Understanding Incidental Findings in the Context of Genetics and Genomics

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Human genetic and genomic research can yield information that may be of clinical relevance to the individuals who participate as subjects of the research. However, no consensus exists as yet on the responsibilities of researchers to disclose individual research results to participants in human subjects research.[1] "Genetic and genomic research" on humans varies widely, including association studies, examination of allele frequencies, and studies of natural selection, human migration, and genetic variation. For the purposes of this article, it is defined broadly to include analysis of DNA collected from humans that has implications for human health (even if the purpose of the study is not medical). This paper addresses both research results of individual research participants that may be an intended product of the research, as well as unanticipated, "incidental" findings.[2]

It has been common practice among researchers to notify participants during the informed consent process that no individual results will be disclosed, "incidental" or otherwise. In addition, research participants do not have a right to all research information collected about them.[3] However, as information obtained in research becomes more voluminous, more accessible, and more informative, this precedent may no longer be appropriate.

Deciding how to deal with genomic research results has become increasingly pressing as technologies for genome-wide analysis have become readily available. For example, James Watson[4] and Craig Venter[5] have had their genomes sequenced in detail and submitted to GenBank. These sequences were not obtained for specific clinical diagnostic purposes, but will be made available for researchers to study. However, it remains unclear how findings of clinical significance for them or their family members will be handled. Extrapolating this question to large-scale studies that generate huge volumes of DNA sequence and/or expression data from large numbers of people indicates a need to develop guidelines for researchers.

Although genomic technology has vastly increased the amount and resolution of data we can collect,[6] these studies have shown much more individual variation than was expected. Earlier calculations of the variation based on single-nucleotide polymorphisms (SNPs) suggested that a haploid genome from any one individual differed from that of another individual at an average of 1 in 1000 nucleotides (0.1 percent). The most recent calculations, however, based on analysis of Venter's genome indicate that other kinds

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of genetic difference such as copy number variation (indicating areas of the genome that deviate from the normal number of copies, e.g., trisomy 21, which is associated with Down Syndrome) insertions, deletions, and inversions account for as much as five times more inter-individual variation than previously estimated. Furthermore, a stunning 44 percent of genes differed from the reference sequence.[7] Other studies conducting genome-wide analysis of copy number variation suggest that copy number variable regions encompass up to 12 percent of the genome[8] and that approximately two-thirds of copy number variants are in regions that do not overlap with genes.[9] The clinical significance, if any, of this variation is thus largely unknown, but these studies indicate that genomic data will contain tremendous amounts of information that, at least initially, is more likely to raise questions than provide answers.

As genomic studies increasingly examine complex traits that involve multiple genetic and environmental factors, the contributions of any one gene are likely to be small. For example, two recent genome-wide association studies found a statistically significant association between a common variant of a region on chromosome 9 and coronary heart disease.[10] However, the risk of heart disease was increased in homozygotes from 1 to 1.6 percent. Thus, the increased resolution and power afforded by new genomic analyses may lead to increased findings of statistical significance, but not necessarily clinical significance.[11]

In addition to increasingly large amounts of genomic data from research, other factors contribute to the need to develop policies for handling "incidental" findings of clinical significance. One is that genomic data are increasingly made available to researchers or even the general public in databases that are accessible online. Another is that these data can be linked to more extensive medical information about individuals. In addition, samples are increasingly used by researchers for multiple studies and then passed on to other researchers for studies other than the study for which the samples were originally collected. Likewise, a growing number of research repositories of tissue and information allow for use of the same sample in multiple studies, or with no defined time limit for use. Thus, the chain of responsibility for dealing with new findings of clinical significance and the length of time those responsibilities may require are not clear.

Empirical research suggests that participants want to know individual research results.[12] Some commentators have argued that harm of such disclosure is low,[13] at least in some circumstances. Both factors argue for reconsideration of the "do not disclose" practice.[14] However, disclosure implies that researchers shoulder certain obligations and could require significant use of resources. Thus, many ethical, legal, and logistic factors must be weighed in the consideration of how to deal with incidental findings or findings of clinical significance.

