# Ethical and Practical Guidelines for Reporting Genetic Research Results To Study Participants: Updated Guidelines from an NHLBI Working Group

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**Running Title:** Return of Genetic Research Results

**Abstract**

In January 2009 the National Heart, Lung, and Blood Institute (NHLBI) convened a 28-member multidisciplinary Working Group to update the recommendations of a 2004 NHLBI Working Group focused on Guidelines to the Return of Genetic Research Results. Changes in the genetic and societal landscape over the intervening five years raise multiple questions and challenges. The group noted the complex issues arising from the fact that the technologic and bioinformatic progress has made it possible to obtain considerable information on individuals which would not have been possible a decade ago. While unable to reach consensus on a number of issues, the Working Group produced five recommendations. The Working Group offers two recommendations addressing the criteria necessary to determine when genetic results *should* and *may* be returned to study participants, respectively. In addition, it suggests that a time limit be established to limit the duration of obligation of investigators to return genetic research results. The Group recommends the creation of a central body, or bodies, to provide guidance on when genetic research results are associated with sufficient risk and have established clinical utility to justify their return to study participants. The final Recommendation urges investigators to engage the broader community when dealing with identifiable communities to advise them on the return of aggregate and individual research results. Creation of an entity charged to provide guidance to IRBs, investigators, research institutions and research sponsors would provide rigorous review of available data, promote standardization of study policies regarding return of genetic research results, and enable investigators and study participants to clarify and share expectations for the handling of this increasingly valuable information with appropriate respect for the rights and needs of participants.

## Introduction

In 2004, the National Heart, Lung, and Blood Institute (NHLBI) convened a Working Group that led to the publication of a conference report and recommendations on returning genetic research results to research participants [1]. In the intervening period the world of genetics has changed dramatically [2-4]. High-throughput technologies have been developed, whole genome sequencing is a reality, additional "omics" measures are now available, and wide data sharing among investigators is expected. Individual genetic results and incidental findings are now distinguished from aggregate results. The appropriateness of returning aggregate results to participants in studies is generally supported in the scientific community, although mechanisms for implementing this process are poorly developed. However, debate continues over when, how and who should return individual results [5-22] to participants. Researchers are finding that many study participants wish to receive individual research results [23-25] and direct-to-consumer (DTC) companies are making genotyping available to consumers at steadily decreasing prices [26,27], with widely variable interpretations of the implications of those individual data. It thus became clear that the recommendations of the 2004 Working Group needed to be reexamined to reflect this rapidly changing landscape.

## Methods

An NHLBI planning committee determined the agenda for a 2-day, January 2009 invitational workshop and invited potential participants. It recommended working group members based on their publications and expertise in relevant disciplines. Of the 40 invitees to the workshop, 11 were unable to attend, and one declined participation. Twenty-eight individuals drawn from 14 states and the District of Columbia accepted the invitation. This group provided expertise in population genetics, laboratory genetics, genomics, statistical genetics, epidemiology, medical genetics, bioethics, genetic counseling, law, public

policy, and patient advocacy. Twenty-seven workshop participants were U.S. experts, one was Canadian, and the focus was on U.S. policy.

The workshop agenda focused on presentations and discussion. Subsequent to the workshop, extensive discussions revealed significant diversity of opinions. The strengths of the process were the involvement of leading thinkers and researchers on return of results and incidental findings, disciplinary diversity, geographic diversity, and extended time and communication to finalize recommendations. The weaknesses were a single meeting with rest of the deliberation electronic, and limited empirical data upon which to base recommendations.

## Charge to the Working Group

The Working Group was tasked with questions of whether individual genetic results should ever be returned to study participants, and if so, what type of results, when should they be returned, and how should they be returned.

## Working Group Recommendations

**Recommendation 1: Individual genetic results should be offered to study participants in a timely manner if they meet all of the following criteria:**

a. **The genetic finding has important health implications for the participant and the associated risks are established and substantial.**
b. **The genetic finding is actionable, that is, there are established therapeutic or preventive interventions or other available actions that have the potential to change the clinical course of the disease.**
c. **The test is analytically valid and the disclosure plan complies with all applicable laws.**

**d. During the informed consent process or subsequently, the study participant has opted to receive his/her individual genetic results.**

The multiple criteria described in Recommendation 1 are summarized in Figure 1. Figure 1 first establishes that informed consent has been obtained and that the study participant's identity and contact information are available. If not, as is the case in anonymous studies and secondary data analyses that provide no means of re-identifying participants, then return of individual results (RoR) is not required.

