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Reporting Genetic Results in Research Studies: Summary and Recommendations of an NHLBI Working Group

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Abstract

Prospective epidemiologic studies aid in identifying genetic variants associated with diseases, health risks, and physiologic traits. These genetic variants may eventually be measured clinically for purposes of diagnosis, prognosis, and treatment. As evidence of the potential clinical value of such information accrues, research studies face growing pressure to report these results to study participants or their physicians, even before sufficient evidence is available to support widespread screening of asymptomatic persons. There is thus a need to begin to develop consensus on whether and when genetic findings should be reported to participants in research studies. The National Heart, Lung, and Blood Institute (NHLBI) convened a Working Group on Reporting Genetic Results in Research Studies to discuss if, when, and how genetic information should be reported to study participants. The Working Group concluded that genetic test results should be reported to study participants when the associated risk for the disease is significant; the disease has important health implications such as premature death or substantial morbidity or has significant reproductive implications; and proven therapeutic or preventive interventions are available. Finally, the Working Group recommended procedures for reporting genetic research results and encouraged increased efforts to create uniform guidelines for this activity.

Keywords

research results; genetic testing; reporting research results

Introduction

Genetic testing is a complex process that utilizes multiple laboratory techniques to analyze human DNA (including chromosomes, genes, and cytogenetic as well as molecular markers), RNA, proteins, and metabolites. The goal of this research is typically to detect genetic variants that directly cause increased disease risk or are indirectly associated with increased risk for disease. Testing of genetic variants can serve diverse purposes, including: diagnosis of disease (diagnostic testing), identification of future health risks (predictive, prognostic, or presymptomatic testing), prediction of drug responses, and assessment of risks for future children (carrier testing). Proven, consistent, and reliable findings of disease associations in genetic studies have the capacity to redefine health and risk assessment [Sze et al., 2004]. Genetic testing provides information not only about the person being tested but also about their family members [Brunger et al., 2001]. Advances in genetic research have begun to affect many areas of medicine and these advances may eventually facilitate the development of genetically-personalized therapies and preventive strategies to help better manage chronic diseases [Collins, 2001; Brunger et al., 2001; Epstein, 2004; Sze et al., 2004].

Despite genetics becoming more familiar to the scientific and lay communities, the difference between research genetic testing and clinical genetic testing is commonly misunderstood [Rosen, 2004]. Most genetic tests are initially conducted for research purposes in research laboratories and are then moved to clinical labs for clinical use once their value in diagnosis, prognosis, or treatment has been established. Currently, for purposes of clinical genetic testing in the United States, only results from Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories can be reported to patients or used in clinical care. Research studies have varied in their practices of reporting genetic results obtained in the course of research. It has been argued that access to genetic testing should be treated the same way as access to new medical procedures; that is, withheld from the general public until proven safe and effective in large-scale clinical trials [Smith, 2000]. However, conducting such large-scale trials often will require considerable time and resources following obtaining these initially promising results.

Population-based epidemiologic studies routinely include genotyping to identify new genetic risk factors in the population. As evidence of the predictive value of these genetic variants accrues, investigators may face growing pressure (from both their own concerns for participants' welfare, and from participants themselves) to report findings that have an influence on disease risk. Although genotype results have considerable potential for risk assessment and appropriate targeting of screening and preventive strategies, genotypes imperfectly predict the development and severity of a condition and genetic associations with disease are often not validated in more extensive studies. Psychological and social harm, as well as financial costs and risks, may result from providing information with significant implications for the health of the individual and his/her family members. These issues should be considered carefully well before any imperative to report genetic results. There is thus a need to begin to develop consensus on whether, when, and how genetic findings should be reported to research study participants.

