

The American Public Is Ready to Accept Human-Animal Chimera Research

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SUMMARY

We report findings from a new survey of US public attitudes toward human-animal chimeric embryo (HACE) research, designed to compare with recently reported Japanese survey data. We find that 59% of the US public can personally accept the process of injecting human induced pluripotent stem cells into genetically modified swine embryos and having human tissues produced in a pig's body transplanted into a human. This is greater acceptance than in Japan, and there is even strong acceptance among those with strong religious affiliations and who self-identify as conservatives. We argue that strong public support for HACE research, as well as the emerging literature suggesting that humanization of research animals is very unlikely, should compel the NIH to lift its current moratorium on HACE research.

INTRODUCTION

In the fall of 2015, the National Institutes of Health (NIH) issued notice NOT-OD-15-158, effectively placing a moratorium on funding research, “in which human pluripotent cells are introduced into non-human vertebrate animal pre-gastrulation stage embryos while the Agency considers a possible policy revision in this area.” The purpose of this moratorium was for the NIH to undertake a deliberative process in an effort to study the state of the science, as well as the ethical, legal, and social implications of human-animal chimeric embryos (HACEs). But other countries are now re-examining their policies toward HACE research (Foong, 2019). In March 2019, Japan's Ministry of Education, Culture, Sports, Science, and Technology lifted the country's ban on conducting research on HACEs beyond 14 days after the introduction of human pluripotent stem cells or the appearance of the primitive streak (Sawai et al., 2019). Four months later, Hiromitsu Nakauchi of the University of Tokyo and Stanford University received permission from the Japanese government to create human-animal embryos to be transplanted into surrogates (Lanese, 2019). In July 2019, a group at the Salk Institute in San Diego announced that, with partners in Spain and China, they had created embryos containing both human and monkey cells (Lanese, 2019).

In 2016, the NIH released notice NOT-OD-16-128, requesting public comment on the proposed changes to

the *Guidelines for Human Stem Cell Research*. The Administrative Procedures Act of 1946 (Pub. L. No. 79-404) requires that federal rulemaking engage the public through public notice and comment. The public comment mechanism reflects an interest in considering public views when making science policy (Kolber, 2009). It is clear that the majority of those who commented in response to NOT-OD-16-128 objected to HACE research (National Institutes of Health). But the degree to which these responses are reflective of the general public were unknown.

In Japan—leading up to the change in government policy—Japanese researchers surveyed the public and identified the overall levels of support as well as the factors contributing to support for HACE research (Sawai et al., 2017a). To better inform policy debates in the United States, we replicated the Japanese study with a sample of Americans. Similar to the Japanese public, we find broad public acceptance for the injection of human induced pluripotent stem cells (iPSCs) into genetically modified swine embryos. We also find evidence of resistance to HACE research—with significantly lower support from individuals who object to animal research generally. Based on these findings, as well as mounting evidence that HACE research can be conducted without causing animal humanization, we argue that the NIH should lift its moratorium and replace it with strict guidelines for ethically sound research.

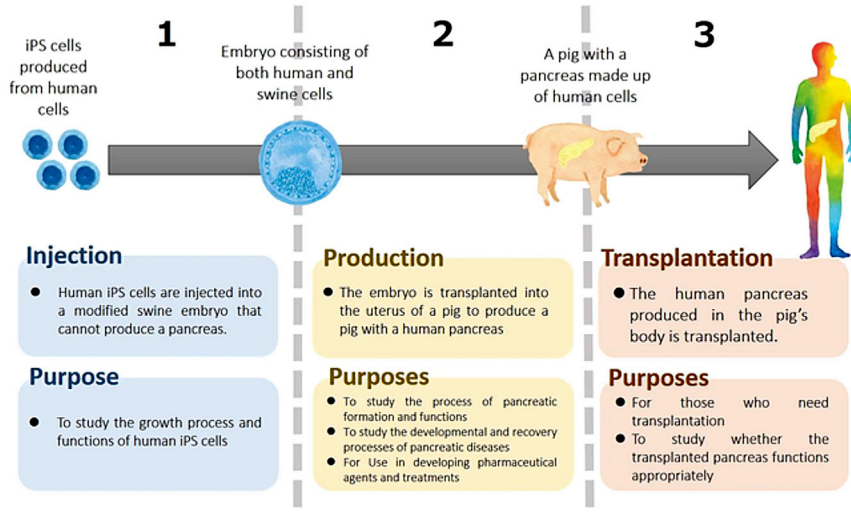


Figure 1. Illustration of the Three Progressive Steps in HACE Research

Image that was shown to survey participants to (adapted from Sawai et al., 2017a).

RESULTS

Analysis of Public Attitudes toward HACE Research in the United States

In July 2018 and June 2020, 430 survey participants, from 48 states, were recruited via Amazon's Mechanical Turk service and completed a survey hosted on the Qualtrics online platform. The demographics of the study participants are reported in Table S1. The survey replicated and adapted the Sawai and colleagues study of Japanese public attitudes on HACE research (Sawai et al., 2017a). While underpowered and not sufficiently diverse to generalize to the American population as a whole, the sample remains national and we gain confidence in our results as they are consistent with other recent data on American public attitudes toward HACE research (Kantor, 2017; Pew Research Center, 2018).

Using the pancreas as an example organ, all participants were shown Figure 1 to demonstrate the progressive steps of HACE research. Participants were then asked, "What steps of this research are you willing to accept according to your personal feelings?"

- **Step 1, Injection:** human iPSCs are injected into a modified swine embryo that cannot produce a pancreas.
- **Step 2, Production:** the embryo is transplanted into the uterus of a pig to produce a pig with a human pancreas.
- **Step 3, Transplantation:** the human pancreas produced in the pig's body is transplanted into a human.
- **None:** participants were also able to note if none the steps were acceptable to them.

This approach allowed us to determine the level of acceptance for each stage of the research, as well as acceptance

for chimerism in other organ and tissue systems. Across the 430 participants in the survey, there was broad acceptance for at least some HACE research, with 83% of the participants in our sample accepting at least injection of human iPSCs into genetically modified swine embryos (step 1), 71% accepting production of a pig with a human pancreas (step 2), and 59% accepting clinical transplantation of the HACE-generated pancreas (step 3; Figure 2).