When contact information is available, the decision to return individual results depends on the nature of the research findings. The research results must have important health implications and be associated with established and substantial risk. Although the 2004 Workshop included an example of significant risk as a relative risk exceeding 2.0, the 2009 Working Group concluded that no firm threshold of risk can be designated, as the importance of genetic information to study participants will depend on both the magnitude of the risk and its consequences. Investigators should consult with available participants in their studies and work with their IRBs to establish what findings are of sufficient health importance that they should be returned. We also recommend below the creation of a central advisory body to provide guidance on decisions about RoR (See Recommendation 3).

In addition to established and substantial risk, the recommendation that RoR *should* occur also requires that the genetic finding must be actionable. Actionable means that disclosure has the potential to lead to an improved health outcome; there must be established therapeutic or preventive interventions available or other available actions that may change the course of disease. Actionable may include

surveillance and interventions to improve clinical course, such as by delaying onset, leading to earlier diagnosis, increasing likelihood of less burdensome disease, or expanding treatment options.

Researchers should consider prospectively whether their study has potential to yield individual research results of clinical importance and describe plans for RoR in consent forms and processes. In this case, participants should be given the opportunity to opt-in or opt-out of RoR. However, not all informed consent documents will mention the return of individual genetic results (particularly for studies in which sample collections were done long ago); in these situations, researchers should consult with their IRB regarding the appropriateness of communicating individual RoR when reliable contact information is available and the result is of high clinical importance.

While the Working Group was highly supportive of the right of study participants to opt-out of receiving genetic results, some Working Group members argued there may be exceptional circumstances where the evidence of potential harm is clear, the magnitude of potential harm is so great, and the potential for reducing the harm associated with the finding is so compelling that the Principal Investigator should confer with the IRB on whether there is an ethical basis to override the wishes of the participant. Other members of the Working Group felt that overriding study participants' opt-out decision should not be allowed, as this action does not respect the wishes of the study participants, who may opt out for strongly-held reasons. Because of the strong arguments in favor of respecting research participant choices and the lack of consensus in our group on overriding the participant's decision in some circumstances, we recommend that when the participant has opted-in or opted-out of receiving results, the investigators honor that decision; when the informed consent is silent, consultation with the IRB on possible options is recommended.

Finally, the test must demonstrate analytic validity and the disclosure plan must comply with all applicable laws. This criterion is not straightforward. In the United States, CLIA certification is required for all laboratories testing human samples for patient care. The Centers for Medicare & Medicaid Services (CMS) is the agency that administers CLIA. According to CMS, research labs are exempt except as defined in 42 CFR § 493.3 b(2) as follows: "It [CLIA] applies to research laboratories as well if they report patient-specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of, individual patients." [28] Working Group members disagreed on the interpretation of what constitutes compliance with the CLIA regulations for the return of research results in genetics studies. This is a high impact issue because sample handling in research studies may not conform to CLIA standards, many research laboratories are not CLIA-certified, newer tests may not be available from CLIA-certified labs, and many existing biobanks and current studies do not use CLIA-certified labs. Some members of the Working Group felt that a regulatory requirement for use of CLIA-certified labs is counter to the ethical obligation of investigators to disclose to study participants information the researchers possess that would be beneficial to those participants, even though the information is not from a CLIA-certified lab. They also argued that results from labs that are not CLIA-certified can still have analytic validity and may be returned by investigators if clearly labeled as research results and accompanied with a warning that the results should not be used for clinical decisions until they are confirmed in a CLIA-certified lab. Then a study participant and his/her physician can take the appropriate next steps as they see fit. This approach would have the added benefit of drawing a line between information generated in research and information generated in the clinical context to guide clinical decisions. However, it is not clear that CMS in interpreting and administering the CLIA regulations will allow this interpretation. Other members of the group felt that it was important for all individual results that were returned to participants to come from a CLIA-certified lab because the CLIA-specified processes offered significant potential benefits to participants (primarily in the realm of

analytic validity and reduced risk of returning results to the wrong person), and that use of a CLIA-certified lab was practicable in nearly all circumstances. Because of the controversy surrounding this issue, the Working Group encourages those making, interpreting, and implementing CLIA policies to revisit and clarify them for research studies in a process that ensures broad input from the research community.

