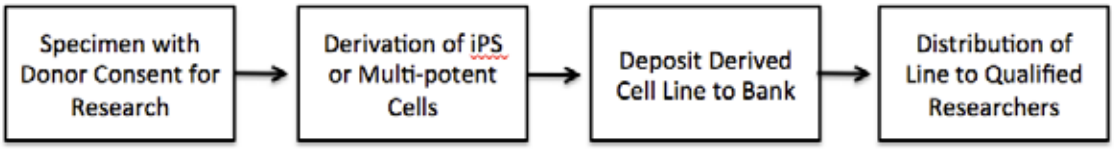


Established specimen collections, typically from blood samples, are also valuable sources of material for developing comprehensive iPSC libraries. Though the precise number of stored human specimens is

unknown, it has been estimated that this number is well over 300 million in the U.S. alone.[3] Certain collections have intrinsic scientific value because they may be well characterized, cover rare ("orphan") diseases, trace the progress of a patient's disease over time or have other unique characteristics.

The DISCUSS Project focuses on the use of previously collected human specimens from adult donors, obtained under general (biomedical) research protocols, and subsequently being used for derivation of iPSC lines and their ensuing deposit into a cell repository for distribution as illustrated in Figure 2. The project goal is to develop consensus on how established collections can be used responsibly (i.e. ethically, scientifically) in stem cell research.

Figure 2: Deriving iPS Cells Using Stored Specimens (DISCUSS)



The term "repository" is used to mean: an actual or virtual entity that may receive, process, store and/or distribute human biological materials (specimens) in support of a research study or multiple studies and their associated data. (OECD, 2010; ISBER 2012).

1.2 The DISCUSS Project: Process

The DISCUSS Project is designed to develop consensus for the responsible use (i.e. ethically and scientifically) of previously collected specimens in iPSC and related biomedical research. The project was initiated in response to recommendations from advisory bodies as well as from concerns raised by researchers, governance bodies and collaborators.[4]

The project involves three discrete phases:

1. Development of preliminary *Points to Consider*
2. Stakeholder engagement
3. Results reporting and development of final *Points to Consider*

(1) Preliminary Points to Consider

In August 2013, *The DISCUSS Project: Induced Pluripotent Stem Cell Lines From Previously Collected Research Biospecimens and Informed Consent: Points to Consider* was published. This publication was designed to elicit feedback on evaluation criteria that

may be used when considering banked specimens for iPSC research. The publication included nine statements intended to guide researchers, repository managers, review boards and/or ethics committees, when considering the utilization of stored specimens for iPSC derivation and subsequent deposit of derived lines into a repository for further distribution.

(2) *Feedback Process*

The DISCUSS team organized a series of fora to elicit feedback on the Points to Consider publication. The process culminated with a workshop in March 2014 where participants reviewed the points to consider along with a summary of comments received.

(3) Reporting of Findings

The purpose of this report is to synthesize the cumulative feedback received from stakeholder engagement into a revised framework for evaluating when it is appropriate to utilize previously collected specimens for iPSC derivation and banking.

2.0 Major Themes from Comments, Forums and the Workshop

The original *Points to Consider* publication includes specific evaluation criteria for considering the use of previously collected specimens in stem cell research. The Points to Consider criteria encourage respect for donors by identifying recurring bioethical considerations and suggesting a framework for their resolution. Throughout the feedback process commenters indicated they found utility in the Points to Consider framework for developing organizational policies to guide specimen utilization.

2.1 Cellular Reprogramming is a Frontier of Science

The DISCUSS workshop was designed to intersperse formal presentations describing contemporary use of cells and tissue in stem cell research with more open-ended ethics-policy deliberations. The intent was to consider ethics-policy issues with an appreciation for the future directions of stem cell science and regenerative medicine.

Scientific-program updates included:

(1) The utilization of genomics and stem cell science in population health initiatives (H3Africa),
(2) Cord blood transplantation for sickle cell treatment (National Cord Blood Program), and
(3) The potential for gene-edited cord blood cells for regenerative medicine.

The H3Africa program includes a focus on cellular reprogramming and the development of repositories to address infectious disease burden, metabolic disease and mental health. The cord blood session described how transplantation has been used to treat a wide range of cancers, genetic diseases and blood disorders. In addition, recent research designed to take advantage of the high cellular plasticity of cord blood suggested it might be a valuable source of cells for bioengineered transplantation therapies.

Participants noted the remarkable potential for stem cell science to advance both individual and population health. This potential underscored the importance of considering how existing and future specimen collections can be utilized ethically in stem cell research.

- The potential for stem cell science to advance public health and regenerative medicine creates an imperative to utilize established specimens effectively.

2.2 The Secondary Use of Specimens is Process Driven

There are comprehensive state, national and international guidelines and regulations governing the collection of donor specimens for stem cell derivation, research and banking. Guidelines developed by the International Society for Stem Cell Research (ISSCR) and the U.S. National Academies' of Sciences (NAS) reflect international policy consensus for informed consent and research oversight. The Workshop included participants from ISSCR, CIRM, NIH, United Kingdom Stem Cell Bank and the Australian National Health and Medical Research Council, among others. Each organization maintains guidelines and policies designed to support research collaboration along with materials and data exchange.

Established guidelines are commonly forward-facing by their nature emphasizing optimal conditions for the prospective collection of research specimens. Indeed, the initial focus of the DISCUSS team was the development of model informed consent protocols for specimen collection for iPSC derivation and banking programs supported by CIRM and NIH. The ISSCR and NAS guidelines offer some direction with regard to the utilization of previously collected specimens emphasizing a provenance and compliance-determination. For example, the 2010 NAS Guidelines state, "new derivation of stem cell lines from banked tissue obtained prior to the adoption of these guidelines are permissible provided that the original donations were made in accordance with the legal requirements in force at the place and time of donation."