The National Heart, Lung, and Blood Institute Working Group Meeting

The National Heart, Lung, and Blood Institute (NHLBI) convened a Working Group on Reporting Genetic Results in Research Studies on July 12, 2004, in Bethesda, MD. Experts in genetics, genetic and cardiovascular epidemiology, clinical research, and ethical, legal, and social implications (ELSI) met to discuss and make recommendations for reporting individual results from genetic tests to participants of heart, lung, blood, and sleep research studies.¹ Working group members were selected for their expertise, experience, and diversity of perspective. No research subjects or lay persons participated in this meeting. The objectives of the working group were to discuss if, when, and how genetic information should be reported to study participants and to begin to formulate criteria and/or guidelines for such reporting. This manuscript reviews the relevant literature on the advantages and disadvantages of reporting genetic research results to study participants and provides a summary of the Working Group recommendations. The recommendations are subject to modification in the future based on experience with implementation and the results of future research.

Evaluation Criteria for Genetic Testing

Prior to determining whether to report genetic research results, the usefulness and applicability of genetic tests results should be evaluated for their analytical validity, clinical validity, clinical utility and ethical, legal and social implications [Burke et al., 2002; Krousel-Wood et al., 2003]. Analytical validity requires analytical sensitivity (probability that a test will be positive when the genetic variant is present) and analytical specificity (probability that a test will be negative when the variant is absent). Clinical validity involves establishing several measures of clinical performance including its clinical sensitivity and specificity (as related to disease) and positive and negative predictive values [SPH, 2000; Burke et al., 2002]. The clinical validity of genetic test results is affected by the heterogeneity of the phenotypes, penetrance of the gene, bias in the study populations, and confounding of phenotypic modifiers. The uncertainty which surrounds clinical validity should be considered in deciding whether to allow genetic research results to be reported to study participants [Burke et al., 2002].

Clinical utility, the likelihood that the test will lead to an improved health outcome, is a key factor in assessing the usefulness of a genetic test [Burke et al., 2002]. The clinical utility of testing varies widely, depending upon the magnitude of the risk, the accuracy of the risk prediction, the potential for risk reduction, the patient's previous life and health experiences, and the needs and experience of family members [Evans et al., 2001]. Other important points in relation to the clinical utility of genetic testing include the effectiveness of available interventions and implications for insurance, employment discrimination, stigmatization, and long-term psychological harm [Burke et al., 2002]. When genetic testing strongly predicts a deleterious clinical outcome and an efficacious early intervention exists, it is of high clinical utility. Knowledge of an inherited predisposition may not lead to measures to reduce risk, thus limiting the clinical utility of predictive genetic testing [Evans et al., 2001]. For example, individuals with a genetic predisposition for Huntington Disease cannot currently reduce their risk, but can use the information for life planning decisions [Epstein, 2004]. However, Huntington Disease is a Mendelian trait with 100% penetrance. Life-planning may not be a relevant consideration when considering low-penetrance alleles.

¹The complete list of recommendations to the Institute and appendices are available via the web at www.nhlbi.nih.gov/meetings/workshops/gene-results.htm.

Ethical, Legal and Social Implications

In genetic testing, as with most medical testing, there is an emotional and behavioral, as well as medical, impact on those receiving the results. There are also implications for family members of persons receiving results. Participants receiving a positive test result indicating a deleterious genetic variation may suffer serious psychological harm, while those receiving negative results for the same test may have other psychological difficulties such as “survivor guilt.” Participants who receive genetic tests results indicating they are lacking disease-associated mutations may experience unwarranted reassurance that they will not develop a disease, e.g. breast cancer in non-BRCA carriers. This could have implications on the participant's future health behavior and lifestyle decisions. If negative test results are returned, the written information provided with results and/or counseling should address the meaning of negative test results to avoid the misinterpretation of results.

In addition to psychosocial concerns, there is a perceived threat of social stigmatization and discrimination in access to employment and health insurance which has important implications for disclosing genetic test results [Mehlman, 2004]. These risks may be increased when results are disclosed. The increased cost of care associated with some illnesses has also caused legitimate concerns about potential discrimination against those thought to be at increased disease risk [Wendler et al., 2002]. Other considerations include the participant's access to testing, as well as the availability and the cost of treatment [Burke et al., 2002].