The Working Group recommendation calls for compliance with "applicable laws." We do not attempt here to resolve the legal question of whether research labs that are not CLIA-certified may return individual research results. Pending further legal clarification, researchers planning new studies should consider either using a CLIA-certified lab initially, or planning to confirm results in a CLIA-certified lab, if there is any expectation of identifying variants that will be of clinical importance to the study participants.

**Recommendation 2: A researcher's obligation to return individual research results to a study participant should not ordinarily extend beyond study funding. Even in the case where investigators have access to alternate funds, investigators may, but should not be expected to, return results beyond the termination of research funding.**

In practical terms, investigators cannot maintain an open-ended commitment to return results and thus should plan to have the results provided before the end of the operating grant period. When funding for a project ends, investigators may no longer have the resources to maintain or re-initiate contact with participants even though the researchers may continue to publish or complete work from the data set. This recommendation suggests that investigators (and funders) make available sufficient resources to implement RoR during the award period. Researchers should make clear to study participants during

the informed consent process that individual research results will ordinarily not be returned after the award period ends. The Working Group concluded that if an investigator is able to return genetic research results after the research funding is exhausted, this is acceptable but not obligatory.

There is one important exception to this limitation. For studies in which an investigator also serves as the clinical care provider to a research participant, the investigator-clinician may be obligated to provide clinically relevant information in his/her possession to the patient even if funding has expired.

**Recommendation 3: For consistency and rigor, an independent, national central advisory committee should be established to review evidence for genetic risk factors to offer guidance to investigators, research institutions, and IRBs regarding when a genetic result is well enough understood and has sufficiently serious clinical implications to justify an obligation to return genetic research results to study participants.**

Having a central body generate guidance on what is reportable in genetic studies would provide an opportunity for broad stakeholder input, allow a more consistent approach across research studies, and provide credible guidance for researchers and IRBs. However, guidance from the central body should be advisory, not mandatory, to allow local consideration by IRBs, institutions conducting research, community members, and researchers themselves. IRBs are local by their nature in order to reflect contextual and community factors that may be highly relevant to decision making. Moreover, research is an institutional responsibility. Local control of data or data access may be uniquely important in some studies (e.g., studies involving American Indian or Alaska Native people), and the demands of a community engagement approach may be difficult to reconcile with mandates from an external and far-removed central body.

The Working Group recommended the creation of a central body to evaluate and provide guidance on RoR using a deliberative process with input from all stakeholders, high-quality synthesis of scientific evidence, and consistent application across studies. The central body should transparently and regularly review its conclusions as new information emerges about the validity and clinical utility (including actionability) of various genetic data. In addition, the advisory body may advise on what results the researcher *may* choose to return, as addressed in our Recommendation 4 below. Resources to assist a central advisory committee already exist (see Table 1) and could be harnessed to make a central body a reality.

**Recommendation 4: Investigators <u>may choose</u> to return individual genetic results to study participants if the criteria for an obligation to return results are not satisfied (see Recommendation 1) but <u>all</u> of the following apply:**

a. **The investigator has concluded that the potential benefits of disclosure outweigh the risks from the participant's perspective.**
b. **The investigator's Institutional Review Board (IRB) has approved the disclosure plan.**
c. **The test is analytically valid and the disclosure plan complies with all applicable laws.**
d. **During the informed consent process or subsequently, the study participant has opted to receive his/her individual genetic results.**

Researchers may choose to return individual results related to reproductive risks, personal meaning or utility, or health risks in select circumstances when the criteria for an obligation to return individual results are not met (see Recommendation 1). Participants who agree to return of their genetic research results may be provided individual results, depending on the judgment of the investigative team and

approval of the IRB. The investigators and IRB may consider any guidance from a central advisory committee (as discussed in Recommendation 3) on options to return results beyond those the researcher is obligated to return. Dissenting members of the Working Group felt that results should not be returned solely based on personal meaning to the participant because assessment of personal meaning to the study participants is difficult, if not impossible, and providing personal meaning is not the role of researchers. However, they recognized that if a focus of the research is to study the personal meaning of results then RoR based on personal meaning would be acceptable.

