# Letters

RESEARCH LETTER

## Moral Concerns and the Willingness to Donate to a Research Biobank

Research biobanks are increasing in number and importance, with great potential for advancing knowledge of human health, disease, and treatment.[1] Recruitment of donors is vital to their success and relies largely on blanket consent, in which donors give one-time permission for any future research uses of their coded specimen. This approach to consent has been endorsed recently in proposed changes to federal regulations.[2]

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Previous studies suggest that donors may have moral, religious, and cultural concerns about the use to which their specimens are put, which may affect their willingness to give blanket consent.[3,4] These earlier studies, however, used convenience samples unrepresentative of the US population.

**Methods** | The institutional review boards at the University of Michigan and Michigan State University approved this study as exempt. Between June 18, 2014, and June 30, 2014, we used the GfK KnowledgePanel (a probability-based online panel of adults aged 18 years or older, designed to represent the civilian, noninstitutionalized US population) to field a survey examining associations between moral concerns and the willingness to donate to a biobank.

Respondents read an introductory description of a fictional biobank and then used a 6-point scale—from strongly agree to strongly disagree—to indicate their willingness to donate, first using blanket consent and then "even if" their samples might be used in each of 7 potential research scenarios presenting moral concerns. We then gave respondents short descriptions of the benefits and consequences of 5 methods of gaining consent and asked them to indicate which were the acceptable, best, and worst options.

All analyses were weighted to correct for the stratified sampling designs and other sources of survey errors including nonresponse and noncoverage. We used conditional logistic regression to compare willingness to consent with blanket consent vs other scenarios. Analyses were done using Stata version 13.1 (StataCorp); all tests were 2-sided, with a threshold of $P = .05$.

**Results** | After excluding 39 surveys with nonresponses to at least half of the substantive survey questions, our final analysis included 1599 participants, resulting in a response rate of 60.2% (1599 of 2654 participants). Respondents were older (51 years vs 45 years for nonrespondents), were more commonly white (82% vs 75%), and had higher levels of education and household income (eTable in the Supplement).

Table 1. Willingness to Give Blanket Consent at Baseline and for 7 Potential Research Scenarios Raising Moral Concerns

| Blanket Consent | Total[a] | Agreed[b] | % (95% CI)[c] | *P* Value[d] |
|---|---|---|---|---|
| At baseline: "I would donate tissue samples and medical information to the biobank, so that it can use them for any research study that it allows, without further consent from me." | 1593 | 1122 | 68.0 (65.5-70.5) | |
| Under research scenario: "I would donate tissue samples and medical information to the biobank, so that the biobank can use them for any research study that it allows, without further consent from me even if researchers might use donations to…"[e] | | | | |
| …develop more safe and effective abortion methods. | 1588 | 790 | 49.5 (46.9-52.1) | <.001 |
| …develop kidney stem cells. They would then try to grow these cells in a pig embryo that would grow into an adult pig with human kidneys. The goal would be to grow kidneys or other organs that could be transplanted into people. | 1592 | 1066 | 64.2 (61.6-66.8) | .007 |
| …develop patents and earn profits for commercial companies. Most new drugs used to treat or prevent disease come from commercial companies. | 1591 | 912 | 55.2 (52.6-57.8) | <.001 |
| …develop stem cells that have the donor's genetic code. These could be kept alive for many years. Scientists might use those stem cells to create many different kinds of tissues and organs for use in medical research. | 1591 | 1151 | 70.1 (67.6-72.6) | .17 |
| …create vaccines against new biological weapons. The government might need to develop biological weapons of its own when it does this research. | 1590 | 918 | 56.6 (53.9-59.2) | <.001 |
| …understand the evolution of different ethnic groups, and where they come from. What they learn might conflict with some religious or cultural beliefs. | 1591 | 1042 | 64.0 (61.5-66.6) | .005 |
| …discover genes that make some people more violent. This could lead to ways to reduce violent behavior. But if these genes are found to be more common among some racial and ethnic groups, this might increase prejudice. | 1591 | 946 | 58.1 (55.5-60.7) | <.001 |

[a] Excluded those who refused to respond to each question.

[b] Selected 4, 5, or 6 on a 6-point scale (1 = strongly disagree and 6 = strongly agree).

[c] Percentages accounted for poststratification weights.

