Informed Consent in Translational Genomics: Insufficient Without Trustworthy Governance

Wylie Burke, Laura M. Beskow, Susan Brown Trinidad, Stephanie M. Fullerton, and Kathleen Brelsford

Introduction

Translational genomic research has taken on increasing importance with advances in genome science. New genomic technologies can evaluate multiple genes — dozens or hundreds — in a single "gene panel," or generate information about the exome (all protein-coding genes) or the entire genome of an individual.[1] These approaches offer an unprecedented opportunity to evaluate inherited health risks, identify genetic changes in cancer tissue, and utilize genomic information to develop new therapeutics. Potential clinical benefits include improved diagnosis of genetic conditions, new approaches to disease classification, improved prevention or management based on genetic prediction, safer or more effective drug prescribing, and new targeted treatments. Specific examples of these benefits have been documented,[2] but potential disadvantages and harms have also been identified. These include the production of unsought and sometimes uninterpretable or misleading information, the associated costs of follow-up assessments, and the potential for research results to lead to psychological distress, family disruption, unnecessary care, or iatrogenic harm.[3]

Translational genomic research has the goal of assessing the benefits and harms of genomic medicine in order to inform ethically sound evidence-based care. Although such research is sometimes construed as referring only to the development of new clinical tools, the continuum of translation from basic knowl-

Wylie Burke, M.D., Ph.D., *is Professor Emeritus and former Chair of the Department of Bioethics and Humanities at the University of Washington. She received a Ph.D. in Genetics and an M.D. from the University of Washington, where she also trained in Internal Medicine and Medical Genetics.* **Laura M. Beskow, M.P.H., Ph.D.,** *is Professor of Health Policy at the Vanderbilt University Medical Center and Director of Research Ethics at the Vanderbilt Center for Biomedical Ethics and Society. She holds a B.S. in nutrition from Iowa State University, an M.P.H. with a concentration in health law from Boston University, and a Ph.D. in health policy and administration from the University of North Carolina at Chapel Hill.* **Susan Brown Trinidad, M.A.,** *is a Research Scientist in the Department of Bioethics and Humanities at the University of Washington School of Medicine. She holds a master's degree from the Interdisciplinary Program in Health and Humanities at Michigan State University (East Lansing, Michigan) and a bachelor of arts in English from the College of William and Mary (Williamsburg, Virginia).* **Kathleen M. Brelsford, Ph.D., M.P.H., M.A.,** *is a Research Assistant Professor in the Center for Biomedical Ethics and Society at the Vanderbilt University Medical Center. She holds a B.A. in Cultural Anthropology from the University of Miami, an M.A. in Anthropology from Northern Arizona University, an M.P.H. from the University of South Florida, and a Ph.D. in Applied Anthropology with an emphasis in Medical Anthropology from the University of South Florida.*

The Journal of Law, Medicine & Ethics, 46 (2018): 79-86. © 2018 The Author(s)
DOI: 10.1177/1073110518766023

edge to clinical application requires a diverse range of studies, including evaluation of gene-disease associations, the use of genomics in the development of drugs and therapeutics, and the evaluation of outcomes from the use of genomic testing in clinical care. Research goals include the investigation of the impact of genomic medicine in defined populations and particular clinical contexts.

The conduct of translational genomic research increasingly poses two important challenges to the informed consent process: the return of individual results to research participants and the retention of collected data and biospecimens for future unspecified uses. Although neither issue is unique to translational genomic research — both arise in other types of clinical research — they pose distinct challenges in this research domain because of the vast quantity and scope of genomic data typically generated, the varied and evolving capacity to interpret their meaning, and the wide array of unspecified topics (including controversial topics) that could be studied.

Return of Research Results

A variety of results can be generated from gene panels and genome-scale platforms, leading to questions about whether, which, and how results should be made available to research participants, and on what basis such decisions should be made. Although medical actionability — that is, the potential for a result to inform screening procedures or treatment to improve an individual's health — is commonly invoked as a rationale for returning results, this criterion is not universally accepted or acted upon.