It has been common practice among researchers to notify participants during the informed consent process that no individual results will be disclosed, "incidental" or otherwise. In addition, research participants do not have a right to all research information collected about them. However, as information obtained in research becomes more voluminous, more accessible, and more informative, this precedent may no longer be appropriate.

Issues to Consider in Genetic and Genomic Research

What, then, are the issues to be considered in deciding whether and how to disclose "incidental" findings or other findings of clinical significance that arise in the course of human genomic and genetic research? What research results should be offered, and what should not be offered? For which research should individual results be offered to research participants, when should they be offered, how, and to whom? And what even constitutes an "incidental" finding in the context of genomic or genetic research?[15]

What is an "Incidental" Finding in Genomic or Genetic Research?

An "incidental" finding in genomic or genetic research depends on the type of research. For some genomic or genetic research, it is difficult to distinguish "incidental" from other findings because the nature of the genomic research question can be very open ended or descriptive. For example, what is the allelic variation at a particular locus? How does a population of "normal" people vary genetically by copy number

throughout the genome? For such studies, it could be said that nearly nothing is "incidental" because very little is outside the scope of the research question. On the other hand, genetic research also occurs on well-studied genes in which case the association of specific variants with disease, perhaps even life-threatening conditions, may be well known. In such research, findings may be of high clinical significance to individual research participants, yet not "incidental" in that the findings may be well within the scope of the study. In both types of studies, whether the finding is regarded as "incidental" or not, the question remains what ethical obligations, if any, researchers may have to disclose the finding to individuals.

Reanalysis of genomic and genetic data over time, by the original or subsequent researchers, also raises the issue of how long the duty persists to report findings after samples are collected or data are generated.

What Research Results Should be Offered, and What Should Not be Offered?

Several factors have already been identified in weighing what research results should be offered, and what should not be offered. Clearly a major concern about offering results is the potential lack of accuracy and understanding of results obtained in the research. Thus, an assessment of analytic and clinical validity is necessary.[16] For genomic data, this may include an evaluation of the strength of genotype-phenotype associations[17] and predictive value.

An assessment of clinical utility is also a consideration, but for genetic data, this is complicated by the fact that the potential benefits of genetic research may be informational only, rather than directly providing therapeutic value. Nevertheless, consideration of circumstances in which the information might change clinical decisions, such as the availability of an effective intervention or prevention, is important.[18] For genomic and genetic data, this could include information about susceptibility to environmental factors, including, for example, indication of susceptibility to a severe drug reaction. Further informational value may accrue by informing reproductive decisions about the health of a future child, rather than immediate health care decisions of the actual research participant.

Disclosure implies that researchers shoulder certain obligations and could require significant use of resources. Thus, many ethical, legal, and logistic factors must be weighed in the consideration of how to deal with incidental findings or findings of clinical significance.

Commercial availability of a genetic analysis that is used in a research context may influence the assessment of whether the research finding should be disclosed to an individual research participant. On the one hand, if a genetic test or analysis is widely available through a laboratory certified under the Clinical Laboratory Improvements Amendments (CLIA),[19] then this implies significant clinical validity and utility, and could thus suggest a researcher obligation to provide the information. On the other hand, wide availability outside the lab lessens the researcher obligation to provide the information, especially if the research lab itself is not CLIA-certified, and instead creates the possibility that researchers will refer participants for testing by certified clinical laboratories.

The capacity of researchers to provide genetic information is clearly a critical consideration.[20] As with research using imaging data, which can be collected for basic or non-clinical research by researchers without clinical training or qualifications, the genetics expertise to determine whether data have clinical significance may be limited.[21] While lack of interpretive expertise or capacity must be an important factor, it cannot be the only factor in deciding whether to return results.

