

## **GARNET Statement on Incidental Findings and Potentially Clinically Relevant Genetic Results**

As part of the primary GARNET analyses, in further studies using GARNET data, and in future clinical trials incorporating genetic studies, investigators may identify genetic abnormalities that might influence the clinical care of an individual. These genetic variants may be identified as a result of data cleaning and/or data analyses; they may be related to the primary focus of the genetic research or may be unrelated, so-called “incidental findings.” These statements and recommendations have been developed to help GARNET and future investigators when they identify any such incidental or research genetic findings. This statement will be provided to any collaborators or future users of GARNET data.

GARNET established a Sub-Committee on Incidental Findings to provide an educational forum for GARNET investigators to learn about and discuss ethical, legal, and practical issues related to returning individual genetic results to research study participants. The GARNET Sub-Committee on Incidental Findings acknowledges an active debate ongoing at local, national, and international levels related to return of genetic results in any research context. This debate encompasses a wide range of perspectives on this topic: for example, some individuals advocate return of all genetic results to interested participants while some advocate no return of genetic results. For a recent example of the range of perspectives, see the conference proceeding from the NHGRI funded grant “Should We Return Individual Research Results and Incidental Findings from Genomic Biobanks & Archives?” ([www.lifesci.consortium.umn.edu/conferences/2011\\_ifbb](http://www.lifesci.consortium.umn.edu/conferences/2011_ifbb)).

### **In addition to providing advice on issues related to returning individual genetic results to study participants, the objectives of the GARNET Incidental Findings Sub-Committee include:**

- Interfacing with other groups conducting genome-wide association studies, such as GENEVA, eMERGE and other consortia.
- Providing a forum for investigators to discuss ethical dimensions and concerns related to returning individual genetic results to individual participants and a forum for investigators seek general advice, as needed.
- Monitoring a list of genetic results found during routine cleaning and analyses of GARNET data that have been catalogued by GARNET investigators along with actions taken and outcomes of such actions for future reference. Note that GARNET has created a website for this documentation ([https://www.garnetstudy.org/Incidental\\_Findings](https://www.garnetstudy.org/Incidental_Findings)) and it is the responsibility of the principal investigators to enter the incidental findings encountered into this database. The Coordinating Center can assist with this as needed.
- Developing a manuscript that suggests guidance for returning genetic research and incidental findings in the context of clinical trials, and other manuscripts as appropriate.

This document has been developed by the GARNET Sub-Committee on Incidental Findings to promote discussion amongst GARNET investigators about incidental findings and return of

results to study participants, and to serve as a general resource for GARNET investigators and other investigators using GARNET data.

For the purposes of this document, the Sub-Committee recognizes that the consent forms of each of the clinical trials participating in the GARNET consortium have been interpreted by the investigators and their governing IRBs to preclude returning individual genetic results to participants. In light of this, the GARNET Sub-Committee on Incidental Findings assumes that when GARNET investigators consider the possibility of returning genetic results to an individual participant, only clinically relevant and actionable individual genetic results are being considered for return. The Subcommittee makes this assumption with the understanding that it may be difficult to determine what genetic results fall into this category—the difficulty in making these determinations is addressed further below.

**The following General Statements apply to GARNET investigators, and the Recommendations apply to GARNET investigators and future users of GARNET data.**

### **General Statements**

- These statements reflect the current presumption that the disclosure of individual genetics results to subjects in a particular study represents an exceptional circumstance, but also that circumstances where investigators need to consider the possibility for disclosure will increasingly occur as the volume of genomic data in clinical trials research grows, as our understanding of genetic contribution to health and illness expands, and as practice norms around giving genetic results to individual participants in research evolve.
- These statements and recommendations are intended to help investigators define what might be appropriate for IRB notification. The Sub-Committee and the investigators in GARNET have agreed that considerations of notifying study participants of any findings should involve discussions between the investigator and his or her IRB.
- There are many reasons why investigators may not be able to return incidental or research results to participants. These may include, but are not limited to, consent agreement and logistical issues. The studies in GARNET have different consent forms, varying proximity to the parent trial, and very different ability to re-contact participants. Thus, it is expected that notification of participants, if possible at all, will vary among studies.
- Blood donation, sample handling, and genotyping in the GARNET studies and indeed in most clinical research trials is for research purposes only and may not comply with CLIA requirements for sample handling for clinical testing or be done in a CLIA-certified environment. To be appropriate for clinical decision-making, current standards and regulations would require test results be confirmed in a CLIA-certified lab and in compliance with CLIA requirements. Doing so may require obtaining a new sample unless a sample for clinical validation was appropriately collected and stored. For more information about CLIA and reporting laboratory results, see the CLIA website ([www.cms.hhs.gov/clia](http://www.cms.hhs.gov/clia)).
- Caution should be used when interpreting incidental findings detected during routine data cleaning and data analyses. In some instances, the age and type of the specimen may affect

test results (for example, cell lines may exhibit chromosomal changes and mosaicism as an artifact of the transformation process or in vitro growth and passaging). Thus, it is advised that preliminary incidental findings being considered for return to participants should be confirmed through additional genetic testing using a process that conforms to CLIA requirements.

