GENEVA Statement on Incidental Findings

August 31, 2009

In the course of routine data cleaning and data analyses, investigators may incidentally identify genetic abnormalities that might influence the clinical care of an individual. These statements and recommendations have been developed to help investigators when they are informed of any such incidental findings.

General statements

- These guidelines and recommendations are presented to help investigators define what may be appropriate for IRB notification, since notification of study participants of any findings should involve discussions between the investigator and his or her IRB.
- GENEVA does not have a policy on return of incidental findings to participants or discussion of specific incidental findings with investigators' IRBs. It neither supports this, nor does it recommend against this if the investigator feels it is justified.
- These guidelines reflect the presumption that the disclosure of research results to subjects represents an exceptional circumstance.
- Caution should be used when interpreting incidental findings picked up 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).
- Blood donation and sample handling in most GENEVA studies was for research purposes only and thus may not comply with CLIA chain of custody regulations for clinical testing.
- The genotyping being done for GENEVA by the Broad Institute and by CIDR is not done in a CLIA-certified environment. To be clinically useful, test results would need to be confirmed and would require obtaining a new sample and repeating the test in a CLIA-certified lab. For more information about CLIA and reporting laboratory results, see the CLIA website [http://www.cms.hhs.gov/clia].
- There are many reasons why studies may not be able to return incidental results to participants. These may include but are not limited to consent agreement and logistic issues. GENEVA studies have very different designs, ability to re-contact participants, and consent forms. It is thus to be expected that notification of participants, if possible at all, will vary from study to study.
- When designing new genomic studies' subject consent forms, investigators are encouraged to discuss with their IRB how to present the possibility that there may be clinically-significant incidental findings.

Recommendations

- GENEVA (primary) Study Investigators (SIs) may want to discuss with their supervising IRBs how to handle incidental findings that may have established clinical relevance for their study subjects. GENEVA recognizes that providing research results to participants may already be excluded by study-specific consent forms and/or institutional IRBs.
- Deciding which findings have 'established clinical relevance' is up to the primary investigator and his/her consultants. Findings that the investigator might consider include the following:
    - Chromosomal abnormalities such as aneuploidy and microdeletions (e.g. loss of an X chromosome resulting in Turner Syndrome [X0] or microdeletion of the chromosome

22q11.2 region resulting in DiGeorge syndrome; see 'GENEVA Aneuploidy Reference Table Version 9-4-2009.xls)

Note: True biologic mismatches between self-reported gender and genetically-defined gender can occur but are quite rare. In our experience, most mismatches are sampling or labeling errors and investigators should attempt to identify the source of the error.

- Pharmacogenetic variants in study populations in which the drug is likely to be used (e.g. HLA-B*5701 allele associated with hypersensitivity to abacavir; see 'GENEVA Important Pharmacogenetic Variants Reference Table Version 9-4-2009.doc') [http://www.pharmgkb.org]

- GENEVA has established a Committee on Incidental Findings. The role of the Committee includes:
  - Developing a catalog of incidental findings that are being found during routine cleaning and analyses of GENEVA data and that may be clinically relevant;
  - Establishing a process for documenting actions taken by GENEVA SIs and outcomes of such actions for future reference (note that GENEVA SIs are encouraged to inform the Committee on Incidental Findings when they discuss incidental findings with their supervising IRB, and to inform the Committee of what action is taken, if any);
  - Periodically reviewing evidence for additional clinically-significant incidental findings, actions taken regarding incidental findings, and outcomes of such actions; and
  - Interfacing with other groups conducting genome-wide association studies, such as eMERGE and other consortia.
- Secondary users of GENEVA data who identify findings that they consider to have clinical relevance may want to consider notifying the primary SI(s) of these findings, but must understand that all decisions related to notification of incidental data reside with the SI(s) and their IRBs.
- This statement should be provided to any collaborators or secondary users of GENEVA data.