In genomic and genetic research, it is common for scientists to conduct research on samples from human subjects with whom the researchers have had no contact. This is increasingly true with the wider availability of samples in tissue and cell banks from which DNA can be analyzed, and with the growth of databanks. However, it is also common, especially in large cohort studies and pedigree studies, for researchers to have a very well-established and long-term relationship with their subjects

and families, sometimes even including the subjects in planning, design, and publication of the studies.[22] The wide range of researcher-subject relationships cannot be ignored because the preservation of trust in these relationships is important and the strength of the relationship implies different obligations with respect to reporting research results.

Finally, an "incidental finding" long known in the practice of clinical genetics that must also be considered in the conduct of genomic and genetic research is misattributed parentage. The standard in clinical genetics outside of research is not to offer this information if "incidental" to the clinical findings because of the potential harm to families and the likelihood of harm outweighing benefits. The standard for a research protocol should be similar, and made clear in the informed consent process.

It is important to consider whether any results of potentially high clinical significance must be offered by researchers. It is also crucial for researchers to remain respectful of participants' right not to know[23] and to begin with the premise that information should be offered rather than disclosed. However, this position leaves researchers in a tight spot if they possess information that they feel is so important that it *should* be given to a research participant, but the individual has asserted a preference not to know. Thus, the process for informing research participants about results and their preferences for receiving information should be worked out in advance, during the informed consent process.

Which Individual Research Results Should be Offered to Research Participants?

The secondary use of archived genomic and genetic data and the possibility of conducting such research on "anonymized" or de-identified DNA samples raise difficult questions of how to address return of individual research results and incidental findings. The separation of research from the people who supplied the data makes it difficult or potentially impossible to return results to individuals. However, even when individuals are still identifiable (e.g., by the researcher who originally collected the DNA samples), and results or incidental findings of clinical significance are found that may meet a threshold of obligation to report, the secondary researcher who has made these findings may not have access to the identities of the individual(s) in question. In addition, research with de-identified data was recently deemed not "human subjects research" by U.S. federal research regulation.[24] However, the researcher conducting secondary data analysis may still have ethical obligations to the research participants (especially if promises about reporting results or incidental findings were made in the informed consent process when samples were originally collected).

Thus, when researchers are collecting samples, they should consider eliciting informed consent to possible secondary uses of the samples and data and establishing a process for dealing with incidental findings and research results of clinical significance. This process may require that the researchers who originally collected the samples contact the participants, even if those researchers did not discover the clinically significant finding. This will require communication between the original and secondary researchers after samples or data are transferred.

When do Researchers Have a Responsibility to Offer Results?

Reanalysis of genomic and genetic data over time, by the original or subsequent researchers, also raises the issue of how long the duty persists to report findings after samples are collected or data are generated. DNA data may be analyzed long after they are collected, and as our understanding of pleiotropy, gene-gene, and gene-environment interaction grows, the same data may have different meaning with time. For example, the apolipoprotein E gene has implications for both cardiovascular disease and Alzheimer disease. Research conducted only on Alzheimer disease that examines the APOE gene potentially reveals information about the individual's predisposition to cardiovascular disease as well. Future research may reveal even more clinical predictive value of this gene, especially in combination with other genetic information.

Furthermore, large amounts of DNA sequence data can be collected but unanalyzed. Data are analyzed primarily to answer planned research questions, so that even if data of clinical significance may be in the possession of researchers, it is questionable whether researchers are obliged to sift through and analyze all collected samples and data in order to uncover findings that do not serve their research. This is true both during research and after the research is completed. If clinically significant findings are uncovered in the course of research years after the DNA was initially collected, it may not be feasible to locate and recontact the research participants. Unless the researcher has an ongoing relationship with the participants, the obligation to disclose findings diminishes over time.

How Should Research Results be Offered?

If it is decided that results or incidental findings should be returned, then there are several logistic and ethical issues to consider in how this should be done. These issues include whether to confirm the

finding in the research sample, as well as determining whether recontact is possible and permitted under the informed consent documents. In addition, for genetic and genomic tests, researchers must consider whether to confirm the findings in a CLIA-certified laboratory or whether the participant should be referred to such a lab for testing.[25] Finally, researchers should consider whether a genetic counselor is necessary to convey and discuss the implications of the findings, and what duties the researchers owe participants to facilitate follow-up care.

