Suggested Policy

Points-to-Consider on the Return of Epigenetic Research Results

The vast majority of current IHEC projects are fundamental epigenome mapping studies that are unlikely to reveal clinically valid and actionable health information that might be of interest to research participants, and in which the identities of participants have been irrevocably removed from research datasets, thus precluding recontact of participants. However, as epigenetics continues to progress and leads to insights into health and disease, the return of individual epigenetic research results to research participants will be of growing importance. This Points-to-Consider document therefore aims to provide forward-looking general guidance, based on the findings of the International Human Epigenome Consortium (IHEC) Bioethics Workgroup Subgroup on the return of results in epigenomic research ("The Subgroup"). Incidental findings, as well as individual findings directly related to the topic of research, may arise during the course of a research project; these Points-to-Consider apply to both types of findings (referred to here as research results), but only if they are epigenetic findings. In particular, epigenetic disease-linked data may have germline or somatic genetic sequence or variation as its source and, in this case, researchers should refer to guidance on the return of results in genomics for such results.[1]

The Subgroup recognizes that cultural, ethical and legal considerations on the return of research results vary between countries and geographic regions. In consideration of this variance, the Points-to-Consider outlined below should be considered as non-binding guidelines provided to assist projects in establishing their own policies on the return of research results to adult research participants. This document falls into the category of IHEC guidelines: "recommendations made by the IHEC working groups" on "best practices" in research.[2]

1. The view is becoming more common in the scientific, bioethics and policy literature, and in ethical guidelines, that clinically valid and actionable individual research results should be offered to participants.[3] However, it is agreed that researchers are not expected to actively search for this information (all clinically valid and actionable individual results) unless it forms part of their standard research practice.

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[1] Knoppers et al. Return of genetic testing results in the era of WGS (2015) Nature Reviews Genetics 16, 553–559 (2015)
[2] IHEC Goals, Structures, Policies, & Guidelines. E. Consortium Policies and Guidelines, page 13.
[3] *Knoppers et al.* Next-Generation Sequencing and the Return of Results *Cold Sring Harbour Perspectives in Medicine* (2016) **6**(10). Wolf SM, Lawrenz FP, Nelson CA, Kahn JP, Cho MK, Clayton EW, Wilfond BS: Managing incidental findings in human subjects research: analysis and recommendations. J Law Med Ethics. 2008, 36 (2): 219-248.

2. In determining the clinical validity and actionability of epigenetic data and communicating epigenetic risk, the following points should be considered:

    a) How accurate are the data? Consider the study's quality control processes and replicating measurements in a clinically-accredited diagnostic laboratory prior to returning research results. Also consider the origin/source of the epigenetic data, which may be important for its interpretation, i.e., the cell and tissue composition, age and sex (not gender).

    b) Epigenetic marks may be dynamic; how stable are the acquired data (are they "temporarily stable")? The research result might require multiple samples at different time points to determine its stability.

    c) Epigenetic variants or marks have the potential to cause disease. Depending on supporting evidence, three types of variants can be distinguished:

        - **Associated variants**: variants supported by statistics only (e.g., in an epigenome-wide association study (EWAS)).
        - **Inferred variants:** variants supported by statistics and inferred functional evidence (e.g., involvement in plausible mechanism inferred from additional data).
        - **Causal variants**: variants supported by statistics and for which disease-causality has been demonstrated (e.g., in conjunction with genetic variants or where genetic variants have been ruled out). Causal variants are candidates for clinical validation as a first step towards actionability.

    d) For clinically-valid variants, what is the level of disease risk and severity?

    e) Epigenetic variants or marks may be diagnostic or a "biomarker" even if they are not causal.

    f) The possibility of treatment or prevention based on the research result, including the potential "reversibility" of epigenetic risk variants. "Actionability" may also include the possibility of making life choices based on the result.

3. Research results may include epigenetic marks from different kinds of exposures (e.g., pollution, behavioral) that fall short of disease-causality, yet which are nevertheless of interest to participants (e.g., enabling them to avoid further potentially harmful exposures).