The determination of compliance at the time of donation, as suggested by NAS, is an important prerequisite, but workshop participants noted

that internationally there is increasing emphasis on having procedures in place to examine the acceptability of new uses of banked specimens in relation to the original donor consent. For example, the U.S. Health and Human Services Secretary's Advisory Committee on Human Research Protections suggests:

> *Institutions should establish mechanisms to determine whether secondary uses are compatible with the original informed consent; this could involve consultation with the IRB that approved the original research, or review by some other body designated for these purposes. Coding should not be used as a means to circumvent the original terms of consent. This is ethically problematic, even if the original project is over and the secondary use is no longer considered to be research involving human subjects.*[5]

Moreover, the deposit of a derived iPSC line to a repository, and its subsequent redistribution may require additional oversight or procedural review given the expanded geographic reach and potential uses of the cells. These are not theoretical concerns; we are aware of cases where repository administrators have expressed concerns over the adequacy of consent protocols associated with newly derived iPSC lines from existing specimens. Specific concerns centered on provenance considerations and on whether it was appropriate to redistribute the cell lines.

- Emerging national and international guidelines for the secondary use of specimens are emphasizing the need for procedural or governance mechanisms to determine whether secondary uses are compatible with the original donor informed consent.

2.3 System Integrity and Trustworthiness are Core Values

Biomedical research increasingly depends upon the development of systems to facilitate the exchange of materials and data. Systems exist for managing cells and tissue, gene sequencing and other "omics" data, images, and molecular tools amongst others. Collectively, these systems support research discovery, validation and knowledge dissemination. Stem cell science is a prime example along with the initiation of numerous projects internationally to derive, characterize, register, bank and distribute cell lines.

Repositories play a central role in mediating the exchange of materials and data. For repository systems, there are established procedures and protocols for the collection, storage, retrieval and distribution of specimens along with data for research.[6] The DISCUSS workshop deliberations and stakeholder comments emphasized how these systems must be designed to enhance their trustworthiness among

research participants and the public. In this context, trustworthiness emanates from a framework of operations and governance that:

- Advances the effective and responsible use of donor specimens;
- Supports research integrity;
- Responds to social or participant needs and concerns;
- Maintains feedback mechanisms to validate the effectives of operations and governance systems.

Established procedures and protocols typically include a variety of governance structures and operational mechanism to support the points above, such as informed consent, procedures to allow withdraw from research, materials transfer agreement as well as independent ethics and scientific oversight. However, operations and governance systems must be "robust and proportionate" according to variation in risk, societal values and scientific needs. For example, in the context of the H3 Africa project there are specific concerns regarding the export of specimens or data outside the continent. In response, the H3 Africa repository program is developing specific requirements regarding data and specimen handing, collaboration agreements and benefit sharing.

- Provenance assessment (which encompasses informed consent determination) is one element of a much larger repository operations and governance system. The DISCUSS Project should incorporate this system perspective into its recommendations.

2.4 Considerations that Apply to Cultured Tissues with the Potential for Transformation

The DISCUSS Project was ostensibly designed to address a specific research context: the derivation of iPSC lines from previously collected research specimens from an adult donor, for subsequent deposit to a repository for distribution and use in biomedical research. This context was chosen because we had encountered instances where both researchers and ethics committees/institutional review boards faced with challenging questions about the acceptability of proceeding with iPSC research protocols. Similarly, they encountered challenges depositing, or accepting for deposit, resulting lines to an existing repository.

Commenters recognized the utility of an iPSC focused effort, given that the DISCUSS Project team was directly involved in supporting stem cell science. However, there was also consensus that the *Points to Consider* are generally applicable to the context of any **cultured human** tissue as well, because of its **potential** for expansion and transformation. For example, in the DISCUSS Workshop scientists described how human cord blood could be readily transformed to pluripotent, multi-potent and differentiated cells. Transformed cells are being applied in a variety of *in*

vitro and *in vivo* applications including disease modeling and therapy development.

- There is utility in the iPSC-specific focus of the DISCUSS project, but the recommendations may be applicable to other contexts. For instance, the model proposed may inform research with cultured human tissue generally.

2.5 Societal Concerns Exist and Should be Addressed

Findings from a U.S. based focus group study that elicited patients' attitudes towards the donation of cells for iPSC research was presented at the March workshop.[7] The study suggests that concerns exist over:

- Re-identification of the donor, privacy infringements and the potential for this information to be used in an unfair or discriminatory manner;
- Inability to control the downstream use of cells and prevent their inappropriate use;
- Commercial aspects of cell utilization;
- Using cell reprogramming to create gametes.

The study also found that mitigating factors could serve to address stated concerns. Specific actions include:

- Robust informed consent procedures; and
- Transparency in disclosing information relating to how materials are and will be used and their commercial potential.

The study's authors suggest that effectively addressing stated concerns could serve to build trust in research, underscoring the importance of system integrity and trustworthiness.

Additionally, the H3Africa initiative identified broader social concerns about the use of cultured tissue. Specifically, in the African context, there are deeply rooted social and cultural beliefs regarding the appropriate use of human tissue and resulting knowledge gained from its use in research. For example, historical experience with the exploitative human trafficking raises concerns over cells being distributed internationally for research. In response, the project is considering a number mitigating procedures and policies designed to ensure benefits to African donors and researchers. The African experience provides important lessons on how to adopt governance mechanisms that respect donor's and communities' socio-cultural sensitivities and concerns.

