Should Incidental Findings be Returned?

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Category: Genetics Research

Background: Improvements in Next Generation Sequencing (NGS) technologies are progressively being incorporated into both research and clinical practices, allowing rapid genetic diagnoses at a cheaper cost. However, studies using NGS or whole-exome sequencing often encounter an ethical dilemma in how to contact study participants in the case that they discover an incidental and medically actionable finding. First, there must be a process for determining what to return and the means for doing so. Secondly, such findings must be retested clinically to ensure valid results. The American College of Medical Genetics and Genomics (ACMG) suggests that clinical diagnostic laboratories that perform either whole-exome or genome sequencing should report, at minimum, any positive result for the 56 known pathogenic or expected pathogenic variant genes as incidental or secondary findings, even when unrelated to the primary medical reason for testing [1].

Scenario: In a specific study, researchers were performing NGS on tissue banked samples of healthy controls and colon cancer patients to validate an assay. The use of healthy controls in a study like this is not uncommon; however, what happens if one of the healthy controls tests positive for a mutation that predisposes to colon cancer using an unvalidated research assay? The samples were obtained from a tissue bank and the researchers were unclear about what the informed consent stated about returning incidental findings, raising the question whether to contact the subject and if contact is attempted, how to do it.

Ethical Considerations: The growing ethical consensus is that medically actionable findings should be returned, with an expert panel such as the ACMG determining which results are actionable. The ACMG established the Secondary Findings Maintenance Working Group to create a process for both forming and updating the list over time as our knowledge of genetic markers grows [1]. In the case of genes that may still predispose an individual to cancer but are outside of the ACMG's 56 specific genetic variants, the tissue bank protocol should include a mechanism for determining which incidentally discovered variants should be returned and how. This should include giving the patient the option to receive this information if discovered. The Clinical Laboratory Improvement Amendments (CLIA) of 1988 prohibits the return of individual research results to participants unless the results were obtained in a CLIA-certified laboratory, which most research laboratories are not [2]. Medically actionable findings must therefore be confirmed in a CLIA-certified laboratory.

Another caution is that the researchers cannot assume that the donor will necessarily want to know about the finding. Previous survey studies have shown that participants express diverse preferences when it comes to learning of incidental findings in studies in which they participate. However, most "agreed that individual choice and participation in the decision-making process were critical [3]." Their rationale revolved around the fact that the findings directly affect those participating, so they should have a say in information returned. The ACMG has released and kept up to date their

own recommendations for the analysis and return of secondary findings when any clinical genomic analysis is pursued. Their suggestions include:

- Obtaining written informed consent by a qualified genetics health care professional regarding the nature of the test
- Addressing the points like interpretive uncertainty, privacy, and impact on one's family
- Informing the patient that laboratories will often analyze specific sets of genes that are deemed to be highly medically actionable if discovered to be pathogenic variants, even when unrelated to the primary medical reason for testing.
- Informing patients during consent that they may opt out of such analysis, but also that there may be consequences in doing so.
- Applying the same policy to pediatric patients but allowing parents to opt out of such analyses with the same follow up on possible ramifications of doing so.
- Applying this routine analysis of medically actionable genes deemed by the ACMG [4].

Expert Opinion: The above scenario is complicated because the cancer predisposing gene was discovered on an experimental assay that had not yet been validated. However, there is still a potential for finding a medically actionable finding in a CLIA certified lab. We therefore consider this case to be a potentially medically actionable finding. We recommended that the study consent form for the healthy participant be obtained and reviewed. Some consents offer the option not to be contacted in the case of an incidental finding, in which case no further action should be taken. If return of results is mentioned in the consent, the process outlined in the consent should be followed. If it is not mentioned in the consent, the research team should consult experts to determine that the result is in fact medically actionable. If it is actionable, and since the ethical consensus is now that patients/participants should be informed about medically actionable findings, we advised the research group to attempt to contact the provider who facilitated consent of the healthy control, who would in turn confer with the participant and offer a consultation with a genetic counselor. If the participant agrees, after consultation with a genetic counselor, a new sample could then be taken and tested in a CLIA approved lab. Regardless of the research being conducted, any genomic/exome sequencing study that has the possibility of unearthing an incidental finding should include a comprehensive consent allowing participants the option to receive medically actionable findings, specifying the procedure to be followed if such a finding is identified. The participant should also be warned that researchers are not directly looking for such findings, but may return them if they do find them in the process of their research.

References

1. Kalia, S.S., et al., *Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics.* Genetics in Medicine, 2017. **19**(2): p. 249-255.
2. *Return of Research Results*. 2017 [cited 2019; There are ongoing discussions among researchers, ethicists, policymakers, and research participants about the return of individual research results (IRRs) and incidental findings (IFs) from genomic research. These issues are not new or unique to genomics, but advances in genomic technologies have brought them to the forefront. NHGRI is currently funding research to examine these questions and inform future NHGRI policy.].
3. Clift, K.E., et al., *Patients' views on incidental findings from clinical exome sequencing.* Appl Transl Genom, 2015. **4**: p. 38-43.
4. *ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing.* Genetics in Medicine, 2015. **17**(1): p. 68-69.