Although general support for HACE research is overwhelmingly positive, we were able to identify subpopulations of Americans who do not personally accept HACE research. Statistical analysis finds that there are significant and substantively meaningful differences in support between participants who (in a separate question) said they support the use of animals for research and those who do not (Figure 3; Table S2). We also found significant differences between conservative and liberal participants, and those who acknowledged the importance of religion in their daily life.

Broken down further, we identified variable levels of acceptance of the contribution of human cells within specific organ/tissue systems. Specifically, Americans were less likely to personally accept the presence of human cells in sperm/egg (44%) and brain (51%), relative to heart (61%), blood (64%), liver (73%), and skin (62%). Ordered logistic regression identified significant differences with individuals opposed to animal research in all organ tissue systems (Figure 4; Table S3). Individuals with a religious affiliation were less likely to accept human cells in sperm/egg, brain, and blood (Table S3).

Although the within-cultural differences between these communities are important, our study allows cross-national comparison with the Japanese results (Sawai et al., 2017a). Figure 4 demonstrates that even the groups with

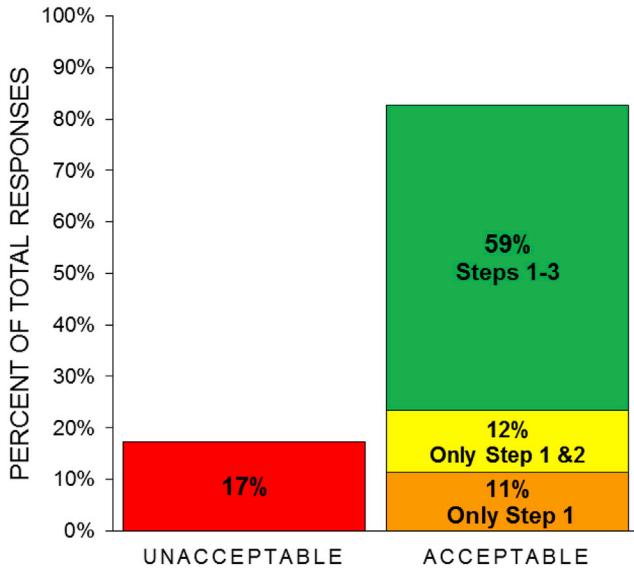


Figure 2. American Public Acceptance of the Three Steps of HACE Research

Graph of the proportion of total survey participants when asked the question: “What steps of this research are you willing to accept according to your personal feelings?”

lower acceptance in the United States are still more accepting than the Japanese general public. For instance, while only 43% of the Japanese public can accept human iPSCs in a pig’s bloodstream, it is accepted by 62% of US conservatives and 48% of US participants who are not favorable to animal research generally (Table S3). These groups are similarly more supportive than the Japanese public of the use of iPSCs in pig’s sperm/egg and brain. It is clear that, compared with Japan, there is wide acceptance of HACE research in the United States.

DISCUSSION

Research involving HACEs has the potential to answer significant questions in human developmental biology and be a source of human organs and tissues that can be used to combat the donor organ shortage across the globe. Our new survey data suggest the American public sees the potential of HACE research and is ready to accept it in a variety of forms.

These results are in support of findings by two separate nationally representative surveys in which a majority of respondents were in favor of HACE research (Kantor, 2017; Pew Research Center, 2018). The present study is unique in that we have provided greater detail on the stages of HACE research for organ production and transplantation and identified personal acceptance for each of these stages. In our study, we identified 11% of respondents whose per-

sonal acceptance of HACE research does not extend beyond the injection of human cells into a pig embryo (step 1), which may suggest a hesitancy toward applications of this technology. Our study was also able to examine how support for HACE research varies across multiple dimensions, with opposition to HACE research in individuals self-described as generally opposing animal research, supporting previous results (Kantor, 2017; Pew Research Center, 2018), as well as in individuals self-described as religious and politically conservative.

The present study was also able to identify personal acceptance of human cells contributing to individual organ/tissue systems. Although personal acceptance of human cells within specific organ/tissue systems is framed in the context of off-target effects from the production of a human pancreas in a pig, these data can be used as a guidepost for policy regarding targeted generation of human organ/tissue systems.

Another unique feature of this survey was the ability to directly compare cross-culturally, suggesting that, even more so than the Japanese public, the American public is ready to accept HACE research. It should be noted that no study, to date, has determined participant comprehension of the concept of HACE research. Future research should examine in greater detail how lay subjects understand HACE research, even when presented in detail as we did in this survey.

As public acceptance of HACE research in both the United States and Japan is emerging, the Japanese government has recently taken the next step to approve studies that involve generating human-animal chimeras (Cyrnoski, 2019). Japan and other countries such as China are continuing to pursue such work, and there is an increase in the number of publications with a focus on multiple tissue systems integrating with gene-editing technologies (Crane et al., 2019a).

Despite the NIH moratorium, American researchers have nevertheless found ways to collaborate with international partners. The promise of this research line, and the strong support of the public for more of it, suggests that these work-around arrangements are likely to increase. Science will not sit idle. The NIH will face significant difficulties in maintaining a strict ethics framework when the research is funded and governed by foreign countries.