Some of these stated concerns apply to tissue use in general (e.g.

potential for re-identification and inability to completely control use) while others (e.g. gamete formation) are more specific to reprogrammed cells.

- Participants will inevitably have concerns relating to risk. Risks cannot be completely eliminated but may be mitigated by (1) applying established governance mechanism including obtaining robust informed consent, establishing a mechanism for participant to withdraw from research, materials transfer agreement and ethics board oversight; and (2), the development of procedures and policies to advance trustworthiness.

3.0 A Revised Evaluation Framework for iPSC Derivation

Based on feedback received from written comments, discussion forums and the DISCUSS Workshop, we have revised our Points to Consider for the use of previously collected specimens. We retain our focus on general biomedical research protocols designed to derive and distribute iPSC lines from previously collected adult research specimens. However, the stakeholder engagement process suggests the Points to Consider should be incorporated within a discussion of the broader repository systems. Thus, we suggest a revised framework that includes both specific evaluative criterion and the broader repository research system in which they should be applied.

The framework combines international consensus on the best practices for the use of specimens and unique points to consider in the context of stem cell research. The framework is designed to assist researchers, cell repositories, oversight and review bodies, as well as funding agencies in the design of programs and policies to support secondary use of specimens in a coherent ethical and governance framework that engenders donor and public trustworthiness.

The original *Points to Consider* have been modified based on comments received during the stakeholder engagement process. The revised *Points to Consider* may be found in Appendix 1.

3.1 International Standards for Bio-banking

Commenters indicated that it was important to emphasize that any repository receiving derived iPSC lines should meet a minimum of core competencies. Guidelines and standards exist for all aspects of collection, storage, retrieval, usage and distribution of specimens.[6] To enhance trust among research participants and the public, it is essential that the repository receiving iPSC lines conform to internationally accepted ethical principles as well as best practice guidelines and standards.

Operationally, the repository should have mechanisms in place to support the responsible use of specimens by qualified researchers. To support responsible use, requests for specimens should undergo scientific and / or administrative review to ensure appropriate utilization by qualified researchers. Material transfer agreements should be utilized to document conditions for use.

3.2 Standards for Specimen Collection and Use

(1) Voluntary Consent and Independent Oversight

Commenters felt it was important to emphasize the need to ensure that original specimen, at a minimum, conformed to core ethical standards of (1) voluntary informed consent and (2) oversight by an independent ethics review board (e.g. IRB or equivalent). In the US context for example, compliance with the Common Rule satisfies these conditions for determining ethical provenance. If such a determination cannot be made, derived cell lines may have limited utility since national and international bio-banking guidelines increasingly require a determination that there was appropriate consent and oversight. Also, it was noted that not all specimens collected under IRB approval could be used for all types of research, so consent evaluation is a necessary step.

(2) Confirm Consent Prior to Derivation and Banking

Figure 3: Opportunities to Confirm Consent

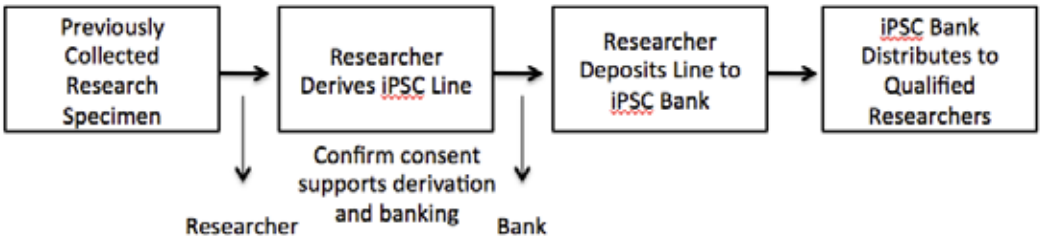


Figure 3 illustrates two points in the derivation and banking cycle where consent evaluation may be performed. Ideally, the researcher will utilize specimens with the knowledge that appropriate consent was obtained at the time of collection. In the case where a previous collected specimen resides in a cell or tissue repository, the researcher proposing iPSC derivation should describe such use a priori. Often a statement of research intent (SRI) is submitted when requesting a specimen. An appropriately constituted neutral third party such as a Tissue Utilization Committee or an IRB should review the research request and consider any restrictions against uses for which there is not appropriate consent.

There may be specimens that are appropriate for iPSC derivation and research use within a confined context, such as a particular laboratory or institution, but not suitable for broad distribution as per instance in a commercial repository. A common example is the case where a researcher may obtain consent from donors to derive iPSC lines with the stipulation that the researcher will retain control of the cell lines. Such lines would not be appropriate for distribution by a third-party.

A number of commenters pointed out that it is standard practice for a banking entity to have a governance system in place in charge of performing a provenance review as suggested by internationally recognized best practice guidelines. The review is intended to determine (1) that the initial collection was conducted with voluntary donor consent and independent oversight (point #1) and (2) whether the informed consent protocol would allow for the deposit and distribution of cell lines. Typically, the repository requires evidence of human subjects oversight and the donor consent associated with a particular cell lines. This review, by the banking entity serves to ensure appropriate (e.g. ethical, scientific) use of research specimens.

(3) Proposed Use Should Not Conflict with Original Consent

Cellular reprogramming, including iPSC derivation and distribution, should not be directly or indirectly precluded by the original consent. Common examples where conflicts may arise are statements (1) directly limiting research to the original specimen or (2) restricting who will use them. For example, some consent documents may contain language expressly limiting research to a collected blood sample. Language stating the principal research and/or the research team will manage the distribution of specimens would not be appropriate for wide distribution unless the research team administers the repository. iPSC lines containing limitations on use should be deposited in a repository only if transfer agreements address restricted uses in conformity with the scope of the donor's consent. Thus, the Material Transfer Agreement should incorporate any restrictions or conditions identified by the bank during its consent review (Figure 3).

