Reporting Results and Incidental Findings to Research Participants

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Context

- Research involving information rich technologies will produce incidental findings that may be clinically relevant
  - Genetic technologies including whole genome or whole exome sequencing
  - Imaging technologies

- What is the obligation of investigators to disclose incidental findings to participants?
Incidental Findings

Definition

“[A] finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study.”

Wolf et al. 2008 J Law Med Ethics;36:219

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### President’s Commission Taxonomy

<table>
<thead>
<tr>
<th>Type of Result</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Finding</strong></td>
<td>Investigator aims to discover A and result is relevant to A</td>
<td>Child tested for immunity status to varicella before varicella vaccine</td>
</tr>
<tr>
<td><strong>Incidental Finding</strong></td>
<td>Aims to discover A but discovers B, known to be associated with A</td>
<td>Misattributed paternity in workup for transplant from related donor</td>
</tr>
<tr>
<td><strong>Incidental Finding</strong></td>
<td>Aims to discover A but discovers C, not known to be associated with A</td>
<td>Genetic test discovers variant with health risk not known when test done</td>
</tr>
<tr>
<td><strong>Secondary Finding</strong></td>
<td>Aim to discover A but also actively seeks D</td>
<td>ACMG recommendations to actively seek variants in 56 genes</td>
</tr>
<tr>
<td><strong>Discovery Finding</strong></td>
<td>Aims to discover A through Z through a test with broad range of results</td>
<td>Full body CT in a healthy individual to discover actionable findings</td>
</tr>
</tbody>
</table>

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The federal regulations in 45CFR46 do not address return of results.

Some debate about whether an obligation to return results could fall under the regulatory requirement that “significant new findings” be conveyed that might relate to the subject's willingness to continue participation.

OHRP guidance does not address return of results.

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Context

- Regulatory/IRB emphasis has been on protection against risk
  - Goal has been to make participants no worse off

- Focus on benefits has been on primary benefits from the research intervention per se
  - Uncertainty about ethical obligation to confer benefits from incidental opportunities

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Secretary’s Advisory Committee on Human Research Protections

- Public release of study data
- Return of general study results to subjects
- Return of individual study results to subjects
- Return of incidental findings to subjects

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Context

- IRB’s are familiar with return of clinical results within a clinical research protocol
- Not been a controversial subject
- Inconsistency in addressing some potentially controversial aspects – e.g., return of pregnancy test results for adolescent women

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Context

- IRB’s: Limited experience with return of experimental results
  - General consensus that it is acceptable and often appropriate to return aggregate results
  - Individual results:
    - Uncertainties about validity and utility of experimental results
    - Prohibitions against return of results from non-CLIA approved lab
- A frustration for research participants who often expect results (IRBs do not hear these frustrations)

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Context

- When results are not returned in research, the informational risk of research is close to zero
  - Excellent track record of protecting privacy and confidentiality (informational risks)
  - Risk of harm increases when results are disclosed
- Ethical challenge is to balance benefits of disclosure vs. risks of disclosure

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Incidental Findings

- Relatively common in some forms of testing
  - Imaging: ~40% of abdominal MRIs
  - Whole genome sequencing:
    - ~1%-3% will have one on the ACMG list of 56 reportable genomic variants

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Prevalence of Pathogenic Variants

- 6,517 participants: 2,204 African Americans, 4313 European Americans
- Identified variants associated with newborn screening conditions (n=39), age-related macular degeneration (n=17), and genes that influence drug response (n=14). Total number of genes evaluated = 70.
- The mean number of risk alleles per individual = 15.3
- Every individual had at least 5 PGx alleles, 99% had at least one ARMD risk allele, and 45% had at least one pathogenic NBS allele
- “Our findings challenge the assumption that actionable incidental results, much less incidental results of potential clinical utility, in ES/WGS are rare.”

*Botkin 2014 |
Research Context

- No debate about certain examples:
  - A brain tumor discovered on a research MRI
  - An extremely high white count on a CBC

- Debate is about extent of the duty in less clear-cut cases

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Research Context

- Advocates for return of results:
  - Investigators have an ethical obligation for ROR based on various theories: reciprocity, duty of care, partial entrustment, or the nature of the investigator-participant relationship
  - ROR primarily relevant to results from tests with analytic validity, clinical validity, and clinical utility
  - Controversial whether “personal utility” is a justification for ROR

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Research Context

Those skeptical of a duty for ROR:

- Confuses obligations of clinicians with investigators
  - A duty to rescue is limited
- Blurs the distinction between clinical care and research, potentially promoting the therapeutic misconception
- May harm some participants through unwanted information or misinformation
- Problems with CLIA
- May create a substantial burden on the conduct of research

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Evaluation of Tests

- **Clinical Utility vs Personal Utility?**

  - Clinical utility = what clinicians can do to improve morbidity or mortality
  
  - Personal utility = what patients can do to make better choices in life planning
    - Knowledge may not improve morbidity or mortality

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The Literature

- National Bioethics Advisory Commission (1999): Appropriate to return results only if:
  - The findings are scientifically valid and confirmed
  - The findings have significant implications for the subjects’ health concerns, and
  - A course of action to ameliorate or treat these concerns is readily available
The Literature

  - Researchers should disclose incidental findings in genetic research:
    - Genetic information revealing significant risk likely to be life-saving
    - Genetic information can be used to avoid or ameliorate a grave condition
    - Genetic information can be used in reproductive decision-making for grave or serious condition

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History


- Researchers may disclose incidental findings
  - Genetic information for significant risk of grave condition that cannot be modified but participant likely to think information important
  - Genetic information likely to be deemed important by participant in reproductive decision-making

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History

  - Researcher **should not** disclose incidental findings if unlikely net benefit from participant’s perspective
ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

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Push Back

Recommendations for returning genomic incidental findings? We need to talk!

