INTRODUCTION

Return of Research Results: What About the Family?

Susan M. Wolf

When work began on return of results in genomic research about a decade ago, few thought about the family. The question of whether researchers owed participants a duty to offer back individual results and incidental findings of potential health importance was vexing enough. At that point researchers customarily refrained from offering results to participants. If consent forms said anything at all about return of results, it was often to clarify that no results would be offered back.[1]

In 2005, the University of Minnesota's Consortium on Law and Values began a project funded by the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH) to examine the question of how incidental findings should be managed in genetic and genomic research.[2] By this point, imaging researchers had recognized and documented the inevitability of incidental findings, including in neuroimaging research using MRI to image the brain. In imaging research, the "unidentified bright object" that could signal a mass or the obvious arterial malformation was hard to ignore in reading the scans. The imaging research community was hard at work developing classification schemes for incidental findings and protocols for ascertaining which findings required clinical attention, and deciding how to communicate these findings to research participants and their physicians. The genetics and genomics research community lagged behind. Our project took the progress made in the imaging context as a starting point for developing consensus recommendations cutting across imaging, genetic, and genomic research.[3]

Others soon took up this difficult problem as well.[4] What made this problem difficult was that it erupted in the research sphere, where investigators were committed to seeking generalizable knowledge. Yet incidental findings discovered in the course of research were troubling because of their potential implications in the clinical sphere, where clinicians were committed to advancing the well-being of individual patients.[5] Researchers wondered whether they had responsibilities to recognize and even hunt for these incidental findings, and then responsibilities to alert the research participant to permit clinical evaluation. After all, they were researchers not clinicians, operating with limited research budgets to seek group results for population benefit. And if they had responsibilities to recognize, analyze, and offer back incidental findings of potential clinical concern, they probably also had duties to evaluate and offer back individual results on variables under study when those research results signalled clinical concerns.

Analyzing return of results and incidental findings has proven enormously challenging, requiring empirical research, new philosophical analysis, legal scrutiny, attitudinal research, and innovation in research design and clinical practice. Over time, the debate has broadened to include the question of whether genomic biobanks and other large collections of data and specimens to fuel research across the globe have responsibilities as well to address the potential for findings of health importance to the source individual. Thanks to NHGRI funding for a follow-up project,[6] the Consor-

Susan M. Wolf, J.D., *is the McKnight Presidential Professor of Law, Medicine & Public Policy; Faegre Baker Daniels Professor of Law; Professor of Medicine; Faculty member, Center for Bioethics; and Chair, Consortium on Law and Values in Health, Environment & the Life Sciences at the University of Minnesota. She is one of three Principal Investigators on NIH/NCI/NHGRI grant 1-R01-CA154517 on return of genomic results to family members, including after the death of the proband.*

tium on Law and Values tackled this biobank question, publishing consensus recommendations in 2012.[7]

At this point in the debate, there is a robust, international literature on return of genomic results and incidental findings. Yet that literature gives short shrift to the next big question – what about the family?[8] After all, when researchers discover that an individual participant has a genetic variant associated with increased risk of breast and ovarian cancer or colorectal cancer, the finding may have health implications for genetic relatives, as well as for the participant. Indeed, investigators studying the genomics of any life-threatening condition may discover risk variants of health significance after the death of the research participant. And biobanks archiving data and specimens long into the future may discover a variant of high health importance after the death of the source individual and face the question of whether to try to contact relatives. These scenarios raise challenging questions: Do investigators have duties to alert family members? What if relatives approach the researchers asking for this information? How should researchers reconcile family need with privacy protections for participants' health information (which under HIPAA continue for 50 years after the individual's death)?

In 2011, investigators at Mayo Clinic's NCI-supported pancreatic cancer biobank began collaborating with partners at the University of California, San Francisco (UCSF) and the University of Minnesota's Consortium on Law and Values to tackle the question of return of results and incidental findings to relatives, including after the death of the research participant. This project was stimulated by actual research findings in deceased biobank participants with potential implications for their family members. The project combined quantitative and qualitative research based at Mayo and UCSF with systematic evaluation of the ethical, legal, and social issues (the ELSI questions) in a Working Group process based at the University of Minnesota. That Working Group was comprised of experts from multiple disciplines in the United States and Canada. Over the course of three years, the Working Group analyzed the issues to develop consensus recommendations on how to approach return of results and incidental findings to relatives, including after the participant's death. The issues were complex, requiring consideration of the science, clinical care, laboratory practice, ethics, and law. The group considered the literature and data, working through multiple drafts. We also met with the Mayo Clinic pancreatic cancer biobank's patient and family representative group (RAPPORT, an acronym for "Representing Advocacy for Pancreas Patients with Outreach and Research Teams"). In addition, we co-organized an international workshop at the Brocher Foundation in Switzerland to compare ethical and legal approaches to return of results to families. We conferred with colleagues in the Clinical Sequencing Exploratory Research (CSER) Consortium formed by NHGRI and NCI to link funded investigators and speed progress.[9] And finally, we presented our draft recommendations at a national conference at the University of Minnesota in November of 2014 to elicit feedback and critique.

This collection of articles will not end the debate. Instead, it will deeply inform policy development and genomic sequencing practice, inspire new analyses, and catalyze the next phase of research on return of results. When focused work on return of results to research participants began a decade ago, the family issues were lurking. Now they are in full view. As genomic research progresses and translation into clinical genomics advances, the challenge of doing right by participants and their relatives looms large.