Working around the NIH moratorium, however, can lead to problematic ethical and policy issues. Our data, for instance, confirm ethical analysis suggesting that there is strong opposition from those who are generally skeptical about the necessity of animal research (Moy, 2017). Our study also identifies specific opposition to the contribution of human cells to the brain and sperm/egg of pigs. As the International Society for Stem Cell Research has recommended, HACE research should be undertaken only within

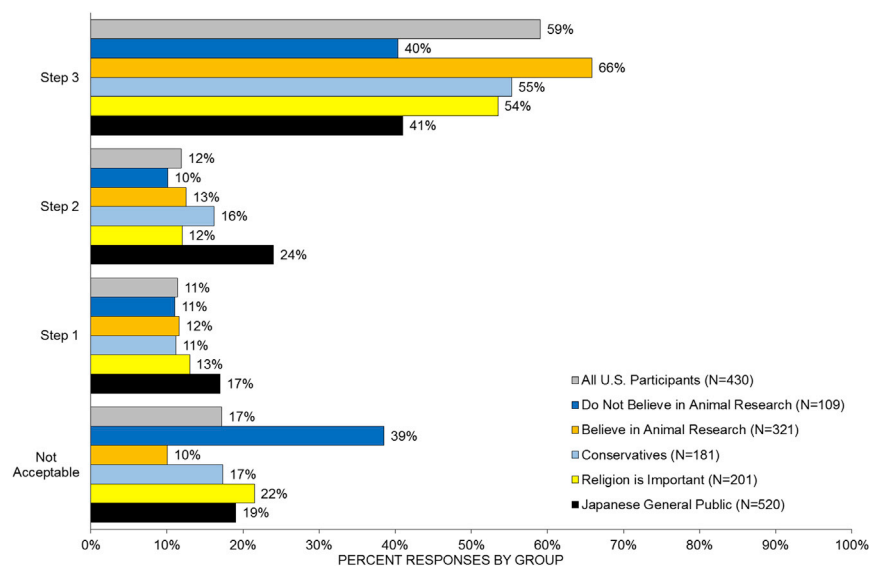


Figure 3. Acceptance of the Three Steps of HACE Research across Different Subgroups of American Participants and in the Japanese General Population

Each horizontal bar depicts the percentage of survey participants who supported up to that step in HACE research. See also Table S2.

clear ethical frameworks and with strict oversight, particularly regarding the contribution of human cells to the brain and reproductive organs. The present results serve to help shape those recommendations and policies, by better clarifying the differential public support for various aspects of the research.

Our literature review of more than 60 scholarly articles exploring the ethics of HACE research identified three primary concerns unique to human chimeric research: (1) infringement upon the natural order/“playing God”; (2) violations of human dignity; and (3) the potential humanization and resulting moral and legal status of the chimeric animal. These issues have been discussed at length elsewhere (Greely, 2011; Palacios-González, 2015; Streiffer, 2019) and should all be addressed when developing a new policy.

Of particular concern among respondents in the current study is the contribution of human cells in the brain of the pigs and the potential neurological humanization of the animals involved in HACE research (Crane et al., 2019b; Sawai et al., 2017b). Assuming humanization is possible, it would require researchers to contend with both the moral status of the resulting chimeric individual and the consequences of blurred species lines, including potential moral confusion (Baylis and Robert, 2007; Hübner, 2018). Some ethicists recommend a precautionary approach, but others argue that partially humanized animals should simply be treated commensurately with a moral worth derived from the animal’s cognitive capacity (Porsdam Mann et al., 2019).

But how likely is it that humanization (however defined) will actually occur? Our recent review of 150 peer-reviewed transplantation studies found that, while a relatively high degree of human-animal neurological chimerism has

been observed in multiple studies, there was no evidence to suggest that integration of human neurons within the non-human animal results in humanization (Crane et al., 2019b). Thus, although humanization *could* theoretically be an issue and should remain a focal point of ethical and legal concern when developing a new policy, HACE research currently being conducted has observed very limited contribution of human cells to a non-human animal brain in preterm human-animal chimeras. It has been previously proposed that, if HACE research should be allowed to resume, investigators monitor the extent to which human cells contribute to a non-human animal brain in a stepwise approach (Crane et al., 2019b) under careful ethical guidelines, to limit the likelihood that “human cells in an animal” will result in “humanization” of the sort that has generated so much ethical concern.

The Path Forward

In light of the strong public acceptance of HACE research, the path forward should be an eventual lifting of the moratorium on HACE research. In its place, the NIH should develop policy that adequately addresses ethical challenges such as animal welfare, human dignity, and neurological humanization. This policy can build on existing guidelines set forth by national and international research societies, current policies of foreign governments, and the well-developed ethics literature in this area, while also considering stakeholder input, including public survey data, to ensure concerns over the contribution to the brain and reproductive organs are addressed. Pursing such a path would garner not only the support of wide swaths of the scientific research community, but that of the vast majority of the American public as well.

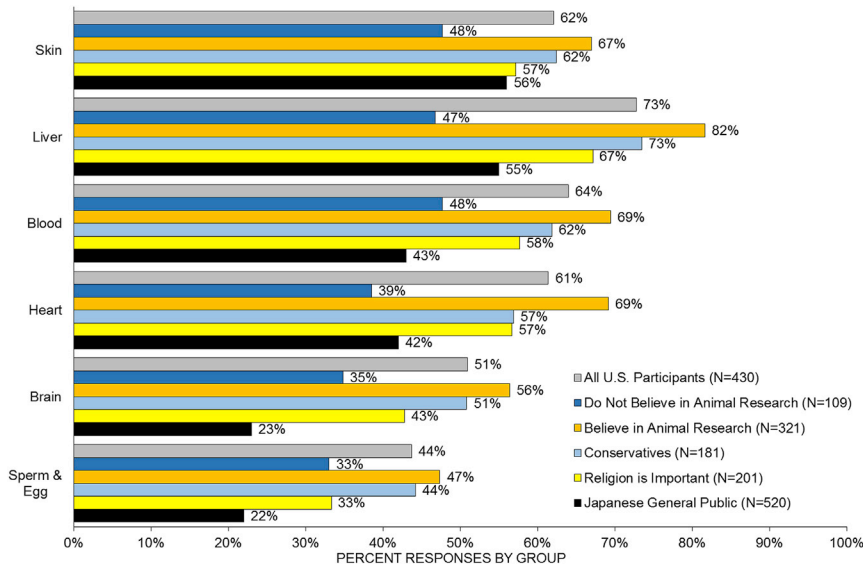


Figure 4. Acceptance of the Contribution of Human Cells to Organ/Tissue Systems across Different Sub-groups of American Participants and in the Japanese General Population

Percentage of survey participants who chose “can accept” or “somewhat can accept” when asked the question: “According to your personal feelings, can you accept the presence of human iPSC cells in the following pig organs?” For each of six organs—liver, brain, sperm/egg, skin, blood, and heart—participants were asked to choose “I can accept it,” “I can somewhat accept it,” “I somewhat cannot accept it,” or “I cannot accept it.” See also [Table S3](#).

