

UBC Research Ethics Boards

Interim Guidance on Incidental Findings in Genetic and Genomic Research

Purpose and Background

While there is no universally agreed upon definition of incidental findings, the Tri Council Policy Statement 2 (2014) ([TCPS2 \(2014\)](#)) describes them as “unanticipated discoveries made in the course of research but that are outside of the scope of the research.” The management of incidental findings is a difficult issue across a variety of scientific research areas and modalities, including genetic sequencing, imaging, biobanking and testing biological specimens, and was the focus of a report issued by the US Bioethics Commission in 2013. Whether and when incidental findings should/must be reported back to the patient/research participant, who ought to decide this and who is the appropriate reporting party are among the many critical questions currently being debated in policy, academic and clinical domains. This interim guidance does not seek to resolve these issues; instead, recognizing that this is an evolving and challenging area for researchers, the purpose is to provide some clarity in terms of expectations for UBC clinical research studies while steps are taken to inform and develop more formal guidance. An important step in this regard will be the collection and analysis of the plans submitted by researchers for addressing incidental findings (please see **Application Guidelines** outlined below). This process will help inform the development of UBC’s forthcoming policy on the management of incidental findings.

Incidental findings are addressed by the TCPS2 (2014). [Article 3.4](#) recognizes an obligation on the researcher to disclose incidental findings that have significant welfare implications for the participant (“material incidental findings”). There is uncertainty and debate on what exactly constitutes a material incidental finding; however, as a ‘rule of thumb’, these are incidental findings that would be disclosed if they arose in clinical circumstances. More specifically, and arguably conservatively, an incidental finding may be said to be material if it: 1) is analytically valid (that is, the finding is accurately and reliably identified and confirmed); 2) indicates an established and substantial health risk, and 3) is clinically actionable (i.e. there is an effective preventative or therapeutic intervention available). It should be noted however, that the third criterion is somewhat contentious and that what constitutes clinically actionable is the subject of much debate in relation to both the clinical and research settings (Shkedi-Rafid et al., 2014). As outlined in the TCPS2 (2014), researchers should consult with colleagues and/or refer to standards in their discipline if they are unsure how to interpret incidental findings or are uncertain as to whether incidental findings are material. The TCPS2 (2014) also provides that a researcher may request an exception to the obligation to disclose material incidental findings, based on impracticability or impossibility of disclosure to the participant. Such exceptions would be made by an REB on a case by case basis (Article 3.4).

Core bioethics principles of non-maleficence, beneficence and respect for participant autonomy underlie much of the debate and discussion around incidental findings. For example, the obligation to disclose material incidental findings outlined in the TCPS2 (2014) (described above) is tempered by the stipulation that researchers should exercise caution in disclosing

incidental findings that may cause needless concern to participants. Chapter 13 of the TCPS2 (2014) addresses managing information (including incidental findings) specifically in the context of genetic research. [Article 13.2](#) and its application addresses the need for researchers to develop, submit to the REB and share with prospective participants a plan for managing information that may be revealed through their research. The application section for 13.2 recognizes that the information revealed through genetic research will vary significantly in terms of (for example) its clinical relevance and the extent to which it is scientifically conclusive, and that these are factors that must be taken into account in the development of the plan. Moreover, and in relation to participant autonomy, [Article 13.3](#) indicates that the participant must be given the opportunity to make an informed choice about whether they wish to receive information about themselves and to express a preference as to whether such information will be shared with others (e.g., biological relatives). While TCPS2 (2014) doesn't specifically address the issue, and while more relevant in some research contexts than others, this should also include consideration as to the participant's preferences in relation to the information being shared with next of kin in the event s/he dies before the incidental findings are available.

In addition to the relevant provisions of the TCPS2 (2014), there is an emerging consensus that these obligations (to disclose 'incidental findings' of potential clinical significance and utility and to offer participants the option of knowing or not knowing such results if they are discovered), are directly applicable to genomic research studies (Wolf et al., 2012). For many studies, exome or whole genome sequencing is likely to be used, if not immediately, then at a future time with stored, banked samples. This technology interrogates all of the genes at once and can, therefore, yield incidental findings of clinical significance and utility.