**Recommendation 5: Investigators conducting research with identifiable communities should engage the community on the return of aggregate and/or individual research results.**

Community advisory boards or other mechanisms of community engagement may be particularly useful for input into how RoR is addressed in the consent process and how results are returned [29,30]. They may be helpful in shaping consent documents to achieve the proper reading level and conceptual presentation, and with inclusion of illustrations that are meaningful to the targeted community in the process of informed consent. They may also help facilitate community input, identify supporting resources, and build trust that would make the study results more acceptable and the RoR more effective.

## Discussion

The primary focus of the 2009 NHLBI Working Group was to update the 2004 Working Group Recommendations to refine guidance on the return of individual research results that strikes an appropriate balance among several compelling goals: the protection/respect of research volunteers, the increasing potential for genetic research findings to affect patient care, and the practical

limitations/constraints facing investigators conducting these studies. The 2009 NHLBI Working Group produced 5 recommendations reflecting, in part, the continuing durability of many of the 14 recommendations from the 2004 Working Group.

Recommendations 1 and 4 address the criteria for when individual research results *should* and *may* be returned, respectively. Recommendation 1 is less specific than the 2004 Working Group recommendations in not giving an example of a threshold for relative risk in order to define results with substantial risk; instead we recognize the need to evaluate both the size and nature of the risk. Recommendation 1 also requires that the study participant has opted to receive his/her individual research results. Recommendations 1 and 4 require compliance with all applicable laws while avoiding specific reference to CLIA regulations. The Working Group felt that this topic needed to be revisited by policymakers with input from the research community. When the criteria for Recommendation 1 are not met, results may be returned if they comply with the criteria in Recommendation 4. The bar is purposely set high for the obligation to return genetic research results to study participants. While many results may not now meet the criteria in Recommendation 1, the Working Group expected that increasing funding for genetic research will lead to more genetic findings meeting these criteria.

Recommendation 2 provides a new recommendation compared to the 2004 Working Group report, but simply formalizes what was described in the text of the 2004 paper that investigators have no obligation to return results after funding for a study has terminated.

Recommendation 3 strives to harmonize approaches across research agencies, professional organizations, IRBs, institutions, investigators, and sponsors, by recommending a central advisory committee to provide scientifically-based, timely and consistent guidance to the latter entities on what

genetic results are appropriate for return to research participants. Finally, Recommendation 5 recognizes the need for community input to clarify the perspectives, needs and expectations of the community and to optimize the approach to returning research results.

It should be noted that these recommendations reemphasize the key role of the IRB in many of the decisions related to the return of genetic research results. This will surely add to the burden of IRBs. There will be a growing need for guidance, resources, and education, particularly genetics expertise on IRBs; geneticists must recognize their obligation to assume that responsibility. Complementary mechanisms to support IRBs may also be needed, such as the creation of a central advisory committee (see Recommendation 3) or local community advisory boards (see Recommendation 5).

The fast pace of progress established in genetic research has put many investigators in an awkward position of wanting to do the "right thing" regarding return of individual genetic research results but not really understanding what the right thing is. It is the hope of the Working Group that these recommendations will provide guidance on a number of difficult issues. Undoubtedly, this area will need to be revisited again in the future as the landscape continues to change, genetic research continues to mature, and new technologies emerge.