[d] From comparisons between willingness to consent under each scenario vs willingness to first give blanket consent, using conditional logistic regression with survey weights. Each conditional logistic regression model used paired binary willingness responses (under each scenario and under blanket consent) from each participant as the dependent variable, and the *P* value was from testing for the significance of the parameter estimate of the indicator for the scenario (vs blanket consent).

[e] Descriptions of scenarios as presented to respondents.

Table 2. Public Opinions on 5 Different Biobank Consent Options

| Consent Options | Description[a] | Respondents, % (95% CI)[b] | | |
|---|---|---|---|---|
| | | Acceptable Option (n = 1587)[c] | Best Option (n = 1555) | Worst Option (n = 1548) |
| Blanket | This means that donors have control over whether to donate but not over how the samples are used in any future research. It gives the biobank and researchers a lot of freedom in deciding how to use samples. | 56.4 (53.8-59.0) | 21.1 (19.1-23.4) | 37.8 (35.3-40.4) |
| Blanket combined with a caution | Donors are alerted in advance with the following statement: "Some people may have moral, religious, or cultural concerns about some kinds of research." Donors can then decide whether they are still willing to donate. Some donors may decide not to donate, resulting in fewer samples for research. | 71.9 (69.5-74.4) | 19.7 (17.7-21.9) | 4.2 (3.1-5.5) |
| Blanket combined with an option to withdraw | Donors first give their blanket consent. The biobank then gives them easy access to information about current research projects being done with donated samples. If donors see research projects that worry them, they can decide to withdraw their tissues. If too many people withdraw their donation, researchers may have trouble finding enough samples to do their research. | 70.8 (68.4-73.3) | 25.5 (23.2-27.8) | 6.2 (5.0-7.8) |
| Blanket combined with limits | Donors are given a short list of types of research projects that might worry some people. The donors then decide which types of research can't use their donation. Research not on the list would still be covered by a blanket consent. This system may cost more, leaving less money for research. | 65.1 (62.5-67.6) | 14.3 (12.6-16.2) | 6.8 (5.5-8.3) |
| Real-time specific for each use of the donated samples | Donors don't give blanket consent. Instead, the biobank contacts them and asks for their consent for each specific project. Donors are given maximum control, but some might get tired of being contacted repeatedly. The cost of recontacting every donor for consent will be high. If too many people refuse to give their consent, many research studies will not be possible. | 57.0 (54.3-59.6) | 19.4 (17.3-21.6) | 45.0 (42.4-47.6) |

[a] Description as presented to respondents.

[b] Percentages were calculated after those who refused to respond to each question were excluded and accounted for poststratification weights.

[c] Respondents could select more than 1 option as acceptable.

Using blanket consent, 68.0% (95% CI, 65.5%-70.5%) were willing to donate. In all but 1 scenario, moral concerns were associated with a significant reduction in willingness to donate (**Table 1**).

When asked about different approaches to gaining consent, 43.6% (95% CI, 41.1%-46.0%) of respondents found the blanket consent method to be unacceptable, and 37.8% (95% CI, 35.3%-40.4%) said blanket consent was the worst among 5 policy options. Specific consent, in which donors are asked to consent to each study using their specimen, was considered the worst option by 45.0% (95% CI, 42.4%-47.6%) (**Table 2**).

**Discussion** | As shown in previous studies,[5] this survey documented that members of the general population are willing to donate to biobank research. Most respondents were willing to donate using a blanket consent. However, willingness to donate waned when they were informed of possible uses of their specimens that raised moral concerns. As recruitment of donors becomes more widespread, such concerns may need to be addressed to moderate possible effects on donation rates.

Respondents' preferences toward biobank consent options are also noteworthy. Specific consent, the option that gives donors the most control over potentially concerning uses, was the least preferred option. But blanket consent, the option currently in widespread use, was not far behind. This suggests that an adequate approach for dealing with donors' moral concerns may lie between these 2 extremes.

Limitations include a response rate of 60%, with respondents and nonrespondents differing on some characteristics that may introduce bias. Because respondents may be more in favor of research, the association between moral concerns and decreased willingness to donate may be a conservative estimate. Also, respondents' views were based on brief scenarios rather than on detailed understanding of the issues. Deliberative engagement with citizens may deepen understanding of public opinion regarding biobank policy.

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**1**. Hewitt RE. Biobanking: the foundation of personalized medicine. *Curr Opin Oncol*. 2011;23(1):112-119.