Another important consideration is the lack of training and expertise of health care providers, especially those not directly involved in genetics, in the interpretation of genetic results [Smith, 2000; Mehlman, 2004]. Genetic risk factors for complex diseases can be particularly complicated and confusing, leading patients and their physicians to overestimate or underestimate the significance of positive or negative test results. Patients often overestimate the accuracy of information revealed by genetic testing because the testing is usually done in a medical context where physician recommendations are more likely to be accepted as the truth [Smith, 2000]. As a result, a common practice in research studies is not to provide participants and their physicians with their genetic test results to protect them from over-interpreting research results of uncertain clinical significance [Smith, 2000; Wendler et al., 2002; Sze et al., 2004; Mehlman, 2004].

Opinions vary as to the appropriate time to report research results [Fernandez et al., 2003a]. To date the courts have had minimal involvement in reporting genetic results (*Ande v. Rock*, 647 N.W.2d 265 [2002], *Pate v. Threlkel*, 661 So.2d 278 [1995], *Molloy v. Meier*, Nos.C9-02-1821 and C9-02-1837 [2004]), but as genetic testing becomes more prevalent the courts will become more involved.

Advocacy for Reporting Research Results

There is a strong voice that supports the right of participants to receive results that may potentially be clinically useful. Recently, there has been pressure from patient advocates and clinical researchers to offer study results to all participants [Partridge et al., 2003]. In the Summit Series on Clinical Trials in 2000, it was recommended that the return of all test results to participants should be considered the ‘ethical norm’ [Summit Series on Clinical Trials, 2000; Partridge et al., 2002; Partridge et al., 2003]. Participants of the summit recommended that subjects should be informed when the results may make a difference in their current or future health care [Partridge et al., 2002]. When surveyed, a majority of oncology clinicians expressed willingness to report results to participants because they

believed that most research participants wanted to be informed and that routine reporting would not have an adverse impact on participants [Partridge et al., 2004].

Despite the fact that reporting results to study participants may not immediately improve their health, it may be beneficial in other ways [Partridge et al., 2002; Fernandez et al., 2003d]. Reporting research results has been used to empower research subjects to become proactive in improving their quality of life by changing their lifestyle to alter risks and to take a vested interest in the research process; it has also been shown to aid in building successful relationships between the community and researchers [Partridge et al., 2002]. Informing study participants of research results may result in better patient-physician communication, ultimately resulting in greater satisfaction with care in the clinical setting. The sharing of genetic results may also lead to participants having an increased understanding of genetics, which would likely lead to better participation and implementation of findings [Bunin et al., 1996; Snowdon et al., 1998; Schulz et al., 2003]. Results from a randomized population sample of 1000 adults, ages 18-85 in Sweden showed that a majority (83.4%) of subjects would like to be informed of research results that would provide information about genetic predisposition to disease [Hoeyer et al., 2004]. A majority (54.9%) also noted that they would like to receive information about the risk of a preventable disease even when they were not informed in advance that this type of information may arise from the research.

In recent years, there has been encouragement to report results to participants in clinical trials, but some advocates believe that this should be extended to participants in all human subject research [Fernandez et al., 2004]. Clinical trial patients may have an immediate and direct benefit from result disclosure based on changes in therapy. Benefits to participants of observational studies may be less concrete, but still offer information on future risk of disease. Advocates of reporting results do not support forcing participants to receive test results, but believe the option should be available. A multidisciplinary group organized by the Office of Genetics and Disease Prevention of the Centers for Disease Control and Prevention came together to develop an informed consent approach for integrating genetic variation into population-based research. This group noted that if the results of a research project was likely to generate information that could lead directly to an evidence-based intervention, the project should collaborate with a CLIA-approved laboratory and participants should be informed about the specific genes to be studied, counseled about the risk and benefits of clinically relevant genetic information, and offered the option of receiving individual results [Beskow et al., 2001]. Participants are not solely interested in their individual risks, or in the benefits and side effects of participating in research studies; they are also interested in the overall outcome of the study and its contribution to public health [Fernandez et al., 2003b].