Points to Consider for Consent Review

The stakeholder engagement process included substantial discussion of the eight statements contained in the original

publication. Discussion centered around three common situations arising during such reviews:

1. Compatibility or consistency: The original consent form (or process) includes language that is consistent with iPSC derivation, research use and banking.

2. Incompatible or inconsistent: The original consent form (or process) includes language that is inconsistent or conflicting with iPSC derivation, research use and banking.

3. Silent: The original consent is silent with regard to iPSC derivation, research use and banking, but such use may be compatible.

As indicated in the previous section, the proposed use of any specimen should not conflict with the original donor informed consent. In some jurisdictions there may be guidelines or policies allowing for the anonymization of specimens thereby enabling expanded or secondary uses. However, there was consensus that iPSC lines derived from such specimens would have limited utility. Limitations result from international guidelines and policies for repositories in general, and stem cell research in particular, which require appropriate informed consent. Thus, we recommend that researchers utilize specimens for which research consent has been obtained. This recommendation is consistent with the U.S. Health and Human Services Secretary's Advisory Committee on Human Research Protections.

Commenters indicated the circumstances that required the most in-depth consideration were research activities not specifically addressed in the original consent form. Review boards typically spend considerable effort to address instances when the consent was silent with regard to iPSC derivation and banking, but such research could be construed as consistent with the research purpose.

In the original publication, Statement 2 proposed that iPSC derivation should be considered as a standard method for disease modeling and therapy development. Similarly, other basic research tools and technologies, like genetic sequencing and characterization, represent contemporary methods for performing biomedical research.

If specimens were collected – and consent obtained – with the intent of understanding disease or developing therapies, then

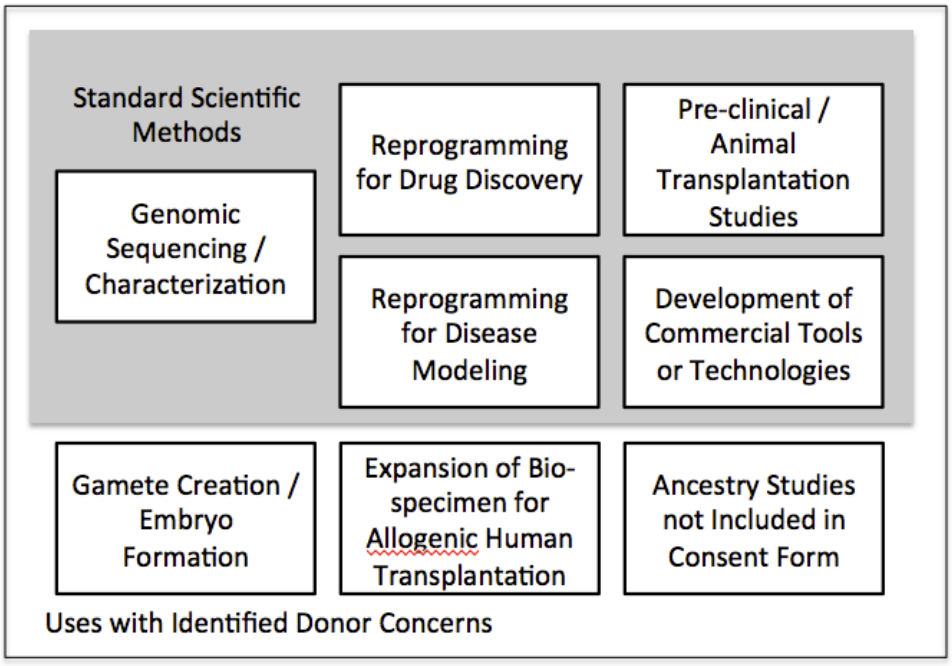
reprogramming and genetic characterization may be viewed as tools to be applied towards these ends. Utilizing them would constitute a "best-science" approach for accomplishing the intended purpose of the research. A best-science approach supports beneficence by seeking to maximize possible benefits of specimen donation.

(4) Utilize Existing Administrative Mechanisms to Address Societal Concerns

Evidence presented at the workshop suggests societal concerns can emerge from the subsequent utilization of cell lines or associated genetic information – e.g., to create gametes or to discriminate or otherwise disadvantage donors. Studies seeking to characterize the ancestry of research participants were specifically highlighted because their results have the potential to effect non-participants who are also members of groups with shared ancestry.