The logistics of recontacting are not trivial because of the importance of respecting the participant's right not to know genetic information. Recontacting to obtain a sample for verification of results without disclosing the results themselves could be a delicate discussion, thus underscoring the need to consider the possibility of this scenario in the informed consent process in studies designed to be prospective.

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To Whom Should Research Results be Offered?

Genetic and genomic research findings also present the possibility of discovering clinically significant information that may have significance for family members of research participants. The need to provide family members with information must be balanced against the privacy and confidentiality of the participants themselves, as well as consideration of promises that may have been made to participants in the informed consent process restricting notification of third parties about research data. However, a discussion about the implications of clinically significant research findings for family members should be a part of any disclosure.[26]

Other Issues

Perhaps the most important consideration is the change in stance that offering research results of clinical significance represents for the researcher-participant relationship. Much effort guiding the ethical conduct of research has been spent in making a clear delineation between the role of the researcher and the role of the treating physician because of the conflict of interest that the dual roles present. In fact, Ellen Wright Clayton and Lainie Friedman-Ross stress the need to avoid the therapeutic misconception implied by the disclosure of research results to participants.[27] Blurring the lines between clinical and research obligations should not be taken lightly. It is important to cross this line only with compelling reason, accurate information, and clear informed consent.

Leah Belsky and Henry Richardson argue that researchers may have a duty to provide ancillary care to subjects of research, based on the principle that participation in research involves at least a partial, even if tacit, entrustment of health to the researchers.[28] Specifically, the scope of this entrustment depends on the vulnerability of the subjects, the extent of uncompensated risks or burdens, the depth of the researcher-subject relationship, and the subjects' dependence on the researchers. How genetic or genomic research fits into this partial entrustment model would depend on the specific nature of the research protocol. Typically, genetic or genomic research does not pose large risks or burdens, but the researcher-subject relationship and subjects' dependence on the researchers may vary greatly. Families with rare genetic conditions, for example, may have very strong and long-term relationships with researchers and may feel dependent on researchers for health information about their conditions as well as the possibility of developing and conducting diagnostic tests and treatments because attention to rare conditions is often so hard to get.

Subjects of genetic or genomic research are not always vulnerable — in the sense of being ill, oppressed, or poor, although they may be. As research on human genetic variation increasingly seeks samples from an ever-wider set of populations worldwide, more vulnerable populations may be included. On the other hand, as common and complex traits affecting large numbers of people, or even those who are apparently disease-free, are included in large genomic studies, less vulnerable populations will also be included. Nevertheless, to hold out research results, especially those derived through cutting-edge technology,[29] to either the more or less vulnerable as a benefit would be a

dangerous move towards encouraging the therapeutic misconception if the results are preliminary and not validated, or their predictive value is not well understood. At this stage of much genomic and genetic research, the clinical significance of results is unclear. Nevertheless, as human genetics matures, it is important for researchers to examine potential obligations to offer results to participants.

Acknowledgements

This article is based in part on discussions of the Working Group on Reporting Results of Genetic Research, which met at Stanford University on July 26-27, 2005 for a workshop organized by the Center for Integration of Research on Genetics and Ethics (CIRGE), and funded by the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH) and the U.S. Department of Energy (DOE) (NIH Grant #5 P50 HG 3389-04), and the Stanford Center for Biomedical Ethics. Members of the Working Group are listed at <http://cirge.stanford.edu/library/reporting_results.html>. Preparation of this paper was further supported by NHGRI grant # R01 HG003178 (Primary Invesitgator, S. M. Wolf; Co-Investigator, J. P. Kahn, F. Lawrenz, C. A. Nelson). The views expressed in this paper are not necessarily those of NHGRI, NIH, or DOE.

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