The broad range of potential results. Many genomic studies are likely to generate results that provide information about at least some participants' health or future risks. For example, a study among people diagnosed with a particular cancer may generate findings about genetic contributors to that cancer. In addition, gene panels, exomes, or whole genomes may generate information unrelated to the study question or clinical conditions present in research participants. To date, when researchers have elected to perform additional analysis of the genomic data generated, beyond what is needed to answer their particular study question, they have focused on genes associated with rare genetic diseases.[4] Although these secondary genomic findings could involve a broad range of health risks, the likelihood of a significant finding for any individual participant is low; gene variants associated with serious genetic disease and considered medically actionable are estimated to occur in only 1-2% of the general population.[5] Sequence data can be assayed for other health-related information, including carrier status, pharmacogenomic variants, and susceptibility variants associated with increased or decreased risk for common complex diseases. Sequence data also include many gene variants of uncertain significance (VUS), reflecting both the magnitude of variation found in the human genome and our current relatively limited understanding of its meaning.[6] Some results may become "returnable" to participants (i.e., meet thresholds for reliability and clinical salience) only after the original study is completed, possibly from additional analyses by other researchers that shed light on their clinical meaning. In addition, genomic analyses can provide results unrelated to health, such as information about ancestry.

The degree to which a particular study generates findings unrelated to the study question is a function of technical and analytic choices. These include what segments of DNA sequence are targeted in a laboratory assay, as well as which portions of the targeted DNA sequence are subjected to detailed analysis. Recommendations from the American College of Medical Genetics and Genomics (ACMG) regarding genome sequencing in clinical practice[7] may influence laboratory procedure in this regard. ACMG recommends the analysis of the DNA sequence of a set of 59 genes whenever clinical exome or genome sequencing is done, in addition to any genes analyzed to address the clinical indication for testing. The ACMG list represents a consensus effort to define genes with medically actionable variants. While this recommendation is intended for clinical use of sequencing, it could lead to a default approach in which laboratories performing both clinical and research testing routinely incorporate all of the genes on the ACMG list. Laboratories could also choose to add other genes to the default analysis. Thus, while there appears to be strong agreement among experts that researchers have no obligation make a deliberate effort to seek additional findings in order to return them to participants,[8] the analytic methods used in a study may nevertheless generate such findings.

A broad range of findings beyond those recommended by ACMG are likely for many translational genomic studies. For example, some research is designed explicitly to include investigation of the frequency with which secondary results of different types occur and of the outcomes associated with returning them. A genomic study focused on a particular clinical problem may thus include analysis of a lengthy list of additional genes to address these research questions. Studies in the Clinical Sequencing Exploratory Research (CSER) Consortium, for instance, funded by the National Human Genome Research Institute and

The Journal of Law, Medicine & Ethics, 46 (2018): 79-86. © 2018 The Author(s)

National Cancer Institute, have analyzed hundreds or thousands of genes unrelated to specific diseases under study, in order to evaluate outcomes of returning secondary findings.[9] This expansive approach is driven by the assumption that such data will hasten clinical genomic testing and that such testing will benefit patients. Thus, some genomics researchers have argued in favor of "aggressively" seeking additional findings in both research and clinical care,[10] in order to expedite understanding of the clinical outcomes associated with different genotypes.

Medical actionability as a criterion for offering results to participants. An emerging consensus among experts favors offering only medically actionable findings to research participants (i.e., not offering clinically valid results if they cannot be used to improve outcomes).[11] However, determining which results meet this threshold may not be simple or straightforward, in part because of the importance of context:[12] what is medically actionable may depend on clinical or personal circumstances, including the patient's age, prior diagnoses, and medical status. For example, the medical actionability of a genetic health risk is likely to be different for an elderly patient who has already been treated for the disease in question compared with a young person who might benefit from targeted preventive care. There is also the question of urgency or immediacy. Should researchers prioritize the use of limited research resources to return only those results that require medical intervention in the near term to avert serious disease, or also those that could potentially inform medical action in the future? Should researchers consider offering results intended to motivate a healthier lifestyle — e.g., results indicating a higher risk of diabetes or coronary heart disease — given that the recommended lifestyle measures would be appropriate for everyone and data suggest such risk information is rarely motivating?[13] Do results unrelated to the participant's own health but potentially relevant to reproductive decision making, such as information about carrier status, merit return?