Limitations of Genetic Epidemiology Studies

Genetic epidemiologic studies are designed to identify the genetic variants associated with specific diseases [Burke et al., 2002]. These studies may identify genetic variants useful for early detection of disease and presymptomatic diagnosis, which in turn could provide new opportunities for intervention and/or prevention. Hirschhorn and colleagues [2002] have concluded that although strong disease-variant associations have been found for monogenic (typically Mendelian) disorders, few consistent associations have been reported for common complex diseases. Their literature review found that only 6 of 166 reported associations had been replicated three or more times. Further, recent meta-analyses suggest that perhaps only one third of replicated gene-disease associations are likely true. In comparison to testing for monogenic diseases, genetic testing for susceptibility to complex disease has considerable inherent uncertainty [Hirschhorn et al., 2002; LeRoy, 2004].

It is important to note that when investigating disease risk in genetic research, association should not be equated with causality. Causality is often difficult to assign because most common diseases are multifactorial [Burke et al., 2002]. The observational nature of most studies further complicates assessment of causality because associations between gene variants and disease can be confounded by variation in other genes, exposures, population stratification, and other differences between cases and controls. Although genotype results have considerable potential for risk assessment and appropriate targeting of screening and preventive strategies, genotypes, like many other laboratory measures, imperfectly predict the development and severity of a condition. Thus, genetic test results are likely to vary in predictive value [Smith, 2000]. For example, not all persons carrying a gene variant for monogenic familial hypercholesterolemia develop cardiovascular disease. There are at least three reasons for this phenomenon: (1) there may be multiple mutations (alleles) in the mutant gene; (2) there may be one or more modifier genes that interact to affect the condition; and (3) there may be interaction of the gene with environmental factors that affect the condition [Harper, 1997]. The inherent heterogeneity and potential for non-genetic effects make identification of susceptibility genes difficult. Results of genetic tests should thus be considered in the context of the aforementioned factors to determine appropriate clinical decisions and the usefulness of the results [Harper, 1997; Krousel-Wood et al., 2003].

Most common diseases are caused by multiple genetic and environmental variables [Newton-Cheh and Hirschhorn, 2005]. Because of the multifactorial nature of complex diseases, a given genetic variant that contributes to the disease generally has a modest effect by itself. At our current state of knowledge of complex diseases, very few genes have relative risks of more than two. In addition, there are often no available treatments or preventive measures to reduce the risk. Many genetic risk factors uncovered by epidemiological studies are going to be probabilistic. Practical results of clinical utility in complex diseases will be difficult to achieve. Data from early studies may not be replicable and therefore harmful by providing false information. These considerations point out important differences between observational epidemiologic investigations that explore the role of novel genetic risk factors in complex diseases as compared with studies on disease therapy or exploration of the role of Mendelian disorders in genetic disease etiology. Genetic population studies in contrast to clinical studies more frequently were exploratory and not expected to lead to clinically applicable results. Under these circumstances, it is recommended that participants not be informed about individual results [Beskow et al., 2001].

How to Report Genetic Research Results

While there are explicit guidelines on how to obtain informed consent in research studies, very little guidance has been presented on how to report research results [Fernandez et al., 2003a]. Persons deciding whether to undergo genetic testing must receive accurate and understandable information about the risks and benefits of testing and appropriate genetic counseling to adequately comprehend the test results [Mehlman, 2004]. Research participants should be involved in the follow-up process and be responsible for providing accurate contact information in order to receive results [Fernandez et al., 2004]. Responsibilities of the investigators cannot extend beyond the period of funding.

In genetic research, focus should be placed on determining the wants and needs of participants when considering approaches to reporting results [Fernandez et al., 2004]. Even small differences in the way genetic information is presented and discussed can affect the attitude of the person as well as the interest in and the extent to which information is recalled and therefore understood [Michie et al., 2004]. Oral communication is often seen as an

appropriate and emphatic way of reporting adverse results, because of the ability to offer immediate support [Fernandez et al., 2003c], but both verbal and written information have been shown to influence decision-making by persons offered genetic testing [Michie et al., 2004]. An accurate, standardized approach to reporting genetic results in research studies would serve an important clinical purpose by providing information in a clear, succinct, and systematic format, ensuring that participants and their physicians understand the results of their genetic tests [Burke et al., 2002].