This symposium issue presents 14 articles resulting from this process. The centerpiece is the Working Group's consensus paper offering analysis and recommendations.[10] Additional articles feature groundbreaking empirical studies, pioneering analysis of where return of results fits in the ethics of translational genomics, incisive investigation of the role of IRBs and of biobanks, multiple articles on return of results from genomic research in children and adolescents, much-needed exploration of return of results to diverse participants and families, and comparison between emerging U.S. approaches and approaches in other countries.

This collection of articles will not end the debate. Instead, it will deeply inform policy development and genomic sequencing practice, inspire new analyses, and catalyze the next phase of research on return of results. When focused work on return of results to research participants began a

decade ago, the family issues were lurking. Now they are in full view. As genomic research progresses and translation into clinical genomics advances, the challenge of doing right by participants and their relatives looms large.

Acknowledgments

Preparation of this article and symposium was supported by the National Institutes of Health (NIH), National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI) grant 1R01CA154517 on "Disclosing Genomic Incidental Findings in a Cancer Biobank: An ELSI Experiment" (Gloria M. Petersen, Barbara A. Koenig, Susan M. Wolf, Principal Investigators). The author's work was also supported in part by Robert Wood Johnson Foundation (RWJF) Investigator Award 69763 (S.M.W., Principal Investigator).

The project benefited from presentations offered at a Nov. 2014 conference funded by the NIH grant at the University of Minnesota (http://consortium.umn.edu/conference/should-we-offer-genomic-results-research-participant-s-family-including-after-death). The project also benefited from a Nov. 2013 international comparative workshop that was funded by an administrative supplement to the NIH grant plus the Brocher Foundation, Wellcome Trust, and Swiss Academy of Medical Sciences, and was led by B.A.K., S.M.W., Jane Kaye, D.Phil., L.L.B. (University of Oxford), and Bernice Elger, M.D., Ph.D., M.A. (University of Basel). Work on this project was also advanced by the investigators' participation in the CSER ELSI Consortium created by NHGRI and NCI, linking funded investigators working on translational genomics, including the ethical, legal, and social issues (ELSI) raised by return of results (https://cser-consortium.org/).

The contents of this article are solely the responsibility of the author and do not necessarily represent the views of NIH, NCI, NHGRI, RWJF, or other funders.

Thanks to Heather Bennett, Elliot Ferrel, Alison Key, Elizabeth Oji, Savir Punia, Emily Scholtes, and Jesse Stark for research assistance at various points in this project. Research Associate Rebecca Branum, J.D., provided important support and collaboration. Thanks also to the Mayo Clinic team including Marguerite Robinson for collaboration on overall management of the "Disclosing Genomic Incidental Findings" grant project. Special thanks to Audrey Boyle for outstanding management of the ELSI portions of the project, including the work yielding this symposium. Finally, sincere appreciation to Jean McEwen, J.D., Ph.D., at NHGRI and Bradford Hesse, Ph.D., and Charlisse Caga-anan, J.D., at NCI for invaluable guidance and support.

References

1. F. Lawrenz and S. Sobotka, "Empirical Analysis of Current Approaches to Incidental Findings," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 249-255.
2. NIH, NHGRI grant # 1-R01-HG003178 (Wolf, PI).
3. S. M. Wolf et al., "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 219-248.
4. See, e.g., R. R. Fabsitz et al., "Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants," *Circulation: Cardiovascular Genetics* 3, no. 6 (2010): 574-580. For a subsequent overview, see Presidential Commission for the Study of Bioethical Issues, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts* (2013), *available at* <http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf> (last visited August 18, 2015).
5. 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; S. M. Wolf, "Incidental Findings in Neuroscience Research: A Fundamental Challenge to the Structure of Bioethics and Health Law," in J. Illes and B. J. Sahakian, eds., *The Oxford Handbook of Neuroethics* (New York: Oxford University Press, 2011): at 623-634.
6. NIH, NHGRI grant # 2-R01-HG003178 (Wolf, PI).
7. S. M. Wolf et al., "Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks and Archived Data Sets," *Genetics in Medicine* 14, no. 4 (2012): 361-384.
8. A few forward-looking articles have begun exploring this issue. See, e.g., L. Battistuzzi et al., "Communication of Clinically Useful NGS Results to At-Risk Relatives of Deceased Research Participants: Toward Active Disclosure?" *Journal of Clinical Oncology* 31, no. 32 (2013): 4164-4165; M. P. Lolkema et al., "Ethical, Legal, and Counseling Challenges Surrounding the Return of Genetic Results in Oncology," *Journal of Clinical Oncology* 31, no. 15 (2013): 1842-1848, at 1846; B. Chan et al., "Genomic Inheritances: Disclosing Individual Research Results From Whole-Exome Sequencing to Deceased Participants' Relatives," *American Journal of Bioethics* 12, no. 10 (2012): 1-8, and related commentaries in that issue; A. M. Tassé, "The Return of Results of Deceased Research Participants," *Journal of Law, Medicine & Ethics* 39, no. 4 (2011): 621-630.
9. CSER: Clinical Sequencing Exploratory Research, *available at* <https://cser-consortium.org/> (last visited August 18, 2015).
10. S. M. Wolf et al., "Returning a Research Participant's Genomic Results to Relatives: Analysis and Recommendations," *Journal of Law, Medicine & Ethics* 43, no. 3 (2015): 440-463.