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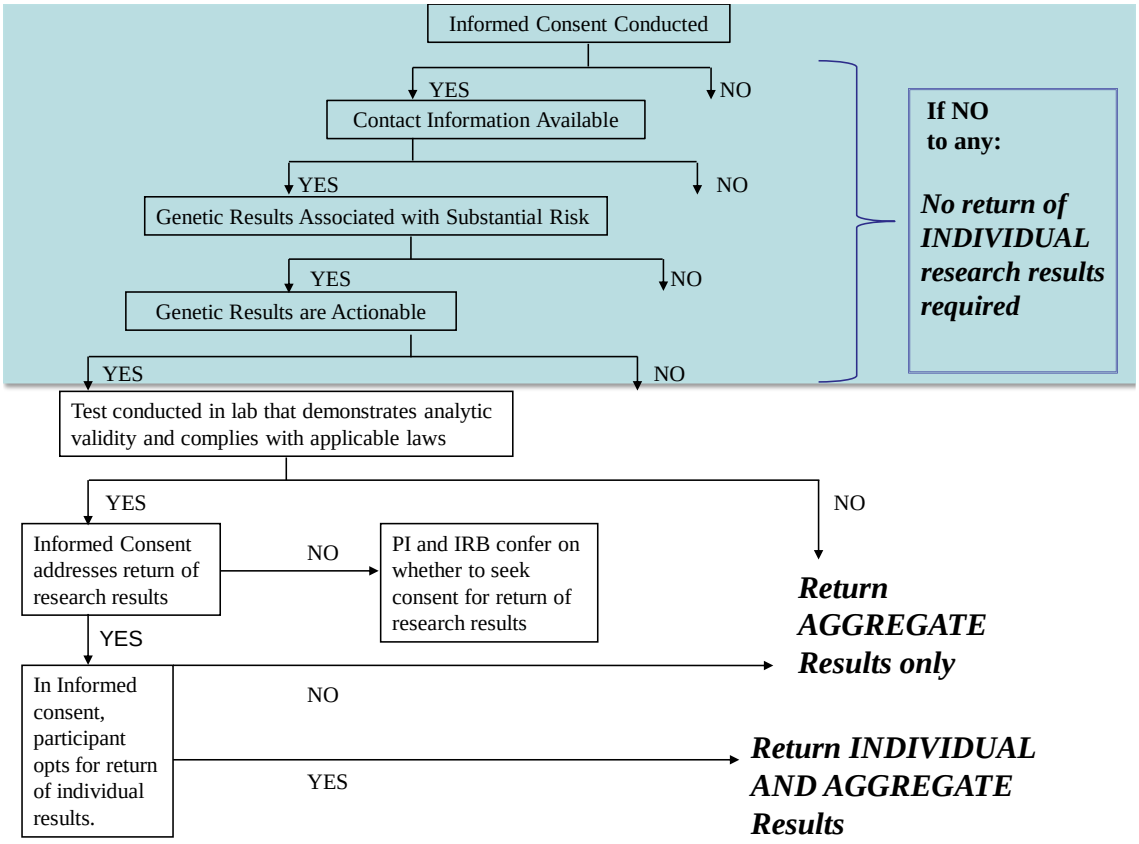
**Figure 1. Decision Flow Diagram on the Return of Individual Genetic Research Results to Study Participants**

Decision Flow Diagram to Determine whether and to What Extent Individual Genetic Research Results Should be Returned to Study Participants (see Recommendation 1)

Table 1: Existing Genetics Resources with Potential to Help Support a Central Advisory Committee to Make Recommendations on What Genetic Research Results Should be Returned to Research Participants

| Resource | Description | Website |
|---|---|---|
| GeneTests database | A publicly funded medical genetics information resource developed for healthcare providers and researchers. Provides current, authoritative information on genetic testing and its use in diagnosis, management, and genetic counseling. | http://www.genetests.org |
| Evaluation of Genomic Applications in Practice and Prevention (EGAPP) | Working group that supports a coordinated, systematic process of evaluating genetic tests and other genomic applications that are in transition from research into clinical and public health practice. | http://www.egappreviews.org/ |
| Genomic Applications in Practice and Prevention Network (GAPPNet™) | Collaborative initiative that aims to accelerate and streamline effective and responsible utilization of validated and useful genomic knowledge and applications, such as genetic tests, technologies, and family history, into clinical and public health practice. | http://www.cdc.gov/genomics/translation/GAPPNet |
| Human Genome Epidemiology Network (HuGENet ™) | A global collaboration of individuals and organizations committed to the assessment of the impact of human genome variation on population health and how genetic information can be used to improve health and prevent disease. | http://www.cdc.gov/genomics.hugenet |
| Institute of Medicine of the National Academies: Roundtable on Translating Genomic-Based Research for Health | Comprised of leaders from academia, industry, government, foundations, and associations with mutual interest in issues surrounding translation of genomic-based research. Seeks to advance the field of genomics and improve the translation of research findings to health care, education, and policy. | http://www.iom.edu/Activities/Research/GenomicBasedResearch.aspx |


Informed Consent Conducted
YES
NO
Contact Information Available
YES
NO
Genetic Results Associated with Substantial Risk
YES
NO
Genetic Results are Actionable
YES
NO
If NO to any:
No return of INDIVIDUAL research results required
Test conducted in lab that demonstrates analytic validity and complies with applicable laws
YES
NO
Informed Consent addresses return of research results
NO
PI and IRB confer on whether to seek consent for return of research results
YES
Return AGGREGATE Results only
In Informed consent, participant opts for return of individual results.
NO
YES
Return INDIVIDUAL AND AGGREGATE Results