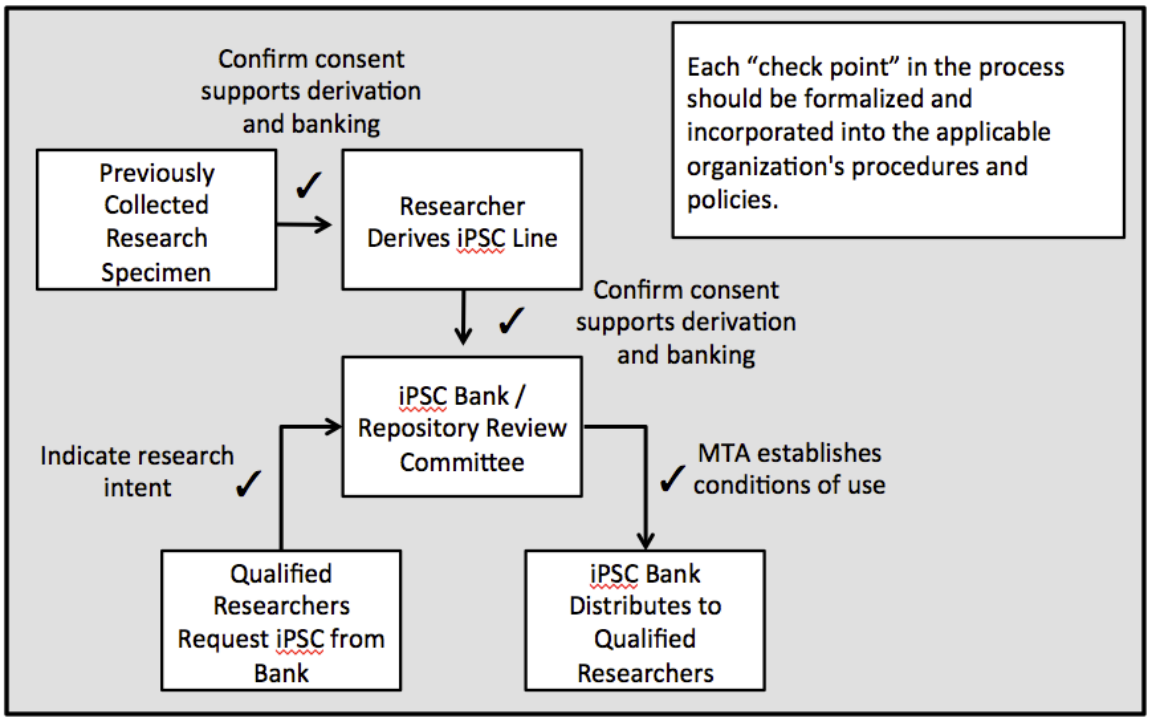
Therefore, it is important to focus on how data or resulting iPSC lines are utilized. Figure 4 illustrates certain activities (gray shade) that appear consistent with research consent aimed at disease research and therapy development. There are also uses for where donor concerns have been identified (white shade).

Figure 4: Standard Methods and Special Considerations



Workshop participants highlighted a variety of mechanisms routinely utilized in repository systems to support responsible use of data and materials. For example, researchers requesting cells from a repository should described the intended use of materials. The repository distributing cell lines can consider whether such use is consistent with the original consent. Further, repositories distributing lines can utilize materials transfer agreements to define the appropriate conditions for use of materials or data. Figure 5 illustrates points where researchers and repository administrators can act to ensure specimens are used appropriately.

Figure 5: Check Points in Repository Systems



4.0 Conclusion & Additional Considerations

4.1 Conclusions

A major goal of the DISCUSS project is to develop consensus on the responsible utilization of previous collected specimens in stem cell research, specifically, and biomedical research generally. This topic is one of international interest as research programs are being initiated to apply cellular reprogramming toward public health and regenerative medicine.

The development of scientific programs generally includes deliberations concerning governance and research ethics. Numerous participants in the DISCUSS project deliberations indicated the guidance provided by *The DISCUSS Project: Induced Pluripotent Stem Cell Lines From Previously Collected Research Biospecimens and Informed Consent: Points to Consider* was useful for supporting program development. Thus, the Points to Consider have been revised in response to feedback and included in Appendix 1.

While the engagement process suggested there is utility to the Points to Consider, there was considerable focus on a systems approach to supporting responsible and trustworthy research. We have attempted to capture this focus in the report by highlighting the relationship between operational aspect of repository systems and the application of the Points to Consider. Thus, we aim to highlight the role of researchers, oversight bodies, and repositories in supporting the responsible conduct of research.

4.2 Additional Considerations

The purpose of this report is to synthesize the cumulative feedback received from stakeholder engagement into a revised framework for evaluating when it is appropriate to utilize previously collected specimens for iPSC derivation and banking. Based on the feedback process, there are additional considerations that warrant further discussion or elaboration. These considerations are identified in Appendix 3.

5.0 Acknowledgements

The DISCUSS Project team would like to thank the following individuals and organizations for their valuable support.

International Society for Biological and Environmental Repositories (ISBER)
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Amy Cheung and Kim Williams CIRM

6.0 References

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[3] Helft, P. R., Champion, V. L., et al. (2007). Cancer patients' attitudes toward future research uses of stored human biological materials. Journal of Empirical Research on Human Research Ethics, 2(3), 15–22.

[4] Institute of Medicine (2012). The California Institute for Regenerative Medicine: Science, Governance, and the Pursuit of Cures. http://www.iom.edu/Reports/2012/The-California-Institute-for-Regenerative-Medicine-Science-Governance-and-the-Pursuit-of-Cures/Report-Brief120612.aspx

[5] FAQs, Terms and Recommendations on Informed Consent and Research Use of Biospecimens The Secretary's Advisory Committee on Human Research Protections (SACHRP) July 20, 20111. http://www.hhs.gov/ohrp/sachrp/commsec/attachmentdfaq'stermsandrecommendations.pdf.pdf

[6] see ISBER (2012). "2012 best practices for repositories: collection, storage, retrieval and distribution of biological materials for research." Biopreservation and Biobanking 10(2): 81-151.

[7] Dasgupta, I., Bollinger, J., et al. (20014). Patients' attitudes toward the donation of biological materials for the derivation of induced pluripotent stem cells. Cell Stem Cell 14: 9-12.