**2**. US Department of Health and Human Services. ANPRM for revision to Common Rule. http://www.hhs.gov/ohrp/humansubjects/anprm2011page.html. Accessed July 28, 2014.

**3**. Tomlinson T, Kaplowitz SA, Faulkner M. Do people care what's done with their biobanked samples? *IRB*. 2014;36(4):8-15.

**4**. Gornick MC, Ryan KA, Kim SYH. Impact of non-welfare interests on willingness to donate to biobanks: an experimental survey. *J Empir Res Hum Res Ethics*. 2014;9(4):22-33.

**5**. Wendler D. One-time general consent for research on biological samples. *BMJ*. 2006;332(7540):544-547.

## COMMENT & RESPONSE

## Heterogeneity in Meta-analysis of FDG-PET Studies to Diagnose Lung Cancer

**To the Editor** Dr Deppen and colleagues[1] conducted a large meta-analysis that showed the limitations of lung cancer diagnosis using fludeoxyglucose F 18 combined with positron emission tomography (FDG-PET) in areas with endemic infectious lung disease. Although the sensitivity and specificity of FDG-PET diagnosis was heterogeneous across the included studies, thereby compromising interpretation of the pooled results, the relevance of presenting an $I^2$ statistic to underscore and interpret the extent of the heterogeneity should be questioned.

The large reported $I^2$ values may be an artifact of their chosen measure (proportions) and may not solely reflect important clinical or contextual sources of heterogeneity. The $I^2$ statistic is perhaps the most popular method to assess the extent of statistical heterogeneity within meta-analyses, mostly due to its uncritical promotion within the Cochrane Collaboration.[2]

The study by Deppen et al demonstrates an overreliance on the $I^2$ statistic and its interpretation that can sometimes be misleading.[3] The value of the $I^2$ statistic is not only a product of between-study variability, it is also influenced by the precision of study estimates,[3] which, for proportions, is a function of sample size and the number of events of interest.

If the actual proportions in the individual studies and the between-study heterogeneity, typically denoted by $\tau^2$, are kept constant, but sample sizes are increased, then the $I^2$ will increase. A quick eyeball test for heterogeneity in the study by Deppen et al suggests larger heterogeneity for specificity rather than sensitivity (Figure 2 in the article); however, the $I^2$ statistic (82% for specificity and 87% for sensitivity) suggests otherwise.

When the $I^2$ statistic was first reported, Higgins et al[2] suggested cutoffs to describe heterogeneity qualitatively (eg, >75% is high). Their benchmark was based on comparative measures (eg, odds ratios), and these behave differently than proportions. More specifically, given equal sample size, the variance of a proportion is smaller than the variance of an odds ratio; therefore, the $I^2$ statistic will tend to be larger for proportions.

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**1**. Deppen SA, Blume JD, Kensinger CD, et al. Accuracy of FDG-PET to diagnose lung cancer in areas with infectious lung disease: a meta-analysis. *JAMA*. 2014;312(12):1227-1236.

**2**. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.

**3**. Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol*. 2008;8:79.

**In Reply** Dr Mills and colleagues wish to deemphasize $I^2$ statistics. We agree that $I^2$ statistics can be problematic and that the naive pooled model (ie, the model assuming no study-to-study heterogeneity) is often inappropriate for meta-analyses. This is why, in our study, $I^2$ statistics were only reported for completeness and never factored into our analysis.

First, Mills and colleagues assume that $I^2$ statistics played a prominent role in our analysis. They did not. They were reported in accordance with PRISMA[1] guidelines but served no other function. We quantified the extent of study-to-study heterogeneity with a component of variance from the best-fit random-effects logistic regression model.

We also modified the traditional forest plot (Figure 2 in article), accordingly; $I^2$ statistics were removed and confidence intervals for combined and overall effects were derived from the random-effects logistic model (instead of the traditional pooled model). To highlight study heterogeneity, we displayed prediction intervals (Figure 3) from our model.

In this context, the difference between prediction and confidence interval length is due to study-to-study heterogeneity. The prediction interval for specificity was wider than that for sensitivity. Even though this is suggested by Mills and colleagues' eyeball test, the formal testing approach we used, based on model selection, is likely to perform better.

Second, in our case, an overreliance on $I^2$ statistics would have led to the same conclusions. The $I^2$ statistics for sensitivity and specificity were both large, indicating the pooled model was not supported by the data. Thus, the pooled model