Participant preferences. These questions are further complicated by data on participant preferences. When asked, most people indicate they wish to receive their personal results from genetic research.[14] While some studies suggest that participants are more interested in medically actionable findings than other kinds of results,[15] other studies find that many participants do not make this distinction.[16] In one study, for instance, 91% of participants said they would want individual research results about health risks "even if there was nothing [they] could do about them."[17] The reasons provided by participants for their preferences point to a range of motivations. In addition to the assumption that the information may guide prevention or treatment, now or in the future, some participants perceive the information as having inherent value, believe that it may benefit family members, or think that researchers should offer results as a matter of reciprocity.[18] Participants also describe seeking out future research opportunities based on knowledge of their genetic status, making life plans, and invoking a fundamental right to information.[19]

Should researchers prioritize the use of limited research resources to return only those results that require medical intervention in the near term to avert serious disease, or also those that could potentially inform medical action in the future? Should researchers consider offering results intended to motivate a healthier lifestyle — e.g., results indicating a higher risk of diabetes or coronary heart disease — given that the recommended lifestyle measures would be appropriate for everyone and data suggest such risk information is rarely motivating? Do results unrelated to the participant's own health but potentially relevant to reproductive decision making, such as information about carrier status, merit return?

Although studies are consistent in demonstrating many participants' strong interest in receiving results, they also raise methodological concerns. Studies tend to ask about what results participants *prefer* to receive, rather than what they would find *acceptable* given necessary tradeoffs with other values and considerations (*e.g.*, dedicating research resources toward the produc-

The Journal of Law, Medicine & Ethics, 46 (2018): 79-86 © 2018 The Author(s)

tion of generalizable knowledge). When the question is asked differently, other perspectives emerge. For example, in cognitive interviews about consent language for a biobank, participants were asked about the acceptability of a statement indicating that individual results would not be returned; two thirds of participants were comfortable with this approach, on the grounds that research differs from medical care, that resources for returning research results may be limited, and that participants may not have prior expectations that results would be returned from biobank research.[20] Similarly, in another study, a participant stated, "If there is an option for me to get results, I'm going to say yes. But if you tell me I'm not going to get them, I'm not really going to care."[21]

A related methodological concern is that studies of participant preferences for particular types of results may provoke "involuntary curiosity," that is, curiosity that arises spontaneously simply because an individual is alerted to an information gap.[22] For example, in one survey, 39% of respondents indicated that they were "very likely" to accept a free home test kit to determine their chances of developing Alzheimer disease; however, when they were asked whether they would want the results of such a test already done by a researcher, significantly more (70%) said they "very likely" would.[23] In explanation of the difference, a participant noted, "I wouldn't seek out such information, but if it's available, I would want to know it."[24]

Implications for informed consent. Providing research participants with detailed information during the initial consent process about the results that might be returned from genomic analysis is difficult if not impossible, given the broad range of potential findings. Although studies of participant preferences suggest that a majority of participants are likely to support broad return of results, the methodological concerns noted above suggest caution in using these studies directly to formulate policies. Even under a policy of broad return, however, decisions need to be made about what is returnable and procedures put in place to account for differences among participants in the specific results they wish to receive.

A number of approaches to this problem have been tried or suggested.[25] For example, as part of the consent process, researchers could ask participants to indicate which categories of results they would wish to receive, such as medically actionable results, carrier test results, or pharmacogenomic results. Another option is a phased (or "staged") approach in which the possibility of returning results is noted at initial consent, followed by additional consent procedures when specific results become available. Alternatively, willingness to receive results deemed appropriate for return by the study team could be defined as a condition of study participation.[26]

Although each of these approaches offers participants information and some degree of choice about the potential research results that might be available to them, consent processes often lack transparency about the fact that additional decisions will be made by others (e.g., determining whether or not particular findings meet criteria for return), including information about who will make these decisions and the procedures they will use. Research is needed to enhance consent processes and forms based on better understanding of what type and level of detail a reasonable person would want to know about this decision-making. Research is also needed to develop robust consent processes for offering and then returning specific results to participants, assuring that they have the opportunity to make informed decisions about which results, if any, they wish to receive.

Retention of Data or Biospecimens for Future Use

Translational genomic research typically involves retaining data and sometimes biospecimens for future analyses. For genomic data in particular, National Institutes of Health (NIH) policies specify that data should be submitted for widespread sharing to a federally approved data repository such as the database of Genotypes and Phenotypes (dbGaP).[27] The primary challenge for informed consent is that future uses — and users — are unknown.