EXPERIMENTAL PROCEDURES

Survey Design

To facilitate cross-national comparison with support for HACE research in Japan, this study translated survey questions from Sawai and colleagues (Sawai et al., 2017a) and adapted questions on demographics for the US population (Supplemental Experimental Procedures). Our survey was conducted using the online survey platform Qualtrics. Qualtrics has been used in many fields, including bioethics (Wangmo and Provoost, 2017) and neuroethics (Cancer et al., 2018). After reading an informed consent page (UMN IRB Approved, study 00001760), participants read a brief page of information describing iPSCs. The information was translated from similar text used in the Sawai survey. Participants then answered a series of 10 questions related to their support of, and concerns about, HACE research. Following this battery of questions, participants then answered a series of background and demographic questions.

Recruitment of Survey Participants

The study includes two waves of data collection. In July 2018, 227 participants were recruited via Amazon’s Mechanical Turk service to participate in our survey hosted on the Qualtrics online platform. To increase our sample size and provide a greater generalization to the American public, an additional survey was conducted in June 2020 and data from 203 participants were combined with those of the 227 participants for a total of 430 participants. We present here the results from analysis of the combined dataset including both waves of respondents. When analyzed independently, the results from the 2018 data and from the 2020 data analysis yield substantively similar conclusions and do not alter the main conclusions of this report. Amazon Mechanical Turk is “a web service that provides an on-demand, scalable, human workforce to complete tasks” (Amazon Mechanical Turk, 2014). Researchers advertise their studies on Mechanical Turk, and participants choose only those studies that interest them. Participants

are paid for completing the studies. Payment is transferred directly to the participants’ credit cards immediately after the completion of a study. We paid participants \$1.00 for completion of the survey. No personally identifying information was collected. Mechanical Turk is regularly utilized by researchers in multiple disciplines to recruit participants to complete online research tasks (Amazon Mechanical Turk, 2014; Buhrmester et al., 2011; Paolacci et al., 2010; Sheehan and Pittman, 2016). A Human Intelligence Task “is a single, self-contained task a Requester creates on Mechanical Turk” (Sheehan and Pittman, 2016). We recognize that participants recruited via Mechanical Turk are not representative of the US public (Mortensen et al., 2018; Walters et al., 2018). Mechanical Turk samples, including ours, are typically younger, more educated, more liberal, and less racially diverse than the US general population (Berinsky et al., 2012; Paolacci and Chandler, 2014; Shapiro et al., 2013).

Ensuring Data Quality

In total, 743 surveys were logged through the Mechanical Turk service. Prior to analysis, survey responses were removed if participants completed less than 97% of the survey questions and if the duration of the survey was less than 100 s. This first pass removed 73 surveys. Ten surveys were then removed due to duplicate individual Mechanical Turk identification numbers. Concern about subjects’ compliance with survey instructions are of special interest with online surveys because subjects cannot be monitored while engaged in the online task. To address this issue, psychologists have developed “attention filters” designed to ascertain whether subjects are in fact following instructions and paying attention to the material being presented to them online. In this study, we employed a modified version of the filter developed by psychologist Oppenheimer and colleagues (Oppenheimer et al., 2009). The design of the attention filter question was such that users who did not read carefully would see, in large font, a headline reading “Background Questions on Sources for News” as well as another large, bold question: “From which of these sources have



you received information in the past month?" A series of checkbox options was provided (e.g., local newspaper, local TV news). Subjects reading carefully, however, were instructed to check only the "magazine" box and to type "654" into the text box provided. The results presented in this article are based only on the "attentive" subjects, i.e., those subjects who were paying attention. Here, 135 of 620 (22%) did not complete the attention filter properly and were excluded from the analysis reported in the article. Finally, surveys in which responses on political ideology were absent were removed, leaving 430 surveys for analysis. Re-running the models reported below with the excluded participants included does not change the substantive results.

Analytic Methods

All statistical analysis was carried out using the program Stata, version 16.1. In addition to summary statistics and basic difference in means test, analysis utilized ordered logistic regression models. This is appropriate because our outcome variables take on values of 0, 1, 2, 3, and so on, i.e., they are non-continuous and they are ordered. Multicollinearity was assessed using the collin package in Stata. The mean VIF was 1.10 for the independent variables included in this model, suggesting no severe multicollinearity issues with the model.

Data and Code Availability

The complete dataset (Table S4), captions for Table S4, and complete survey are available in the Supplemental Information.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at <https://doi.org/10.1016/j.stemcr.2020.08.018>.

AUTHOR CONTRIBUTIONS

Conceptualization, A.T.C., F.X.S., T.S., T.H., M.F., and W.C.L.; Methodology, A.T.C., F.X.S., J.L.B., J.P.V., and W.C.L.; Formal Analysis, A.T.C., F.X.S., J.L.B., and M.R.E.; Writing – Original Draft, A.T.C., F.X.S., W.C., and W.C.L.; Writing – Review & Editing, A.T.C., F.X.S., J.L.B., W.C., M.R.E., J.P.V., T.S., T.H., M.F., and W.C.L.

CONFLICTS OF INTEREST

W.C.L. serves as a consultant for Saneron, is chief scientific officer for Regenevida, and is a founder of Metsalex. All other authors declare no competing interests.

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Supplemental Information

**The American Public Is Ready to Accept Human-Animal Chimera
Research**

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Table S1. Demographics of Experimental Subjects. Related to Experimental Procedures.

Education	Subjects	U.S. Census
Less than HS	1%	18%
High school / GED	19%	30%
Some college	3%	20%
Assoc. degree	9%	7%
Bachelor's	51%	17%
Graduate Degree	17%	10%

Gender	Subjects	U.S. Census
Male	60%	49%
Female	40%	51%

Political Ideology	Subjects
Very Liberal	11%
Liberal	19%
Somewhat Liberal	11%
Moderate	17%
Somewhat Conservative	12%
Conservative	22%
Very Conservative	8%

Age Groups	Subjects	U.S. Census
18-24	8%	13%
25-34	49%	18%
35-44	21%	19%
45-59	17%	27%
60 +	5%	23%

Religious Affiliation	Subjects	U.S. Census
Yes	44%	61%
No	56%	39%

Animal Experiments Necessary	Subjects
Strongly Agree	30%
Somewhat Agree	44%
Somewhat Disagree	19%
Strongly Disagree	7%

Table S1.