Appendix 1: Original Points to Consider, Comments & Revisions

Original Statement	Comments	Comment / Revised Statement
1. A review should be performed to ensure that iPSC derivation and distribution is not specifically precluded by, or otherwise in conflict with, the original informed consent. Common examples of where conflicts may arise include language indicating: • The original principal researcher and/or the primary research team will manage the distribution of specimens or their products. • The specimen will only be utilized to study a particular disease or condition. • The specimen or resulting information will not be used for commercial purposes. • The specimen will only be utilized or distributed within a certain jurisdiction. iPSC lines containing limitations on use should only be deposited in a repository if transfer agreements address such restricted uses in conformity with the scope of the donor's consent. Moreover, subsequent transfer agreements for secondary or tertiary research should comply with any restrictions stipulated in the original donor's consent.	• Simply stated, "repurposing should not violate the original purpose." • One future challenge may be how particular disease conditions are defined. • The US HHS Secretary's Advisory Committee oh Human Research Protections letter dated July 20, 2011 provides additional guidance for such reviews.	Statement was not modified in response to comments. The HHS 7/20/11 statement was reviewed and the original statement appears to be consistent with the SACHRP recommendations.
2. iPSC derivation and use should be considered a standard method for modeling disease and developing therapies. In cases where the original biospecimen collection is designed to study a particular disease condition, iPSC derivation and use (i.e. as a tool for research on that particular disease) should be considered consistent with this purpose. If the consent protocol indicated that biospecimens would only be utilized to study a particular disease or condition, the use of biospecimens to derive iPSCs in order to study the specified disease condition should be considered consistent with the intended purpose (ie., even if iPSCs were not mentioned explicitly in the previous consent protocol). Material transfer agreements accompanying	• Expansion upon the rationale for supposing that consent to collect and use specimens also includes the derivation of iPSC would be helpful.	2. If the consent protocol indicated the specimen would be utilized in disease research, iPSC derivation and use should be considered compatible with this purpose. iPSCs have become a standard tool for modeling disease and testing potential therapies. The consent review should consider whether it is reasonable to conclude that donors were informed that a best-science approach would be used to perform disease research. In this context, iPSCs serve as a research tool in contemporary disease research. A best-science approach supports beneficence by seeking to maximize possible societal benefits of specimen donation.

distributed biospecimens and iPSC lines should reflect any limitations related to the disease or condition that may be studied.		If the consent protocol indicated that biospecimens would only be utilized to study a particular disease or condition, the use of biospecimens to derive iPSCs in order to study the specified disease condition should be considered consistent with the intended purpose (ie., even if iPSCs were not mentioned explicitly in the previous consent protocol). Material transfer agreements accompanying distributed biospecimens and iPSC lines should reflect any limitations related to the disease or condition that may be studied.
3. A reference to the possibility of sharing biospecimens with other researchers in the original consent form is sufficient for distributing material via an iPSC repository. Obtaining consent to share biospecimens with other researchers has become common practice and is consistent with broad data sharing goals that have been articulated in order maximize the public benefits of funded research. Repositories are a primary means of distributing iPSC lines. Therefore, deposit in a repository can be deemed to be consistent with a broad reference to sharing biospecimens with other researchers. As the sharing of de-identified biospecimens to derive iPSC lines and the deposition of those lines becomes widespread, it is important to ensure that donors are broadly aware of such practices.	• A specific statement about sharing may be too narrow. There may be robust consent where the donor is informed that the specimens will be used broadly in research. Absent the narrow conditions described in statement 1 (e.g. will only be used by the research team, will not be shared), there may be consents that nonetheless support sharing and distribution without using those precise words. Attention should be given to how "research" is characterized.	3. A reference to the sharing biospecimens with other researchers in the original consent form is sufficient for distributing material via an iPSC repository. Indicating the specimens will be use broadly in research may also be sufficient provided wide distribution is not precluded (see statement 1). Sharing biospecimens with other researchers has become common practice and is consistent with broad data sharing goals that have been articulated in order to support beneficence and maximize the societal benefits of publicaly-funded research. Repositories are a primary means of distributing iPSC lines. Therefore, deposit in a repository can be deemed to be consistent with a reference to sharing biospecimens with other researchers and/or broad research use provided the repository employs operational standards described in section 3.1.
4. A reference to genetic research and the risks thereof should have been included in the original consent form if raw individual-level genotypic data is to be deposited in an open access database. The reporting of raw, individual genotypic information in open access databases affects the privacy interests of the donor (see, for example, [6]),	• The term "raw" genotypic data may not be clear, should include technically precise language. • The concept to consider here is: do not deposit data that could be reasonably anticipated to result in the identification of the donor	4. A reference to genetic research and the risks thereof should have been included in the original consent form if individual-level genotypic sequence data are to be deposited into a research database (e.g. one that is widely accessible). A determination should be made that the deposit

whether or not the data have been de-identified. Such reporting should not take place unless the donor is informed of, and has consented to, genetic studies or genomic analysis being an integral part of the proposed research. However, the absence of such a disclosure does not necessarily mean that genomic analysis is inappropriate in the context of a specific study, or that population-level genomic data cannot be shared. For example, genotypic analysis may be integral to research intended to elucidate a disease mechanism. This statement pertains only to the conditions under which "raw" individual genotypic data may be placed in the broadly accessible databases.	unless the donor has been informed. • Individual genetic information should not be "open access" minimal administrative controls should be employed. • Should consider this standard with regard to controlled access database too. • This may be problematic internationally. For example, French law requires specific consent for genetic studies.	does not result in substantial new risks to the donor about which they have not been informed, and there are no legal restrictions on such deposit. The reporting of individual genotypic data affects the privacy interests of the donor (see, for example, [6]), whether or not the data have been de-identified. Such reporting should not take place unless the donor is informed of, and has consented to, genetic studies or genomic sequencing. In addition, the repository receiving the data should maintain a level of administrative control sufficient to determine who has accessed specific sequence data. However, the absence of such a disclosure does not necessarily mean that genomic analysis and characterization is inappropriate in the context of a specific study, or that population-level genomic data cannot be shared. For example, genotypic analysis may be integral to research intended to elucidate a disease mechanism. This statement pertains only to the conditions under which individual genotypic sequencing data may be placed in the broadly accessible databases.
5. A reference to commercial use should have been included in the original consent form if resulting cells lines will be used to develop commercial products. The donor should be informed that materials may be used for commercial purposes (e.g., as a drug assay by a pharmaceutical company) and that the donor will not have legal or financial interest in any resulting commercial development or patents. Absent this disclosure, materials or resulting cell lines should only be used for non-commercial (research use only) purposes.	• This statement should make clear that the actual cells or direct derivatives would not become a commercial or transplantation product. Knowledge gained from use of the lines may contribute to commercial products or the lines may be used to test products. The scope of this statement should be on the iPSC cells and be oriented to not selling peoples cells without consent. • More definition of 'commercial use' would be beneficial; for example, an aliquot of derived iPSC that is sold to another researcher for their research use. Where is	5. A reference to commercial use should have been included in the original consent form if resulting cells lines or derivatives (e.g. proteins or nucleic acids) are developed as commercial products. The donor should be informed that materials may be used for commercial purposes and that the donor will not have legal or financial interest in any resulting commercial development or patents.