Value of data sharing. Strong arguments can be offered for retaining data and biospecimens and enabling broad access to them for future research purposes. Doing so supports the scientific values of replication and transparency. In addition, data repositories and biobanks provide a resource for addressing questions beyond the scope of the original study or not anticipated at the time the data were collected. Further, they enable research aimed at methods development — for example, comparison of alternative methods for clarifying gene-disease associations or interpreting the clinical significance of gene variants. In these ways, retaining and sharing data and biospecimens can contribute to the reliability and efficiency of scientific research and the ultimate goal of generating knowledge to improve health. Repositories may also reduce participant burden and improve cost effectiveness by enabling a wide range of studies to be conducted from a single instance of sample and data collection.

The Journal of Law, Medicine & Ethics, 46 (2018): 79-86. © 2018 The Author(s)

Oversight procedures. Permission from an Institutional Review Board (IRB) or Privacy Board is generally required for submission of data or biospecimens to a centralized repository. This process promotes appropriate protections for identifying information and allows researchers to define any restrictions on future use. For example, for dbGaP submissions, IRBs are asked to specify data-use limitations based on statements or promises made in the original consent form.[28] Once data are placed in a repository, however, their use is governed by whatever decision-making bodies and procedures are in place. The dbGaP repository utilizes Data Access Committees (DACs) staffed by federal employees who evaluate each request for data, to ensure that the proposed study is consistent with any data use restrictions and that the requester is a qualified researcher. To streamline the data request process, this repository has also developed a browser that provides researchers with view-only access to compiled individual-level data approved for general research use.[29]

Potential for controversial uses of shared data or biospecimens. As with return of results, it is not feasible or even possible to describe all the potential future uses of stored data or biospecimens. Thus, consent forms and processes often rely on general descriptions of the purpose of a given repository (e.g., "research on health and disease" or "research associated with aging"). Given such broad scope, current oversight measures do not ensure that data uses will be generally acceptable, either to the participants who provided the data or to the public. Recent examples of potentially controversial research either using shared data or basing analysis on such studies include publications on links between genetics and educational attainment and cognitive impairment,[30] country-level average IQ,[31] political ideology,[32] and anti-social behavior.[33] Data from the Human Genome Diversity Panel have been used to study associations between genetics and race/ethnicity, addiction, mental illness, and brain size, among other topics that could be considered objectionable or stigmatizing.[34]

Implications for informed consent. The recently revised Common Rule for the protection of human research participants endorses broad consent for future use of data and biospecimens,[35] but specifies that the process must "include sufficient information to permit a reasonable person to expect that the broad consent would permit the types of research conducted."[36] Required elements include the disclosure of whether identifiable private information or biospecimens may be used, whether such materials may be shared with other researchers, and what kinds of institutions or investigators may be granted access. In recognition of the limitations of this approach for achieving informed consent, the Rule further specifies that participants be informed that they will not be given information about the purpose or procedures involved in future studies, and that they "might have chosen not to consent to some of those specific research studies"[37] had they had the opportunity to do so.

Beyond these requirements, prospective participants could be provided with basic information about the processes by which future uses and users will be approved. As with return of results, research is needed to support informed decision making by elucidating what people would reasonably want to know about this decision-making that will occur on their behalf.

The challenges described here demonstrate that the traditional, study-specific approach to informed consent is insufficient for translational genomic research. As discussed above, researchers can fully predict neither the range nor type of individual results that may be generated nor specify future uses or users of study data or biospecimens. Because participants cannot be provided with all relevant information at the time of enrollment, the model of autonomous decision-making based on adequate information does not apply to all aspects of the research.