Table S1 provides the summary demographics for the 430 participants in our online survey alongside available data from the 2010 U.S. Census.

Table S2. Results of ordered logistic regression by group. Related to Figure 3.

	Personally Acceptable (0-3 scale) Coef./(se)
Disagreement with Need for Animal Experiments	-0.807**/ (0.120)
Conservative Ideology	-0.108*/ (0.055)
Age	0.000/ (0.009)
Religiously Affiliated	-0.346*/ (0.202)
Ever Been Married	-0.107/ (0.227)
Education Level	0.087/ (0.072)

Table S2.

Table S2 presents the ordered log-odds (logit) regression coefficients and standard errors of the individual regression coefficients (in parentheses) from the ordered logistic regression model, N=430. The outcome variable takes on the values 0, 1, 2, and 3, with 0 indicating that the research is not acceptable, and 1, 2, and 3 representing acceptance of Step 1, Step 2, and Step 3 as described in Fig S1. Statistical significance is marked as follows: *** p<.01, ** p<.05, * p<.10. We checked for multicollinearity using the collin package in Stata. The mean VIF was 1.10 for the independent variables included in this model, suggesting no severe multicollinearity issues with the model.

Table S3. Results of ordered logistic regression by group and organ. Related to Figure 4.

	Liver Coef./(se)	Brain Coef./(se)	Sperm/egg Coef./(se)	Skin Coef./(se)	Blood Coef./(se)	Heart Coef./(se)
Disagreement with Need for Animal Experiments	1.108** (0.12)	0.625** (0.107)	0.467** (0.109)	0.815** (0.112)	0.666** (0.108)	0.892** (0.113)
Conservative Ideology	0.055 (0.052)	0.009 (0.048)	0.024 (0.049)	0.016 (0.05)	0.064 (0.049)	0.088 (0.05)
Age	-0.001 (0.008)	0.006 (0.008)	0.009 (0.008)	0.002 (0.008)	-0.003 (0.008)	-0.001 (0.008)
Religiously Affiliated	0.27 (0.187)	0.563** (0.18)	0.653** (0.181)	0.299 (0.182)	0.465* (0.181)	0.211 (0.181)
Ever Been Married	0.278 (0.214)	0.119 (0.199)	0.004 (0.199)	0.247 (0.206)	0.512* (0.203)	0.147 (0.204)
Education Level	0.033 (0.07)	-0.012 (0.064)	-0.051 (0.065)	0.062 (0.066)	0.083 (0.066)	0.111 (0.066)

Table S3.

Table S3 presents the ordered log-odds (logit) regression coefficients and standard errors of the individual regression coefficients (in parentheses) from the ordered logistic regression model analyzing participant responses to the survey question, "According to your personal feelings, can you accept the presence of human iPS cells in the following pig organs?" N=430. The outcome variable takes on the values 1-4, with 1="I can accept it," 2="I can somewhat accept it," 3="I somewhat cannot accept it," and 4="I cannot accept it." Statistical significance is marked as follows: *** p<.01, ** p<.05, * p<.10. We checked for multicollinearity using the collin package in Stata. The mean VIF was 1.10 for the independent variables included in this model, suggesting no severe multicollinearity issues with the model.

Table S4. Replication data for the analysis reported here is attached in the Excel sheet named TableS4.xlsx. Related to Experimental Procedures.

Codebook for TableS4:

Variable Name	Variable Label
recordid	Unique de-identified participant ID
personalaccept	What steps of this research are you willing to accept according to your personal feelings? 1 = step 1, 2 = through step 2, 3 = all steps, 4 = No steps
unaccept_ips_liver	According to your personal feelings, can you accept the presence of human IPS cells in the following pig organs? LIVER (1 = yes, 0 = no)
unaccept_ips_brain	According to your personal feelings, can you accept the presence of human IPS cells in the following pig organs? BRAIN (1 = yes, 0 = no)
unaccept_ips_sperm	According to your personal feelings, can you accept the presence of human IPS cells in the following pig organs? SPERM (1 = yes, 0 = no)
unaccept_ips_skin	According to your personal feelings, can you accept the presence of human IPS cells in the following pig organs? SKIN (1 = yes, 0 = no)
unaccept_ips_blood	According to your personal feelings, can you accept the presence of human IPS cells in the following pig organs? BLOOD (1 = yes, 0 = no)
unaccept_ips_heart	According to your personal feelings, can you accept the presence of human IPS cells in the following pig organs? HEART (1 = yes, 0 = no)
animalexperiments	Animal experiments are required for the development of medicine. (1 = strong agree, 2 = slight agree, 3 = slight disagree, 4 = strong disagree)
religious	Do you have a religious affiliation? (1 = yes, 0 = no)
religion	Please describe your main religious affiliation. 1= Christian, 2 = Buddhism, 3 = Islam, 4 = Judaism, 5 = Hinduism, 6 = Other
religion_important	How important is the doctrine of your religion for you in your daily life? (1 = very important, 2 = somewhat important, 3 = not very important, 4 = not important at all)
state	State (1 = Alabama, 2 = Alaska, 3 = Arizona...)
gender	Gender. 1 = Female, 2 = Male, 3 = Other
age	Age
education	Please tell us your educational background (the highest degree you have earned). (1 = less than HS, 2 = HS, 3 = vocational school, 4 = junior college, 5 = college degree, 6 = Masters, JD, MBA, 7 = doctorate)
married	Please tell us your marital history. (1= unmarried, 2 = married, divorced, widowed)
noanimalresearch	Participant disagrees that animal experiments are required for the development of medicine
conservative	Politically, I consider myself: (1) very liberal, (2) liberal, (3) somewhat liberal, (4) moderate, (5) somewhat conservative, (6) conservative, (7) very conservative.