- GARNET has created a database for cataloguing all identified incidental findings and/or potentially clinically relevant genetic abnormalities, results of discussions with IRBs, and actions taken, if any. This database is accessible on the GARNET website at [https://www.garnetstudy.org/Incidental\\_Findings](https://www.garnetstudy.org/Incidental_Findings). It is the responsibility of the principal investigators to enter the incidental findings encountered into this database. The Coordinating Center can assist with this process as needed. The Sub-Committee on Incidental Findings will monitor this database and report to the Steering Committee periodically, so that all individuals involved in GARNET will have a sense of the scope of these issues.
- Links to this Statement will be posted on each study's dbGaP download site.

### **Recommendations**

- GARNET investigators are strongly encouraged to catalogue all identified incidental findings and/or potentially clinically relevant genetic abnormalities, results of discussions with IRBs, and actions taken, if any, using the database created by GARNET for this purpose and accessible on the GARNET website at [https://www.garnetstudy.org/Incidental\\_Findings](https://www.garnetstudy.org/Incidental_Findings). As noted above, the Sub-Committee on Incidental Findings will monitor this database and report to the Steering Committee periodically, so that all individuals involved in GARNET will have a sense of the scope of these issues.
- After identifying a potentially actionable incidental finding, GARNET Study Investigators should discuss with their supervising IRBs how to handle the genetic research results in light of the study-specific consent forms.
- Future users of GARNET data who identify findings that they consider to have clinical relevance should inform the primary study investigator of these findings, but must understand that all decisions related to notifying research participants of incidental or research genetic results reside with the primary study investigators and their IRBs.
- Investigators should use on-going national and international efforts that are coordinating the determination of clinical validity and utility/actionability of sequence and structural genetic variants to identify genetic findings that have "established clinical relevance." These include resources such as ClinAction [see [www.genome.gov/Pages/About/NACHGR/February2012AgendaDocuments/CONCEPT\\_CLE\\_ARANCE\\_ClinAction.pdf](http://www.genome.gov/Pages/About/NACHGR/February2012AgendaDocuments/CONCEPT_CLE_ARANCE_ClinAction.pdf)], an NHGRI sponsored multidisciplinary effort to catalog and curate a list of genetic findings with potential clinical relevance. Other resources include policies and practices related to incidental findings and return of individual genetic research results developed in other research efforts such as GENEVA

([www.genevastudy.org/Incidental\\_Findings\\_Files](http://www.genevastudy.org/Incidental_Findings_Files)), eMERGE ([www.genome.gov/Multimedia/Slides/ClinAction/ClinAction\\_Jarvik.pdf](http://www.genome.gov/Multimedia/Slides/ClinAction/ClinAction_Jarvik.pdf)), Pharmacogenomics Research Network [PGRN] ([www.nigms.nih.gov/Research/FeaturedPrograms/PGRN](http://www.nigms.nih.gov/Research/FeaturedPrograms/PGRN)), and Coriell Personalized Medicine Collaborative ([www.cpmc.coriell.org](http://www.cpmc.coriell.org)).

- If research participants ask for their individual genetic results, and investigators and their IRBs have determined that no individual genetic results will be returned to participants, at a minimum, the investigator should explain the study rules and try to determine the nature of the participant's interest. If appropriate, the investigators should refer individuals to a local genetic medicine clinic that offers genetic evaluation, diagnosis, assessment, genetic testing and interpretation, counseling and management, as well as referrals to appropriate resources for individuals with genetic disorders. As norms evolve within the genetic research community with regard to returning individual genetic research results, it is anticipated that investigators will face these types of request more frequently, and may begin to find a categorical stance against providing participants with these results more difficult to sustain. It is recommended that members of the genetic research community continue to consider when and how return of results would be appropriate, as well as the infrastructure and resources that would be required.
- Any return of genetic results to study participants should be done with the assistance of and in collaboration with a genetic medicine clinic that offers genetic evaluation, diagnosis, assessment, genetic testing and interpretation, counseling and management, as well as referrals to appropriate resources for individuals with genetic disorders.
- When preparing for further contact with participants in a research cohort (for example, informing participants of important findings that might affect their continued participation in a research study, as part of a re-consent process for the next phase of a longitudinal study, or even during a regularly scheduled periodic newsletter), as when designing new clinical trials with associated genetic studies, investigators are strongly encouraged to
  - Discuss with their IRB how to present the possibility that there may be clinically relevant incidental and research findings and outline circumstances and procedures for return of these results that respect the individual participant's preferences, local IRB requirements, and national recommendations;
  - Acknowledge in the consent forms and associated educational materials that this is an area of rapid change and to leave open the possibility that unforeseen circumstances may necessitate further discussion between investigators and participants;
  - State in their consent forms and associated educational materials that study participants may not be informed of important genetic results if investigators and their IRBs decide that no individual genetic results will be returned to participants. In clinical trials, clinically relevant laboratory results and laboratory measures often are given to participants or their physicians for decisions about action. Participants frequently interpret silence about test results as an indication of lack of important abnormality.

Silence about genetic testing results might also be interpreted in a similar manner unless the issue is discussed explicitly and at the beginning of participation.