	the line between sharing a biospecimen with other researchers and commercially providing a research tool?	
6. If specimens are to be used to create a cell line or cell product intended for human transplantation, the donor should have been informed that his or her specimen may be used to create human transplantation products. Although we expect it to be rare that a biospecimen previously collected for research purposes will be re-directed to create cell lines/products for human transplantation or clinical use, there might be a particularly valuable cell line amenable to this purpose. Donors should consent explicitly to the use of their specimens in human transplantation.	No comments received; statement is unchanged.	
7. Reference to unspecified or unforeseen future studies or research in the consent document should be interpreted to refer to activities designed to develop or contribute to generalizable scientific knowledge. However, such a reference to unspecified or unforeseen studies or research should not be interpreted to include commercial product development or human transplantation.	• See Statement 5 comments	7. Reference to unspecified or unforeseen future studies or research in the consent document should be interpreted to refer to activities designed to develop or contribute to generalizable scientific knowledge. However, such a reference to unspecified or unforeseen studies or research should not be interpreted to include developing the resulting cells lines or derivatives (e.g. proteins or nucleic acids) into commercial or human transplantation products.
8. iPSC should not be used for studies intended to generate gametes or embryos without a specific consent. In addition to ensuring that applicable law, policy, and material transfer agreements are followed, the development of gametes from somatic cells should only take place with specific consent from the original donor. We are hesitant to suggest exceptional conditions be placed on the use of iPSC, but also believe, especially in the context of previously collected specimens, that such use would be outside of what a donor could have reasonably contemplated during the consent process. We have previously recommended that gamete creation and embryogenesis be specifically highlighted and addressed in the prospective consent context. Given the sensitivity of this line of research, researchers have a responsibility to be transparent with donors about the use of their specimens in this research. (see section 2.5)	No comments received; statement is unchanged.	

Appendix 2: Workshop Participants

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Appendix 3: Additional Issues & Topics for Consideration

Issue / Topic	Comments
1. Specimens form children or other special populations: international recommendations and policy documents suggest minors should provide new or revised consent when they become legally competent.	The DISCUSS recommendations are narrowly tailored to address the "repurposing" of specimens obtained from adult donors. Many commenters highlighted the need to address the special context of children and minors as donors. We concur that there may be a need to additional polices and procedures to govern specimens from minors and other special populations. The DISCUSS is intended as a foundation to be built upon to address these broader considerations.
2. Use of specimens where consent is silent: some participants express concerns over the use of specimens where consent is silent preference should always be for new consent when the proposed use is outside the scope of the original consent.	We found the issue of consent being silent for a particular application to be the most challenging. There is a diverse range of evolving views on this point. Many commenters suggested it is difficult to develop clear guidance. Rather each case needs to be considered in the context of the existing consent and the proposed research application. Figure 4, Check Points in Repository Systems suggest an how a deliberative approach is made operational. Also, the DISCUSS report emphasizes the U.S. HHS Advisory Committee recommendation that anonymization of specimens not be utilized as a means of circumventing the consent process.
3. High-value samples should not be excluded: There will be samples or diseases of high importance where re-consent is impossible or impracticable. Such specimens may have been collected in accordance with legal / ethical norms, but do not align with more contemporary standards.	In out original points to consider, we suggest there may be a compelling scientific reason to use a line where re-contact is impossible or impracticable. Such a situation is likely to exist for certain well-characterized cell lines obtained prior to the development of contemporary guidelines for stem cell research. In such circumstances we recommend: • The scientific rationale / imperative be documented as when depositing the line to the iPSC repository • The repository should have a policy receipt and distribution of such lines and apply the policy consistently for iPSC collections
4. Inconsistent or arbitrary policy: Advocating for "consistency" with the consent but saying samples should not be excluded appears to be a contradictory position.	There are numerous initiatives underway to derive and bank libraries of iPSC lines. These collections are being developed in accordance with consent procedures for iPSC derivation. Thus, the majority of iPSC lines deposited to international repositories conform to contemporary guidelines. We anticipate there will be some lines that do not conform to contemporary standards, but this deviation will be limited. We emphasize providing a compelling scientific rational for the deposit of such lines to define the conditions when exceptions are scientifically warranted.
5. Statement 9 is ambiguous: The original DISCUSS recommendations include consideration of the donor's ability to withdraw from "the proposed iPSC	We agree this statement is ambiguous and, therefore, dropped it from the revised Points to Consider in Appendix 1.

research." Commenters pointed out that the DISCUSS project was focused on specimens that were not originally intended for iPSC research. Therefore, the original Statement 9 is not applicable and ambiguous.	
6. Bio-specimens subject to withdraw: There are differing views on what materials should be subject to withdraw. Numerous commenters asked whether cells or cell products derived from somatic cells would be subject to withdraw from a repository.	The donor's right to withdraw specimens from research should be stipulated in the original research consent. Options may include, destruction of all materials including derivate products, destruction of original donated specimens, deidentification of original and or derived specimens. If derived iPSC are deposited to a repository, a mechanism should be in place to ensure the donor may withdraw consistent with the consent provisions. There are justifiable reasons for limiting a donor's ability to withdraw derived iPSC lines. For example, many consent forms for iPSC derivation include a provision that derived lines may continue to be distributed, though only if deidentified. However, this limitation should be described in the donor consent. Absent this disclosure, transformation of somatic cells to iPSC cell should not limit a donors ability to withdraw specimens from research.