4. As epigenetic data results from both heredity and environmental exposures, individuals who might benefit from receiving this information through further disclosure could eventually include research participants' non-biological relatives, neighbors, co-workers, or others with shared exposures. Such disclosure should only be done with the participant's and other individuals' consent or in accordance with local laws and policies.

5. Public communication of the general results of epigenetic research may have an important, yet often neglected, impact on how individuals interpret their individual epigenetic results. While few epigenomic research projects currently produce

clinically valid and actionable individual research results, many are generating research findings that are of interest to the public and to the media. Good public communication of epigenetic risk by researchers and science communication professionals should be encouraged.

Procedural Points

1. An epigenomic project's policy on return of research results should be in place, included in the ethics review for the project, and should be clearly explained to participants during the informed consent process prior to any sample collection.[4] This includes transparency about how results will be assessed for potential return of results. For fundamental research projects not meant to generate clinically valid, actionable results, there should be a statement that results will not be returned, except in the exceptional circumstance where unforeseen findings arise which are clinically valid and actionable, and recontact and consent of participants is feasible (e.g., data are not irreversibly de-identified).
2. The return of research results should occur with the free and informed consent of adult participants[5], in a way that respects their autonomy, including their right to decline the information if they so choose (the "right not to know".)[6]
6. Specific policies should be established for pediatric research and for research involving adults who have been deemed incapable of giving informed consent.[7] For example, it may not be appropriate for parents or legally authorized representatives to refuse to receive actionable results on behalf of children or incapable adults.
3. Elements to consider in setting up procedures for offering the return of results include:[8]
4. the expiration of any duty to return results (e.g., at the end of the research project);
5. the estimated cost of the process;
6. human resources that will be involved (e.g., genetic counselors, family physicians, and others), and the respective roles of researchers and physicians;
7. the necessity of establishing a convenient procedure to collect and update the contact details of participants and to re-identify them if warranted;

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[4] Canadian College of Medical Geneticists (2015), *Position statement: The clinical application of genome-wide sequencing for monogenic diseases in Canada*; Canadian Institutes of Health Research, Canadian Tri-Council Policy Statement: *Ethical Conduct for Research Involving Humans (TCPS2) (2014)*. U.S. Presidential Commission, *Report on the Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Context (2013)*.

[5] The Quebec Network of Applied Medical Genetics (RMGA), *Consolidated Statement of Principles (2016)*; Organization for Economic Co-operation and Development (OECD), G*uidelines on human biobanks and genetic research databases (2009)*.

[6] Declaration of Helsinki (2013); Oviedo Convention (1997) Chapter III, Article 10.2.

[7] Canadian College of Medical Geneticists, (2015), *Position statement: The clinical application of genome-wide sequencing for monogenic diseases in Canada*; Public Population Project in Genomics and Society, *Return of whole-genome sequencing results in paediatric research: A statement of the P3G international paediatrics platform (2014)*; European Society of Human Genetics, *Developing a policy for paediatric biobanks: Principles for good practice (2013)*.

[8] U.K. Medical Research Council and Wellcome Trust Framework (2014), Council of Europe *Whole-genome sequencing in health care: Recommendations of the European Society of Human Genetics (2013),* Fabsitz RR, McGuire A, Sharp RR, et al., Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from an NHLBI Working Group (2010).

8. potential privacy and security risks of holding participant identities and contact information and ways to mitigate these risks;
9. the approach that will be taken regarding disclosure of results to family and other potentially exposed individuals depending on laws and jurisdictions; and
10. the possibility that epigenetic information may not be protected information under genetic information anti-discrimination laws in a given jurisdiction, and the need to adapt procedures accordingly. Participants should be aware of any additional risks this presents at the time of the initial consent to sample collection.

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Stephan Beck (Co-Chair of Bioethics Workgroup)
Yann Joly (Co-Chair of Bioethics Workgroup)
Stephanie O.M. Dyke (Chair of Bioethics Subgroup on Return of Results)
Charles Dupras
Karen Maschke
Tomi Pastinen
Dena Procaccini
Mark Rothstein
Katie M. Saulnier
Reiner Siebert
Jörn Walter
Amy P. Webster

For the IHEC Bioethics Workgroup.