Supplemental Experimental Procedures

[Complete Survey](#)

Revised Sawai Questionnaire

Start of Block: MTurkID

Q35 The accuracy of this survey requires that we ensure that you have not previously taken the survey. So that we can check this, please enter your MTurk ID below:

End of Block: MTurkID

Start of Block: Default Question Block

Q1 Research Purpose Thank you for your interest in participating in this study. This page outlines the purposes of the study and provides a description of your involvement and rights as a participant.

The purpose of this study is to learn about public opinion on a new scientific technology. There are less than minimal risks associated with completing this survey. There are no direct benefits to participating in this study.

We estimate that the survey will take you no more than 15 minutes to complete, and you will be compensated with \$ 0.75 for your participation.

Your participation in this research is voluntary. You have the right to withdraw at any point during the study if you no longer wish to participate. Your decision whether or not to participate will not affect your current or future relations with the University of Minnesota.

NO personally identifying information will be collected. The records of this study will be kept private. In any sort of report we might publish, we will exclude any information that will make it possible to identify a subject. Research records will be stored securely and only researchers will have access to these records. All study data will be encrypted. These records will be accessed only by members of the research team.

If you would like to contact the Principal Investigator in the study to discuss this research, please e-mail: Principal investigator: Francis Shen Contact: Fxshen@umn.edu Research Organization: University of Minnesota, Twin Cities If you have any questions or concerns regarding this study and would like to talk to someone other than the researcher, you are encouraged to contact the Research Subjects' Advocate Line, D528 Mayo, 420 Delaware St. Southeast, Minneapolis, Minnesota 55455; (612) 625-1650.

By continuing, you are agreeing to participate in this research study.

End of Block: Default Question Block

Start of Block: block 1.5

Q33

Study Specifics: Induced pluripotent stem cells (iPS cells) are stem cells generated from adult tissue which can give rise to all cells in the human body. A broad range of studies using iPS cells have received widespread attention. Some of those studies involve infusing animal embryos with human iPS cells. Currently, discussions to establish better rules for such studies are underway. However, it is not clear what kind of expectations and concerns researchers engaging in iPS cell research and the general public have. This survey was planned to collect answers from both researchers engaging in iPS cell research and the general public to compare and examine their responses. This research aims to examine a few aspects of future iPS cell research. We would appreciate your understanding of the purpose of this survey as well as your participation in it. The contents of your response might be published in the form of research results in academic conferences, journals and websites where individuals cannot be identified.

Currently, a variety of studies on human induced pluripotent stem cells (iPS cells) are being conducted, such as injecting human iPS cells into swine embryos.

In this research human iPS cells are injected into a swine embryo, and the embryo is returned into a pig uterus to produce a pig with a human pancreas.

This research has the following purposes:

- (1) To study the growth and function of human iPS cells injected in swine embryos.
- (2) To study the process of pancreatic formation, pancreatic functions, and the developmental and recovery processes of pancreatic diseases, as well as to develop pharmaceutical agents and treatments by producing pigs with a human pancreas.
- (3) To potentially benefit those who need a transplant by studying whether the transplanted pancreas functions appropriately. (The pancreas is produced in a pig body, but the pancreas is human).

With current technology it is possible that human iPS cells will become a part of organs and tissues other than the pancreas during production of a pig with a pancreas made up of human cells.

End of Block: block 1.5

Start of Block: Block 2

Q2 From here, we would like to ask questions about your own opinions about the implementation of research injecting human iPS cells into swine embryos. What steps of this research are you willing to accept according to your personal feelings? Please select all steps you think are acceptable.

- 1) Click here if you feel that **ONLY Step #1 is acceptable: Human iPS cells are injected into a genetically modified swine embryo that cannot produce a pancreas.** (1)
- 2) Click here if you feel that **BOTH Steps #1 and #2 are acceptable: The embryo is transplanted into the uterus of a pig to produce a pig with a human pancreas.** (2)
- 3) Click here if you feel that **ALL 3 Steps #1, #2, and #3 are acceptable: The human pancreas produced in the pig's body is transplanted.** (3)
- 4) Click here if you feel that **NONE of the steps are acceptable, i.e that this is totally not acceptable (the actions in and of themselves).** (4)

End of Block: Block 2

Start of Block: Block 3

Q60 Up to which research steps do you think should be socially accepted?
Please select the farthest step you think should be socially accepted.

1. Human iPS cells are injected into a genetically modified swine embryo that cannot produce a pancreas. (1)
2. The embryo is transplanted into the uterus of a pig to produce a pig with a human pancreas. (2)
3. The human pancreas produced in the pig's body is transplanted. (3)
4. Totally not acceptable (the actions in and of themselves). (4)

End of Block: Block 3

Start of Block: Block 4

Q36 Now, we would like to ask questions about providing your own cells (blood, skin etc.) for the research by injecting human iPS cells into a swine embryo. Up to which step would you

be willing to provide your own cells to be used for the research by injecting human iPS cells into a swine embryo explained earlier?

- 1. Your iPS cells are injected into a genetically modified swine embryo that cannot produce a pancreas. (1)
- 2. The embryo is transplanted into the uterus of a pig to produce a pig with your pancreas. (2)
- 3. Your pancreas produced in the pig's body is transplanted. (3)
- 4. Totally not acceptable to use your cells. (4)

End of Block: Block 4

Start of Block: Block 5

Q32 Next, we would like to ask questions about providing a family member's cells (blood, skin etc.) for the research by injecting human iPS cells into a swine embryo.

Up to which step would you be willing to provide a family member's cells to be used for the research by injecting human iPS cells into a swine embryo?

- 1. A family member's iPS cells are injected into a genetically modified swine embryo that cannot produce a pancreas. (1)
- 2. The embryo is transplanted into the uterus of a pig to produce a pig with a family member's pancreas. (2)
- 3. A family member's pancreas produced in the pig's body is transplanted to you. (3)
- 4. Totally not acceptable to use a family member's cells. (4)

End of Block: Block 5

Start of Block: Block 6

Q30 If for instance, you were in need of an organ transplant, would you accept the following organs?