There are costs involved in returning genetic research results to participants. These include the costs of database design, the extra effort required to maintain contact with participants, the costs of the disclosure procedure, and providing referrals for medical care and/or psychosocial care after disclosure [Fernandez et al., 2004]. The costs of returning genetic results to research participants are affected by the mode of the result dissemination and the size and duration of the study. Costs of referrals for medical and psychological care after receiving results should also be considered [Fernandez et al., 2003d]. Since the costs of reporting clinical results to participants are included in many research studies, budgets for genetic research studies that are testing for mutations known to be of clinical significance should include the costs and duration of funding needed to offer genetic research results to participants and the counseling needed to explain the meaning of results [Fernandez et al., 2004]. How costs should be born when unanticipated genetic associations with high clinical importance are discovered late in or after a research study is concluded is much more problematic. However, simply not reporting the results because of costs seems unethical.

Recommendations of the NHLBI Working Group

There are conditions in which genetic results should be offered to research participants. The decision to report genetic results should not depend solely upon the discretion of the investigator, but should include a broader range of perspectives as is found in Institutional Review Boards. When genetic research results are under consideration for reporting, standard criteria/guidelines should be developed and followed that include careful consideration of the risks and benefits to participants. While returning research results may serve a number of significant functions, it is important to keep the subject's best interests in mind. Returning information that is preliminary and not validated by other studies should be approached with extreme caution.

When returning genetic research results, if a genetic counselor is not available, personnel who explain the genetic results should have training and experience in human genetics and counseling. Also, concise and accurate written information should accompany the results. Consent forms as well as post-study information provided to research participants should include a section that addresses the future personal and/or reproductive implications for the participant and his/her family.

The NHLBI Working Group on Reporting Genetic Results in Research Studies was convened to consider the existing literature, as summarized above, and provide recommendations for guidelines on reporting individual results to research participants in heart, lung, blood, and sleep studies. These recommendations are generalized for wider application.

Under what circumstances should genetic results be offered to research participants?

1. Genetic results should be offered to study participants if they meet the following criteria:
 - a. There is established analytic validity.²

AND

- b. The associated risk for the disease is replicable and significant, e.g. relative risk >2.0. Variants with greater penetrance or associated with younger age of onset should receive priority.

AND

- c. The disease has important health implications, such as premature death or substantial morbidity.

AND

- d. Proven therapeutic or preventive interventions are available. Research results on genetic diseases or traits that do not affect the participants' health but carry significant reproductive risks for disease among offspring should be considered for reporting to study subjects.
2. In general, genetic test results should not be withheld if they meet the criteria described above, assuming that participants have agreed to receive results. Results should never be forced on research participants. Examples of current genetic tests meeting these criteria include homozygous Factor V Leiden, cystic fibrosis transmembrane conductance regulator (*CFTR*) and breast cancer *BRCA1/BRCA2* mutations.
 3. A list of genetic tests that meet these criteria, such as the list included in the appendix of the working group report (www.nhlbi.nih.gov/meetings/workshops/gene-results.htm), should be reviewed to identify tests appropriate for consideration for reporting. Note that practically all of the more than 250 tests listed in that table relate to specific mutations of monogenic diseases and do not include polymorphisms that are usually investigated in genetic epidemiologic population studies. No such list can be considered exhaustive, given the changing nature of the field, but should provide examples and guidance for deciding which tests should be offered to participants. These suggested tests should be reviewed by investigators from individual studies for appropriateness for reporting in their study. The process of creating the list of available genetic tests should be repeated on a periodic basis by a group with sufficient expertise to judge the evolving scientific foundation for reporting these results.
 4. Decisions regarding reporting of research results should not be made by the investigator alone, and should be done only with IRB approval after careful consideration of risks and benefits.

When should genetic results be offered to research participants?