Consent to Governance

The challenges described here demonstrate that the traditional, study-specific approach to informed consent is insufficient for translational genomic research. As discussed above, researchers can fully predict neither the range nor type of individual results that may be generated nor specify future uses or users of study data or biospecimens. Because participants cannot be

The Journal of Law, Medicine & Ethics, 46 (2018): 79-86 © 2018 The Author(s)

provided with all relevant information at the time of enrollment, the model of autonomous decision-making based on adequate information does not apply to all aspects of the research. In this context, the consent process takes on an added dimension. In addition to the traditional goal of voluntary consent to participate in a particular study or biobank, participants are asked to agree to procedures that will be undertaken by others to determine what type of results are offered to them and how their data or biospecimens may be used in the future. In essence, as alluded to above, they are being asked for consent to have these and related key decisions made on their behalf by others.[38]

Arguably, then, what potential participants need to know about return of results and the retention and broad sharing of data and samples is how decisions will be made, by whom, and under what governing principles. The decision-making process differs for these two issues and requires different procedures and expertise. For example, deciding what results might be offered to participants is in part a technical matter — related to the nature of the results and their analytic validity — and in part a set of judgments related to criteria for return (*e.g.,* clinical validity, medical actionability) and whether a particular result has met them. Decision-making power usually resides with study investigators, although additional oversight may be required by the institution in which the research occurs, *e.g.*, approval by an IRB for return of specific results. Decisions about data or biospecimen use rest primarily with the repository where the data or biospecimens reside. Typically, a DAC or similar body makes decisions in response to requests from researchers for data or specimen access and taking into account any restrictions placed on the data and specimens at the time they were submitted. In addition, decision-makers could consider the professional qualifications of the researchers seeking access, the scientific value of the proposed research, or other considerations such as the potential for group harm from the use of samples derived from socially identifiable groups. The degree to which such issues are considered is often not obvious, yet may well influence participants' trust in the process and perhaps their willingness to cede decision-making to others.

These observations point to the need to clarify and strengthen governance of translational genomic research. While the immediate concern is to provide participants with sufficient information to understand how return of results and data and biospecimen sharing will be managed, the long-term need is to ensure that these decisions — and others that may arise in translational genomic research — are ethically managed, and to determine who is accountable for doing so. O'Doherty and colleagues have argued that trustworthy biorepository governance must recognize the collective interests of research participants and the public, and ensure adaptive practices that respond to developments over time.[39] They identify 5 conditions for trustworthiness: consideration of a full range of stakeholder interests, auditing of data use with consequences for any violations of data use agreements, transparency about operations and decision-making, regular assessment of practices, and sustainability. These observations underscore that informed consent for return of results and futures uses of data and biospecimens is only one component of a broader set of actions needed to ensure trustworthy research practice.

In the effort to develop trustworthy governance for return of results and data sharing, empirical data are needed, both about the information participants would like to receive as part of the informed consent process and about the procedures they would consider trustworthy. Research should include studies to clarify the views of participants, researchers, and other stakeholders about the values and principles that should govern decision-making; development of procedures based on those values and principles; feasible approaches to implement them; and rigorous approaches to evaluate them. An important question to be addressed is how the values and perspectives of the public and of research participants might be incorporated. Participatory approaches, such as Participant or Community Advisory Boards, can be used to bring affected communities' values and priorities to bear on research oversight and decision-making processes[40] and to help align governance and research activities with participants' interests and expectations.[41] This approach may be especially important when research is focused on local conditions, such as exposures to particular environmental hazards, or involves participation of socially identified communities that are vulnerable to stigma. Public deliberations about biobank governance point to the importance of public input and support procedures that enable review of biobank-enabled research that is independent of funders and researchers.[42] A survey of U.S. biobanks indicated that while most biobanks are mindful of their responsibilities for stewardship, only 26% had a Community Advisory Board (CAB); 81% had expert-driven oversight bodies such as a scientific review committee or an internal advisory group.[43]

To some degree, available data support the use of CABs to enhance biobank governance. For example, one study found that strategies to engage community members and build trust, including involving community members in decision-making, increased hypothet-

The Journal of Law, Medicine & Ethics, 46 (2018): 79-86. © 2018 The Author(s)

ical willingness to join a biobank.[44] Yet some scholars question the effectiveness of community involvement in practice, noting that CAB members may be chosen arbitrarily, be restricted to particular roles (*e.g.*, lawyer, consumer advocate), lack independence, and lack accountability to a larger public.[45] Empirical data also support these concerns. In a study of public perspectives on CABs,[46] participants recognized the benefits of CAB involvement in biorepository oversight, but anticipated problems with regard to impeding medical research and progress, the composition and functioning of the CAB, and the relationship of CABs to IRBs, communities, and industry. Clearly, more empirical research is needed to address these potential weaknesses and to evaluate alternative approaches.