NO	YES			
	I would accept it (1)	Perhaps I would accept it (2)	Perhaps I would not not accept it (3)	I would not not accept it (4)
1. A part of the pancreas of a living family member (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. A part of the pancreas of a family member in cardiac or respiratory arrest (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. A part of the pancreas of a brain-dead family member (in a condition where the brain is dead and the body is alive) (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. A part of the pancreas of an unrelated living person (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. A part of the pancreas of an unrelated person in cardiac or respiratory arrest (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. A part of the pancreas of an unrelated brain-dead person (in a condition where the brain is dead and the body is alive) (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

7. Human pancreas produced in a pig body using human iPS cells (7)

8. A pancreas containing both swine cells and human cells (8)

9. A pancreas from a pig (9)

End of Block: Block 6

Start of Block: Block 7

Q28 If for instance, a family member were in need of an organ transplant, would you want for them to receive the following organs?

	I would want it (1)	Perhaps I would want it (2)	Perhaps I would not want it (3)	I would not not want it (4)
1. A part of the pancreas of a living family member (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. A part of the pancreas of a family member in cardiac or respiratory arrest (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. A part of the pancreas of a brain-dead family member (in a condition where the brain is dead and the body is alive) (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. A part of the pancreas of an unrelated living person (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. A part of the pancreas of an unrelated person in cardiac or respiratory arrest (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. A part of the pancreas of an unrelated brain-dead person (in a condition where the brain is dead and the body is alive) (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Human pancreas produced in a	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

pig body using
human iPS cells
(7)

8. A pancreas
containing both
swine cells and
human cells (8)

9. A pancreas
from a pig (9)

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

End of Block: Block 7

Start of Block: Block 8

Q34 Next, we would like to ask questions about your expectations and concerns regarding the research by injecting human iPS cells into a swine embryo.

What kind of expectations do you have regarding the research by injecting human iPS cells into a swine embryo? (Select all applicable items).

- 1. It allows the development of research of human iPS cells. (1)
- 2. The mechanisms of diseases are clarified. (2)
- 3. New treatment methods are developed. (3)
- 4. New drugs are developed. (4)
- 5. Organs available for transplantation are produced. (5)
- 6. I have no expectations. (6)
- 7. Other: (7) _____

End of Block: Block 8

Start of Block: Block 9

Q62 What kind of concerns do you have regarding the research by injecting human iPS cells into a swine embryo? (Select all applicable items).

- 1. It is not natural. (1)
- 2. It undermines human dignity. (2)
- 3. Traditional values are diminished. (3)
- 4. It produces humanized animals. (4)
- 5. The tendency to use animals as tools (means) is enhanced. (5)
- 6. It is possible that human cells end up a part of organs and tissues other than the pancreas regardless of the original intention (6)
- 7. I have no concerns. (7)
- 8. Other: (8) _____

End of Block: Block 9

Start of Block: Block 10

Q9 Research steps of the "research by injecting human iPS cells into a swine embryo".

With current technology it is possible that human iPS cells will become a part of organs and tissues other than the pancreas during the production of a pig with a pancreas made up of human cells.

According to your personal feelings, can you accept the presence of human IPS cells in the following pig organs?

	I can accept it (1)	I somewhat can accept it (2)	I somewhat cannot accept it (3)	I cannot accept it (4)
1. Liver (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Brain (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Sperm, ovum (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Skin (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Blood (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Heart (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

End of Block: Block 10

Start of Block: Block 11

Q9 According to your personal feelings, what percentage of human cells can you accept in the following porcine organs, tissues and cells?

	0% (1)	1-25% (2)	26-50% (3)	51-75% (4)	76-99% (5)	100% (6)
1. Liver (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Brain (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Sperm, ovum (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Skin (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Blood (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Heart (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

End of Block: Block 11

Start of Block: Block 12



Q44 Please let us know your thoughts and share any comments you might have on the research by injecting human iPS cells into a swine embryo. Any kind of answer is acceptable, but please be as specific as possible. If you have nothing to say, please leave the box blank.

End of Block: Block 12

Start of Block: Block 13

Q14 Have you ever had a pet? Please check the appropriate answer for each item.

	Current pet(s) (Select all applicable items) (1)	Previous pet(s) (Select all applicable items) (2)
Dog (1)	<input type="checkbox"/>	<input type="checkbox"/>
Cat (2)	<input type="checkbox"/>	<input type="checkbox"/>
Bird (3)	<input type="checkbox"/>	<input type="checkbox"/>
Rabbit (4)	<input type="checkbox"/>	<input type="checkbox"/>
Hamster (5)	<input type="checkbox"/>	<input type="checkbox"/>
Fish (6)	<input type="checkbox"/>	<input type="checkbox"/>
Other (7)	<input type="checkbox"/>	<input type="checkbox"/>
None of the above (8)	<input type="checkbox"/>	<input type="checkbox"/>

End of Block: Block 13

Start of Block: Block 14

Q26 How much do you usually participate in volunteer activities (blood donation, charitable donation, community activities etc.)?

- 1. I participate often. (1)
- 2. I participate occasionally. (2)
- 3. I don't participate very much. (3)
- 4. I don't participate at all. (4)

End of Block: Block 14

Start of Block: Block 15

Q48 Please select the appropriate answer regarding the following behaviors related to medical care.

	Yes (1)	No (2)
1. My intention to donate my organs is indicated on an organ donor card, driver's license or health insurance card. (1)	<input type="radio"/>	<input type="radio"/>
2. I have participated in medical research. (2)	<input type="radio"/>	<input type="radio"/>
3. I have a primary care doctor. (3)	<input type="radio"/>	<input type="radio"/>
4. When choosing a medical institution, I require the facility to be able to provide diagnoses and treatments based on innovative medical technology. (4)	<input type="radio"/>	<input type="radio"/>

End of Block: Block 15

Start of Block: Block 16

Q46 Please select the appropriate answer regarding the following attitudes towards medical care.