Appendix 4: Final Points to Consider

Statement 1: A review should be performed to ensure that iPSC derivation and distribution is not specifically precluded by, or otherwise in conflict with, the original informed consent.

Common examples of where conflicts may arise include language indicating:

- The original principal researcher and/or the primary research team will manage the distribution of specimens or their products.
- The specimen will only be utilized to study a particular disease or condition.
- The specimen or resulting information will not be used for commercial purposes.
- The specimen will only be utilized or distributed within a certain jurisdiction.

iPSC lines containing limitations on use should only be deposited in a repository if transfer agreements address such restricted uses in conformity with the scope of the donor's consent. Moreover, subsequent transfer agreements for secondary or tertiary research should comply with any restrictions stipulated in the original donor's consent.

Statement 2: If the consent protocol indicated the specimen would be utilized in disease research, iPSC derivation and use should be considered compatible with this purpose.

iPSCs have become a standard tool for modeling disease and testing potential therapies. The consent review should consider whether it is reasonable to conclude that donors were informed that a best-science approach would be used to perform disease research. In this context, iPSCs serve as a research tool in contemporary disease research. A best-science approach supports beneficence by seeking to maximize possible societal benefits of specimen donation.

If the consent protocol indicated that biospecimens would only be utilized to study a particular disease or condition, the use of biospecimens to derive iPSCs in order to study the specified disease condition should be considered consistent with the intended purpose (ie., even if iPSCs were not mentioned explicitly in the previous consent protocol). Material transfer agreements accompanying distributed biospecimens and iPSC lines should reflect any limitations related to the disease or condition that may be studied.

Statement 3: A reference to the sharing biospecimens with other researchers in the original consent form is sufficient for distributing material via an iPSC repository. Indicating the specimens will be use broadly in research may also be sufficient provided wide distribution is not precluded (see statement 1).

Sharing biospecimens with other researchers has become common practice and is consistent with broad data sharing goals that have been articulated in order to support beneficence and maximize the societal benefits of publicaly-funded research. Repositories are a primary means of distributing iPSC lines. Therefore, deposit in a repository can be deemed to be consistent with a reference to sharing

biospecimens with other researchers and/or broad research use provided the repository employs operational standards described in section 3.1.

Statement 4: A reference to genetic research and the risks thereof should have been included in the original consent form if individual-level genotypic sequence data are to be deposited into a research database (e.g. one that is widely accessible). A determination should be made that the deposit does not result in substantial new risks to the donor about which they have not been informed, and there are no legal restrictions on such deposit.

The reporting of individual genotypic data affects the privacy interests of the donor (see, for example, [6]), whether or not the data have been de-identified. Such reporting should not take place unless the donor is informed of, and has consented to, genetic studies or genomic sequencing. In addition, the repository receiving the data should maintain a level of administrative control sufficient to determine who has accessed specific sequence data.

However, the absence of such a disclosure does not necessarily mean that genomic analysis and characterization is inappropriate in the context of a specific study, or that population-level genomic data cannot be shared. For example, genotypic analysis may be integral to research intended to elucidate a disease mechanism. This statement pertains only to the conditions under which individual genotypic sequencing data may be placed in the broadly accessible databases.

Statement 5: A reference to commercial use should have been included in the original consent form if resulting cells lines or derivatives (e.g. proteins or nucleic acids) are developed as commercial products.

The donor should be informed that materials may be used for commercial purposes and that the donor will not have legal or financial interest in any resulting commercial development or patents.

Statement 6: If specimens are to be used to create a cell line or cell product intended for human transplantation, the donor should have been informed that his or her specimen may be used to create human transplantation products.

Although we expect it to be rare that a biospecimen previously collected for research purposes will be re-directed to create cell lines/products for human transplantation or clinical use, there might be a particularly valuable cell line amenable to this purpose. Donors should consent explicitly to the use of their specimens in human transplantation.

Statement 7: Reference to unspecified or unforeseen future studies or research in the consent document should be interpreted to refer to activities designed to develop or contribute to generalizable scientific knowledge. However, such a reference to unspecified or unforeseen studies or research should not be interpreted to include developing the resulting cells lines or derivatives (e.g. proteins or nucleic acids) into commercial or human transplantation products.

Statement 8: iPSC should not be used for studies intended to generate gametes or embryos without a specific consent.

In addition to ensuring that applicable law, policy, and material transfer agreements are followed, the development of gametes from somatic cells should only take place with specific consent from the original donor. We are hesitant to suggest exceptional conditions be placed on the use of iPSC, but also believe, especially in the context of previously collected specimens, that such use would be outside of what a donor could have reasonably contemplated during the consent process. We have previously recommended that gamete creation and embryogenesis be specifically highlighted and addressed in the prospective consent context. Given the sensitivity of this line of research, researchers have a responsibility to be transparent with donors about the use of their specimens in this research.