In pursuing this research agenda, informed consent procedures must be viewed as occurring within a broader context of research governance. Empirical and conceptual studies, public deliberations, and demonstration projects are needed to fully develop all the components of robust governance systems for decision-making about return of results and future use of stored data and biospecimens. This should ideally be an iterative process that includes opportunities for stakeholders to review emerging approaches and develop consensus about the best ways to address the challenges posed by the open-ended and rapidly evolving nature of translational genomic research.

Note

Dr. Burke reports grants from National Institutes of Health, grants from Greenwall Foundation, outside the submitted work. The other authors have no conflicts to disclose.

Acknowledgements

This work was supported in part by the National Institutes of Health (NIH) and National Human Genome Research Institute (NHGRI) grants R01HG006621 and P50HG03374 and by NIH, NHGRI and National Cancer Institute (NCI) grant R01HG008605. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the authors' respective institutions.

References

1. L. G. Biesecker and R. C. Green, "Diagnostic Clinical Genome and Exome Sequencing," *New England Journal of Medicine* 370**,** no. 25 (2014): 2418-2425; H. L. Rehm, "Evolving Health Care Through Personal Genomics," *Nature Reviews Genetics* 18, no. 4 (2017): 259-267.
2. L. R. Cardon and T. Harris, "Precision Medicine, Genomics and Drug Discovery," *Human Molecular Genetics* 25, no. R2 (2016): R166-R172; M. Pirmohamed, "Personalized Pharmacogenomics: Predicting Efficacy and Adverse Drug Reactions," *Annual Review of Genomics and Human Genetics* 15 (2014): 349-370.
3. A. Blanchard, "Mapping Ethical and Social Aspects of Cancer Biomarkers," *Nature Biotechnology* 33, no. 6 (2016): 763-772; P. L. Sankar and L. S. Parker, "The Precision Medicine Initiative's All of Us Research Program: An Agenda for Research on its Ethical, Legal, and Social Issues," *Genetics in Medicine* 19**,** no. 7 (2017): 743-750.
4. J. S. Berg et al. and Members of the CSER Actionability and Return of Results Working Group, "Processes and Preliminary Outputs for Identification of Actionable Genes as Incidental Findings in Genomic Sequence Data in the Clinical Sequencing Exploratory Research Consortium," *Genetics in Medicine* 15**,** no. 11 (2013): 860-867; L. G. Biesecker, "Opportunities and Challenges for the Integration of Massively Parallel Genomic Sequencing into Clinical Practice: Lessons from the ClinSeq Project," *Genetics in Medicine* 14, no. 4 (2012): 393-398.
5. L. M. Amendola et al., "Actionable Exomic Incidental Findings in 6503 Participants: Challenges of Variant Classification," *Genome Research* 25, no. 3 (2015): 305-315.
6. T. Frebourg, "The Challenge for the Next Generation of Medical Geneticists," *Human Mutation* 35, no. 8 (2014): 909-911.
7. R. C. Green et al. and the American College of Medical Genetics and Genomics, "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing," *Genetics in Medicine* 15, no. 7 (2013): 565-574; L. G. Biesecker, "ACMG Secondary Findings 2.0," *Genetics in Medicine* 19, no. 5 (2017): 604.
8. G. P. Jarvik et al. and members of the CSER Act-ROR Working Group, "Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices in Between," *American Journal of Human Genetics* 94**,** no. 6 (2014): 818-826; S. M. Wolf, "Return of Individual Research Results and Incidental Findings: Facing the Challenges of Translational Science," *Annual Review of Genomics and Human Genetics* 14 (2013): 557-577; National Heart, Lung, and Blood Institute Working Group and R. R. Fabsitz et al., "Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from a National Heart, Lung, and Blood Institute Working Group," *Circulation Cardiovascular Genetics* 3**,** no. 6 (2010): 574-580.
9. R. C. Green et al. and the Clinical Sequencing Exploratory Research Consortium, "Accelerating the Evidence-Based Practice of Genomic Medicine," *American Journal of Human Genetics* 99, no. 1 (2016): 1051-1066.
10. L. G. Biesecker, "Incidental Variants Are Critical for Genomics," *American Journal of Human Genetics* 92, no. 5 (2013): 648-651.
11. See Jarvik et al., *supra* note 8.
12. L. M. Beskow and W. Burke, "Offering Individual Genetic Research Results: Context Matters," *Science Translational Medicine* 2, no. 38 (2010): 38cm20.
13. G. J. Hollands et al., "The Impact of Communicating Genetic Risks of Disease on Risk-reducing Health Behaviour: Systematic Review with Meta-analysis," *British Medical Journal* 352 (2016): i1102; doi: 10.1136/bmj.i1102.
14. D. Kaufman et al., "Subjects Matter: A Survey of Public Opinions about a Large Genetic Cohort Study," *Genetics in Medicine* 10, no. 11 (2008): 831-839; D. Wendler and E. Emanuel, "The Debate over Research on Stored Biological Samples: What do Sources Think?" *Archives of Internal Medicine* 162**,** no. 13 (2002): 1457-1462.
15. J. M. Bollinger et al., "Public Preferences for the Return of Research Results in Genetic Research: A Conjoint Analysis," *Genetics in Medicine* 16, no. 12 (2014): 932-939; F. M. Facio et al., "Intentions to Receive Individual Results from Whole-genome Sequencing among Participants in the ClinSeq Study," *European Journal of Human Genetics* 21**,** no. 3 (2013): 261-265; C. S. Bennette et al., "The Cost-effectiveness of Returning Incidental Findings from Next-generation Genomic Sequencing," *Genetics in Medicine* 17, no. 7 (2015): 587-595.
16. See Kaufman et al., *supra* note 14; see Wendler and Emanuel, *supra* note 14.
17. See Kaufman et al., *supra* note 14, at 835.
18. J. Murphy et al., "Public Expectations for Return of Results from Large-cohort Genetic Research," *American Journal of*

