Returning Research Results

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Why return research results?

- Acceleration in the pace of genetic and genomic research

- Possible important implications for participants, patients, families – e.g. health, reproductive decisions

- Increasing discourse about investigators’ ethical responsibility to offer participants access to research results

- Consistent with ethical principles of Beneficence and Respect for Persons, and Reciprocity

Bookman et al. 2006; Wolf et al. 2008; Fabsitz et al. 2010; Bredenoord et al. 2011; Tabor et al. 2011; Ravitsky & Wilfond 2006; Dressler 2009; NBAC 1999
What types of results might be generated?
Genetic Research Results

- Research focused narrowly on a few genes, targeted sequencing, or broadly on non-functional variants possibly linked to functional changes

- Incidental findings
  - Chromosomal rearrangements
  - Sex chromosome aneuploidy
  - Variants in candidate genes associated with other traits or diseases
  - Misattributed parentage
Genomic Research Results (esp. WES/GS)

- Will identify a very large number of “functionally relevant” variants for each person
- Likely to produce more clinically useful and actionable results
- Known variants in genes for autosomal dominant diseases and traits
- Known genetic risk factors for complex diseases, pharmacogenomics response
- Unanticipated findings
  - Previously, no obligation to look because these findings were “incidental” to the content and purpose of original research
  - Now, major aim is to identify all variants in an exome/genome – minimizes the distinction between so called “incidental findings” and primary findings

Tabor et al. 2011
Where might results be returned?
Basic Science Research

- Authorization of research labs to return results
- Obligations and skills of researchers to evaluate, return, and explain different kinds of results
- Recontacting research participants (e.g. participants in biorepositories)
Clinical Research

- Clear communication of return of results process to participants as part of the informed consent process
- Blurring of the distinction between research and clinical care
When is it appropriate to return results?

- **Clinical validity**
  - The genetic variant being analyzed relates to the presence, absence or risk of a specific disease

- **Clinical utility**
  - Genetic information that clearly indicates a high probability of a serious condition for which an effective intervention is readily available

- **Functional relevance**
  - Known to be related to a function, but no clinical validity or utility

Berg et al. 2011; Beskow & Burke 2010
# Proposed Binning System

(Berg et al, 2011)

<table>
<thead>
<tr>
<th>Criteria:</th>
<th>Clinical Utility</th>
<th>Clinical Validity</th>
<th>Unknown Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bins:</td>
<td>Bin 1 Medically actionable incidental information</td>
<td>Bin 2A Low risk incidental information</td>
<td>Bin 2B Medium risk incidental information</td>
</tr>
<tr>
<td>Examples:</td>
<td>BRCA1/2, MLH1, MSH2, FBN1, NF1</td>
<td>PGx variants and common risk SNPs</td>
<td>APOE Carrier status for recessive Mendelian disorders</td>
</tr>
<tr>
<td>Estimated number of genes/loci:</td>
<td>10s</td>
<td>10s (eventually 100s – 1000s)</td>
<td>1000s</td>
</tr>
</tbody>
</table>

## Alleles that would be reportable (YES) or not reportable (NO) in a clinical context

<table>
<thead>
<tr>
<th>Variants</th>
<th>Known deleterious</th>
<th>Presumed deleterious</th>
<th>VUS</th>
<th>Presumed benign</th>
<th>Known benign</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
<td>YES/NO</td>
<td>YES/NO</td>
<td>YES/NO</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td>N/A</td>
<td>YES/NO</td>
<td>YES/NO</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>N/A</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
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<td></td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

N/A: not applicable; VUS: Variant of uncertain significance

1 Reporting through decision making with an appropriate provider if elected by the patient.

2 By definition, variants in genes with unknown implications could not be considered deleterious.

3 By definition, SNPs or PGx variants will either be present or absent.

4 Variants in genes with unknown clinical implications would not be reported; however, they may serve as an important substrate for research, potentially uncovering new disease genes.
How should results be returned?
Individual versus Aggregate Results

- Samples may be collected anonymously or pooled, limiting option of method of return
- Participants have expressed preference for individual research results
- Increased likelihood of participation in studies that returned individual research results compared to those that offered only summary reports
- Individual results may help build trust between participants and researchers

O’Daniel & Haga, 2011; Dixon-Woods et al. 2006; Berg et al. 2011; Schulz et al. 2003
In-person, Web Portal, etc.