5. Genetic research results should be offered and, if accepted, shared with participants as soon as possible after determining that the genetic test(s) performed in the study are analytically and clinically valid, e.g. manuscript with associated relative risks of

²The test(s) should be performed in a CLIA-certified laboratory. If the test was performed in a non-CLIA-certified laboratory, there are three alternatives which may depend on budgetary considerations. 1) The patient should be referred to a CLIA-certified laboratory for confirmation of results on a redrawn sample. 2) If a genetic test is available only in the research laboratory, it should be run by two different methods and/or the research laboratory should work under direct supervision of a CLIA-certified laboratory to confirm results. 3) The research laboratory should obtain CLIA certification. (The expectations for sample handling in a CLIA-certified laboratory are identical to those expected of research samples to avoid mix-up, and the availability of clear written protocols for all relevant procedures is often helpful in training new personnel in the laboratory. Under these circumstances, findings from a research laboratory that has been CLIA certified could be reported directly to a research participant and/or their physician.) Results reported by a research laboratory should be identified as 'research' results when reported to participants and their physicians.

genetic variant accepted in a peer-reviewed journal, results are replicated by other studies, etc.

How should genetic results be offered to research participants?

6. Genetic research results meeting the criteria outlined in #1 should be offered as part of the original consent process. Research study participants should be given the opportunity to decline receiving genetic results and remain eligible for participation if receiving the results is not central to the conduct of the research.
7. Consent forms should address results with personal health implications, implications for family members, and reproductive implications separately, as by a two-part question such as, “We will be studying genes that affect cardiovascular disease but may find other genetic disorders. Do you want results reported that have significant health implications for yourself or your family members? Reproductive implications for yourself or your family?” Consent forms should note that the confirmation of the genetic research results in a clinical setting and psychosocial and/or medical care that may be needed will be the responsibility of the participant. People administering informed consent for genetic tests should be trained to explain the personal, familial, and reproductive implications of reporting.
8. At the time of consent, a counselor/consultant should be provided to explain the nature of the study, implications of participation, and the potential relevance of the genetic results, including any risks of harm or potential for benefits for participants, their families or communities; this person need not be a certified/licensed genetic counselor, but must have training and experience in human genetics and counseling to execute this responsibility appropriately.
9. Results may be returned by letter or in person by a qualified person (see recommendation #8). If results are disseminated by letter, access to genetic counseling should be included. Follow-up by telephone may be needed to confirm the receipt of results and make sure the participant comprehends the information. Legitimate and brief information, preferably on a single page, should accompany test results to inform clinicians about what to do with the genetic test/marker results. Ideally, these information sheets should be standardized and available from a responsible source, perhaps as part of a website relating this information. Findings with reproductive implications, including implications for the relatives or offspring of the subject, should follow the same guidelines.
10. Referrals for appropriate medical and psychosocial care should be available to research participants. Attempts should be made to identify accessible resources for uninsured participants.

How can a standard approach for reporting genetic results in research studies be established?

11. A process should be developed for educating non-geneticist members of the research team (investigators, IRB members, subject advocates, etc.) on the difference between highly penetrant monogenic genetic diseases as compared to genes of small effect contributing to complex polygenic traits. Such understanding is required to assess the risks and benefits of reporting or not reporting results to participants.
12. Recommendations regarding reporting of genetic results arising from this NHLBI working group should be coordinated and harmonized across agencies involved in conducting such research, if possible.

13. Consensus panels by professional organizations (American College of Medical Genetics, American Society of Human Genetics, National Society of Genetic Counselors, International Genetic Epidemiology Society, etc.) may be valuable in assessing these criteria and/or establishing additional guidelines, so that recommendations developed by specific organizations are not viewed as designed to serve their own agenda.
14. Based on our recommendations and the results of the consensus panels of relevant organizations, formal, uniform guidance should be issued for IRBs, institutions, investigators and sponsors with respect to best practices for testing and reporting genetic results in human research studies.

It is hoped that these recommendations will serve as the first steps toward establishing formal guidelines on reporting genetic results in research studies. In addition to the development of guidelines, there is a need for constant monitoring of progress in the field to address the evolving nature of genetic research. More research is needed on gene-gene and gene-environment interactions to enable better application of genomic information in the development of diagnosis, prevention, and treatment strategies. Research is also needed on the potential ethical, legal, and social implications of reporting genetic results to research study participants. Finally, the effects of reporting results on recruitment should be studied.

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