Bioethics 8, no. 11 (2008): 36-43; L. M. Beskow and S. J. Smolek, "Prospective Biorepository Participants' Perspectives on Access to Research Results," *Journal of Empirical Research in Human Research Ethics* 4, no. 3 (2009): 99-111; S. Daack-Hirsch et al., "'Information is Information': A Public Perspective on Incidental Findings in Clinical and Research Genome-based Testing," *Clinical Genetics* 84, no. 1 (2013): 11-18.

19. L. M. Beskow et al., "Research Participants' Perspectives on Genotype-driven Research Recruitment," *Journal of Empirical Research on Human Research Ethics* 6, no. 4 (2011): 3-20; see also Murphy et al., *supra* note 18; see also Daack-Hirsch et al., *supra* note 18.
20. L. M. Beskow and E. Dean, "Informed Consent for Biorepositories: Assessing Prospective Participants' Understanding and Opinions," *Cancer Epidemiology Biomarkers and Prevention* 17, no. 6 (2008): 1440-1451. See also Beskow and Smolek, *supra* note 18.
21. J. M. Bollinger et al., "Public Preferences Regarding the Return of Individual Genetic Research Results: Findings from a Qualitative Focus Group Study," *Genetics in Medicine* 14, no. 4 (2012): 451-457, at 453.
22. G. Loewenstein, "The Psychology of Curiosity: A Review and Reinterpretation," *Psychological Bulletin* 116, no. 1 (1994): 75-98, at 91.
23. D. Wendler and R. Pentz, "How Does the Collection of Genetic Test Results Affect Research Participants?" *American Journal of Medical Genetics Part A* 143A (2007): 1733-1738.
24. *Id*., at 1736.
25. G. E. Henderson et al., "The Challenge of Informed Consent and Return of Results in Translational Genomics: Empirical Analysis and Recommendations," *Journal of Law, Medicine & Ethics* 42, no. 3 (2014): 344-355; P. S. Appelbaum et al., "Models of Consent to Return of Incidental Findings in Genomic Research," *Hastings Center Report* 44, no. 4 (2014): 22-32.
26. See Appelbaum et al., *supra* note 25.
27. NIH Sharing Policies and Related Guidance on NIH-funded Research Resources, *available at* <https://grants.nih.gov/policy/sharing.htm> (last visited May 28, 2017).
28. E. M. Ramos et al., "A Mechanism for Controlled Access to GWAS Data: Experience of the GAIN Data Access Committee," *American Journal of Human Genetics* 92, no. 4 (2013): 479-488; K. A. Tryka et al., "NCBI's Database of Genotypes and Phenotypes: dbGaP," *Nucleic Acids Research* 42, Database issue (2014): D975-D979.
29. K. M. Wong et al., "The dbGaP Data Browser: A New Tool for Browsing dbGaP Controlled-Access Genomic Data," *Nucleic Acids Research* 45, no. D1 (2017): D819-D826.
30. A. Okbay et al., "Genome-wide Association Study Identifies 74 Loci Associated with Educational Attainment," *Nature* 533, no. 7604 (2016): 539-542; C. A. Rietveld et al., "Common Genetic Variants Associated with Cognitive Performance Identified Using the Proxy-Phenotype Method," *Proceedings of the National Academy of Science* 111, no. 38 (2014): 13790-13794.
31. D. Piffer, "A Review of Intelligence GWAS Hits: Their Relationship to Country IQ and the Issue of Spatial Autocorrelation," *Intelligence* 53 (2015): 43-50.