- Limited public understanding of genetics
- Some participants prefer to receive results in-person
  - Increased cost and burden with this approach
- Novel tools are needed for participants to “revisit” their data and interpretations
- Online approach could create transparency, enable participants to stay informed of research progress, and increase engagement

O’ Daniel & Haga 2011; Fernandez et al. 2007
Who are key players in the return of results process?
Deliverer(s) of Results

- Researcher, nurse, genetic counselor, participant’s physician
- Participants more likely to choose to learn their results from their physician more than researcher (*O’Daniel & Haga 2011*)
- Large number of researchers did not consider returning results, and among those who did, most common factors considered - whether results were clinically useful, respect for participants (*Heaney et al 2010*)
- Delivery and follow-up require significant time & resources
Recipient(s) of Results

- Participants, families, populations, children
- Lack of receiving results can be a deterrent for research enrollment
- Participants see the potential familial benefit as an advantage of participating in research
- Accuracy of results, personal relevance, clinical utility more important than potential for discrimination
- Participants desire the option to decide what type of information they want to learn
- Generally, participants desire access to results, even if they are upsetting or not considered clinically valid or useful

O’Daniel & Haga 2011; Murphy et al. 2008; Wheeler et al. 2008; Fernandez et al. 2007; Schulz et al. 200; Biesecker 2012
Table 1. Summary of key U.S. guidelines on the return of genetic research results

<table>
<thead>
<tr>
<th>Disclosure policy</th>
<th>To whom information can be disclosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Bioethics Advisory Commission, 1999</td>
<td>Research participant</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention, 2001</td>
<td>Research participant</td>
</tr>
<tr>
<td>RAND Corp., 2003</td>
<td>Public: via internet, newsletter, scientific meeting</td>
</tr>
<tr>
<td>National Heart, Lung, and Blood Institute (NHLBI), 2004</td>
<td>Research participant</td>
</tr>
<tr>
<td>National Cancer Institute (NCI), 2007</td>
<td>Research participant, participant’s health care provider, family</td>
</tr>
<tr>
<td>Public Responsibility in Medicine and Research, 2007</td>
<td>Research participant</td>
</tr>
<tr>
<td>National Institutes of Health Genome-Wide Association Studies, 2007</td>
<td>Downstream users disclose to contributing investigator</td>
</tr>
<tr>
<td>National Human Genome Research Institute, 2008</td>
<td>Research participant</td>
</tr>
<tr>
<td>NHLBI, 2010</td>
<td>Research participant</td>
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Cassa et al. 2012
International Guidelines

- Approximately 15 international laws and guidelines
- Existing international norms are inconsistent
  - Use ambiguous terminology and conflate different concepts
- Spanish 2007 Law on Biomedical Research
  - Affirms participant’s right “not to know” about incidental findings
  - Allows a close family member or representative to be informed of incidental findings if this will avoid a serious health problem for the participant or his/her biological relatives

Zawati & Knoppers 2012
International Guidelines

- WHO’s European Partnership on Patients’ Rights and Citizens’ Empowerment’s 2004 report:
  - Because “research includes matters of unknown future import, sometimes unexpected findings can be generated,” and when “an immediate and clear benefit to identifiable individuals can be achieved...[which] will avert or minimize significant harm to the relevant individuals,” such findings should be returned.

Zawati & Knoppers 2012
Summary

- Lack of consensus on many key aspects of the debate

- Decision-making process about returning results should be informed by:
  - Relationship of researchers with participants
  - Informed consent document
  - Resources available to analyze, confirm, and return results

- Researchers planning to return results need to make decisions about:
  - How to distinguish variants of known clinical utility, possible clinical utility, and unknown significance
  - What kinds of results to return, with input from participants
  - How to approach possible recontact of participants
  - Practical personal, institutional, and healthcare resources
Moving Forward

- Additional empirical research
  - Perspectives of various stakeholders
  - How recipients understand & utilize results over time
  - Assess psychological, social, and health outcomes
  - Assess impact on clinical care and costs

- Increased support/funding for empirical research and the development of relevant guidelines – local and global

- Development and dissemination of tools for managing the return of results as indicated