	Strongly agree (1)	Slightly agree (2)	Slightly disagree (3)	Strongly disagree (4)
1. Animal experiments are required for the development of medicine. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. I think brain death (a condition where the brain is dead and the body is alive) equals death. (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. If I got an incurable disease, I think I would try every available treatment even if the chance of being cured was low. (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Medical research should proceed in accordance with people's views on ethics. (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

End of Block: Block 16

Start of Block: Block 17

Q18 Have you or your family members experienced the following serious diseases (with very serious life threatening symptoms)? Please check all appropriate answers.

	Yourself (1)	Your Family (2)	N/A (3)
1. Cancer (malignant neoplasm) (1)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Heart disease (cardiac disease) (2)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Stroke (3)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Pneumonia (4)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Other serious symptoms (5)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. No experience of serious diseases (with very serious life-threatening symptoms) (6)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

End of Block: Block 17

Start of Block: Attention Check

attention **Background Questions on Sources for News** In this experiment, you have been asked to make decisions after evaluating information. Most modern theories of decision making recognize the fact that decisions do not take place in a vacuum. Individual preferences and knowledge, along with situational variables can greatly impact the decision process. In order to facilitate our research on decision making we are interested in knowing certain factors about you, the decision maker. Specifically, we are interested in whether you actually take the time to read the directions; if not, then some of our questions will be ineffective. So, in order to demonstrate that you have read the instructions, please ignore the question below. Instead, please click only the "Magazines" button and then type 654 into the Other field at the bottom of the screen, and then click on the next button below to proceed to the next screen.

From which of these sources have you received information in the past month?

(Click all that apply and answer according to the directions above)

- Local newspaper (1)
- National newspaper (2)
- Local TV news (3)
- Nightly network news (4)
- Cable TV news (5)
- Magazines (6)
- Speaking with family / friends (7)
- Radio newscast (8)
- Internet web sites (9)
- Other (10) _____

End of Block: Attention Check

Start of Block: Block 18

Q20 Have you or your partner visited a clinic/hospital for infertility treatment?

- 1. Yes (1)
- 2. No (2)

End of Block: Block 18

Start of Block: Block 19

Q8 Do you have a religious affiliation?

- 1. No (2)
- 2. Yes (3)

End of Block: Block 19

Start of Block: Block 20

Q40 Please describe your main religious affiliation.

- 1. Christianity (1)
- 2. Buddhism (2)
- 3. Islam (3)
- 4. Judaism (4)
- 5. Hinduism (5)
- 6. Other religion: (6) _____

End of Block: Block 20

Start of Block: Block 21

Q22 How important is the doctrine of your religion for you in your daily life?

- 1. Very important (1)
- 2. Somewhat important (2)
- 3. Not very important (3)
- 4. Not important at all (4)

End of Block: Block 21

Start of Block: Block 22: State

Q34 In which state do you currently reside?

▼ Alabama (1) ... I do not reside in the United States (53)

End of Block: Block 22: State

Start of Block: Block 23

Q54 Please tell us your gender.

- Female (1)
- Male (2)
- Other (3)

End of Block: Block 23

Start of Block: Block 24

Q50 Please tell us your age.

End of Block: Block 24

Start of Block: Block 25

Q52 Please tell us your educational background (the highest degree you have earned).

- 1. Junior high school graduate (1)
- 2. High school and technical college graduate (2)
- 3. Vocational school graduate (3)
- 4. Junior college graduate (4)
- 5. University graduate (5)
- 6. Master's or Professional (e.g. JD, MBA) degree (6)
- 7. Doctoral degree (7)

End of Block: Block 25

Start of Block: Block 26

Q56 Please tell us your marital history.

- Unmarried (1)
- Married/ Divorced/Widowed (2)

End of Block: Block 26

Start of Block: Block 27

Q10 Do you have children? If you have one or more children, please choose all applicable ages.

- 1. Child/children [under 7 years] (1)
- 2. Child/children [7 years or more but under 13 years] (2)
- 3. Child/children [13 years or more but under 19 years] (3)
- 4. Child/children [19 years or more but under 23 years] (4)
- 5. Child/children [23 years or more] (5)
- 6. No children (6)

End of Block: Block 27

Start of Block: Block 28

Q16 Have you obtained a medical license?

- Yes (1)
- No (2)

End of Block: Block 28

Start of Block: Block 29



Q24 How many years of clinical experience do you have? Please indicate the total years of experience including all past experience. If you have no clinical experience, please enter 0 years

End of Block: Block 29

Start of Block: Block 30

Q38 Please choose the medical discipline closest to your specialization. * If you choose "Other", please specify your medical discipline.

- 1. Internal medicine (1)
- 2. Surgery (2)
- 3. Orthopedic surgery (3)
- 4. Plastic surgery (4)
- 5. Neurosurgery (5)
- 6. Pediatrics (6)
- 7. Obstetrics and gynecology (7)
- 8. Dermatology (8)
- 9. Urology (9)
- 10. Ophthalmology (10)
- 11. Otorhinolaryngology (11)
- 12. Psychiatry (12)
- 13. Other: (13) _____

End of Block: Block 30

Start of Block: Block 34

Q35 Politically, I consider myself:

- Very Liberal (1)
- Liberal (2)
- Somewhat Liberal (3)
- Moderate (4)
- Somewhat Conservative (5)
- Conservative (6)
- Very Conservative (7)

End of Block: Block 34

Start of Block: Debrief



comments Thank you for participating in this survey.

The images used were created by the Uehiro Research Division for iPS Cell Ethics, Center for iPS Cell Research & Application, Kyoto University, Kyoto, Japan and are copyrighted by the Center for iPS Cell Research and Application, Kyoto University.

Thank you to our collaborators at Kyoto University for allowing us to use their survey as a model. Their original research titled "Public attitudes in Japan towards human-animal chimeric embryo research using human induced pluripotent stem cells" can be found here: <https://www.ncbi.nlm.nih.gov/pubmed/28332949>

Your validation code for mTurk is `#{e://Field/mTurkCode}`.
Please write this number down, and then enter it into MTurk.

The University of Minnesota will continue to conduct attitude surveys regarding studies using iPS cells in the future. Please give us your thoughts, for example regarding your concerns about research or questions that you want to ask the general public, as specifically as possible. If you have nothing to say, please answer leave the box blank.

End of Block: Debrief