32. P. K. Hatemi et al., "Genetic Influences on Political Ideologies: Twin Analyses of 19 Measures of Political Ideologies from Five Democracies and Genome-Wide Findings from Three Populations," *Behavioral Genetics* 44, no. 3 (2014): 282-294.
33. B. C. Haberstick et al., "MAOA Genotype, Childhood Maltreatment, and Their Interaction in the Etiology of Adult Antisocial Behaviors," *Biological Psychiatry* 75, no. 1 (2014): 25-30.
34. S. M. Fullerton and S. S-J. Lee, "Secondary Uses and the Governance of De-identified Data: Lessons from the Human Genome Diversity Panel," *BMC Medical Ethics* 12 (2011): 16; doi: 10.1186/1472-6939-12-16.
35. Department of Homeland Security et al., "Final Revisions to the Common Rule," *Federal Register* 82, no. 12 (2017): 7149-7274, *available at* <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html> (last visited May 28, 2017).
36. *Id*., sec__. 116(d)(2), at 7267.
37. *Id*., sec__.116(d)(5), at 7267.
38. K. C. O'Doherty et al., "From Consent to Institutions: Designing Adaptive Governance for Genomic Biobanks," *Social Science & Medicine* 73, no. 3 (2011): 367-374; B. Koenig, "Have We Asked Too Much of Consent?" *Hastings Center Report* 44, no. 4 (2014): 33-34.
39. See O'Doherty et al., *supra* note 38.
40. C. M. Simon, E. Newbery, and J. L. Heureux, "Protecting Participants, Promoting Progress: Public Perspectives on Community Advisory Boards (CABs) in Biobanking," *Journal of Empirical Research on Human Research Ethics* 6, no. 3 (2011): 19-30; R. P. Strauss et al., "The Role of Community Advisory Boards: Involving Communities in the Informed Consent Process," *American Journal of Public Health* 91, no. 12 (2001): 1938-1943.
41. S. M. Fullerton et al., "Meeting the Governance Challenges of Next-Generation Biorepository Research," *Science Translational Medicine* 2, no. 15 (2010): 15cm13.
42. K. C. O'Doherty, A. K. Hawkins, and M. M. Burgess, "Involving Citizens in the Ethics of Biobank Research: Informing Institutional Policy through Structured Public Deliberation," *Social Science & Medicine* 75, no. 9 (2012): 1604-1611; J. E. Olson et al., "The Mayo Clinic Biobank: A Building Block for Individualized Medicine," *Mayo Clinic Proceedings* 88, no. 9 (2013): 952-962; D. M. Secko, M. Burgess, and K. O'Doherty, "Perspectives on Engaging the Public in the Ethics of Emerging Biotechnologies: From Salmon to Biobanks to Neuroethics," *Accountable Research* 15, no. 4 (2008): 283-302.
43. G. E. Henderson et al., "Stewardship Practices of U.S. Biobanks," *Science Translational Medicine* 5 (2013): 215cm7.
44. C. L. Overby et al., "Prioritizing Approaches to Engage Community Members and Build Trust in Biobanks: A Survey of Attitudes and Opinions of Adults within Outpatient Practices at the University of Maryland," *Journal of Personlized Medicine* 5, no. 3 (2015): 264-279.
45. See O'Doherty et al., *supra* note 38.
46. See Simon et al., *supra* note 40.

The Journal of Law, Medicine & Ethics, 46 (2018): 79-86. © 2018 The Author(s)