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ACMG List

- Explicitly relevant to whole genome/exome sequencing in CLINICAL medicine

- Identified 57 genes associated with 24 conditions (revised to 56 later) with
  - Known clinical validity
  - Known clinical utility

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ACMG Recommendations

- Constitutional mutations found in the genes on the minimum list ... should be reported by the laboratory, regardless of the indication for which the clinical sequencing was ordered.

- The Working Group recommends that laboratories seek and report only the types of variants within these genes that we have delineated.

- It is the responsibility of the ordering clinician/team to provide comprehensive pre- and posttest counseling to the patient.
ACMG Recommendations

- The Working Group recommends that the ACMG, together with content experts and other professional organizations, refine and update this list at least annually.
ACMG Recommendations

- These results should be generated on all WGS/WES samples regardless of the indication for the test and patient age or preference
- The clinician is supposed to determine whether to disclose to the patient
- Patient preferences not ascertained prior to testing. They can decline testing if they do not want results generated on IF’s
- Disclosure of adult-onset conditions will occur with WGS/WES in children in order to alert family to risk in adults

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ACMG Recommendations

- These recommendations are for clinical sequencing
- Active discussion of how these clinical recommendations should apply to the research context

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Attitudes of Genetics Professionals

- 760 genetics professionals completed a survey (response rate = 9%)
- 85% thought incidental findings should be offered to adult patients undergoing ES/WGS, 75% to healthy adults, and 74% to parents of a child
- 62% thought incidental results for adult-onset conditions and carrier status should be offered to the parents of children
- 81% thought individual preferences should guide return of results

Many research-based tests are not conducted in CLIA certified laboratories

42 CFR 493.3(b)(2) -- Exception

These rules do not apply to components or functions of research laboratories that test human specimens but do not 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.

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Some authors contend that return of research results to participants from non-CLIA certified laboratories is acceptable when the results are clearly described as experimental and confirmation of laboratory results in a CLIA certified lab is encouraged for clinical decision-making.
COMMON MISCONCEPTION #1

"If a clinical trial has IRB approval, and the patients are notified that their testing is investigational, it is not necessary for the testing to be performed in a CLIA-certified laboratory."

✓ TRUE or FALSE?

Answer: FALSE
Literature on IRB Policies and Procedures


- Identified 20 IRBs with ROR for genetic research
  - 37 IRB websites sequentially selected from 118 IRBs in institutions known to conduct GWAS to identify 20 with ROR language
  - In 39 documents containing references to return of individual results, 49% stated ROR was NOT an option, 26% stated ROR was an option, 25% gave investigators the option of disclosure or no disclosure

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Literature on IRB Policies and Procedures

  - In-depth interviews with 31 IRB professionals at 6 sites across US
  - “There was general agreement (29/31) that preliminary, unvalidated results should not be returned.”
  - “Overall, most respondents were supportive of returning validated individual results if the research subject desired…” but was conditioned on a variety of factors
    - “Foremost … was the need to respect and consider the research subject’s desire to know or not know the research result.”
    - “The most frequent conditions or criteria .. favored a clinical utility perspective (25/31)…”
Literature on IRB Policies and Procedures


**Process Issues**

- “Most respondents indicated that a team of people should be involved in ROR decisions including the research investigator, scientific and other medical peers, other experts in the field, a genetic counselor, a medical geneticist, and the individual’s treating physician.”

- “[R]espondents did not agree on the specific role that the IRB should play in the decision-making.”

- Some support for IRB’s overseeing the ROR process but not be a primary decision-maker about what is returned.
President’s Commission Report

- **Recommendation 12**

Researchers should develop a plan to manage anticipatable incidental findings, including but not limited to those findings known to be significant and clinically actionable (and, when relevant, analytically valid and clinically valid). The plan should be reviewed and approved by an institutional review board.

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Recommendation 13

Researchers should develop a process for evaluating and managing unanticipatable findings. The plan should be reviewed and approved by an institutional review board. During the informed consent process, researchers should notify participants about the possibility of unanticipatable incidental findings, including lifesaving incidental findings, and the plan for their management. Researchers who discover an unanticipatable incidental finding of concern should assess its significance, consulting with experts as appropriate.
Recommendation 14

Researchers should consider carefully the decision to actively look for secondary findings. In certain circumstances, with approval from an institutional review board, researchers can justifiably adopt a plan that includes looking for selected clinically significant and actionable secondary findings. Approved plans should be disclosed to prospective participants during the informed consent process.
Conclusions

- No regulations or OHRP guidance on this issue
- What to disclose is not ripe for IRB regulations or guidance
- Investigators clearly have some responsibilities to disclose IF’s with high clinical validity and clinical utility
Conclusions (Personal)

- Investigators do not have an obligation to look for incidental findings.
- It is acceptable for investigators to “gate” or filter test data in order to avoid obtaining results that are not directly relevant to the research.

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Conclusions (Personal)

- **Appropriate roles for IRB’s:**
  - Expect investigators to address the issue in the protocol (one way or the other) when relevant
  - Set a general institutional standard for disclosure criteria (how stringent the criteria should be)
  - Develop IC templates and approve the consent language regarding IFs
  - Approve and oversee the process for IF review and disclosure
  - Review and approve disclosure of IF’s
  - Monitor the safety of IF disclosures

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Thank You!