In light of the above considerations, and at a minimum, UBC's REBs recommend that for studies with the potential to generate clinically relevant genetic incidental findings, research participants be informed of this possibility, be provided with the option of whether or not to be notified if such findings occur, and be advised what to do to change their decision at a later time. More specifically, UBC's REBs agree that for studies where there is the potential for clinically relevant genetic incidental findings the consent document should address these issues. Finally, and in recognition of the fact that disclosing such information can reasonably be interpreted as a medical act, UBCs REBs recommend either that a clinician associated with the study assume such responsibility or else that arrangements be made to ensure that the information is provided (with the participant's permission/ consent) to a care giver who is trained and qualified to provide and discuss clinical genetic findings with patients so that this care giver can inform the participant.

References:

1. **UBC REBs Guidance (Article 12.4 Genetic Testing)**
<http://research.ubc.ca/ore/ubc-clinical-research-ethics-general-guidance-notes#art12pt4>
2. UBC REB Guidance (Article 13.4 Material Incidental Findings in Individual Research Participants)
<http://research.ubc.ca/ore/ubc-clinical-research-ethics-general-guidance-notes#art13pt1pt4>
3. **TCPS2: Article 3.4: Incidental Findings;** <http://www.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter3-chapitre3/#toc03-1>
4. **TCPS2: Article 13.2; Plans for Managing Information Revealed through Genetic Research**
<http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter13-chapitre13/#toc13-1b>

5. **American College of Medical Genetics (ACMG)** Green et. al.. ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. *Genet Med.* 2013 Jul;15(7):565-74. doi: 10.1038/gim.2013.73
 - https://www.acmg.net/docs/ACMG_Policy_Stmnt-Reporting_Incidental_Findings_CESCGS_GIM_AOP_6_20_13.pdf
 - https://www.acmg.net/docs/Incidental_Findings_in_Clinical_Genomics_A_Clarification.pdf
 6. **Managing incidental findings and research results in genomic research involving biobanks and archived data sets.** Wolf et al., *Genetics in Medicine* (2012 Jun; 20) Volume:14, Pages: 361–384; doi:10.1038/gim.2012.23 <http://www.nature.com/gim/journal/v14/n4/full/gim201223a.html>
 7. **Statement of Principles on the Return of Research Results and Incidental Findings.** Quebec Network of Applied Genetic Medicine (Réseau de médecine génétique appliquée (RMGA)) (March, 2013). Available at: http://www.rmga.qc.ca/en/documents/Brochure_angl_18avril2013_soumisRMGA.pdf
 8. **Defining and Managing Incidental Findings in Genetic and Genomic Practice.** Shkedi-Rafid et al (2014) *J Med Genet*, doi:10.1136/jmedgenet-2014-102435. Available at: <http://img.bmj.com/content/early/2014/09/16/jmedgenet-2014-102435.full>
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Application & Consent Guidelines

Application Guidelines:

If a research project has the potential to identify incidental findings from genetic testing or genomic research, the following should be included in any new application or amendment submitted to the REB. If this is not possible or appropriate within the context of the particular research project, a rationale for not including it should be provided.

1. **Attach to Box 9.8 a document that describes** the researcher's plan for handling incidental findings. This should address:
 - a) How the possibility of incidental findings will be covered with the participant in the consent process (see 2 below);
 - b) How the researcher will determine whether an incidental finding is 'actionable' either in terms of future health risks and/or treatment;
 - c) How clinical validation will be done, by whom and who will pay for this;*
 - d) How and who would disclose an actionable incidental finding to the participant and/or relative (if applicable); and
 - e) Who would be involved with clinical follow up, including contacts at the clinical service point.

** Please note that while the template consent language (below) suggests that it is acceptable to tell the participant that there may (or may not) be a cost to them associated with clinical validation of the incidental finding, in practice UBC REBs strongly urge researchers to resolve this question one way or the other prior to participant enrolment and to clearly reflect whether there will or will not be a cost to participants in the consent form.*

Consent Guidelines:

2. When applicable, **the consent document in any new application submitted or in any amendment where prospective consent or re-consent is being obtained** should include the following:
 - a) A general description of genetic research, inherited genes and incidental findings, including a description of the types of incidental findings that will be reported (*see sample wording below*);
 - b) Potential related risks such as loss of privacy, discrimination, impact on employment, insurance, lifestyle choices, risks to family members etc., (*see sample wording below*);
 - c) Whether there may be any cost to the participant (in the event that the tests are not covered by MSP and/or the Hereditary Cancer Program) (see 1(c) above and sample wording below); and
 - d) An indication that the participant has the right not to be told about Incidental Findings, and that they may change their mind by letting the study doctor know. This may be accomplished, for example, by having an option on the signature page where the participant may choose at the outset 'not to be notified', and that they understand that they may change their decision at any time by contacting the study doctor (*see sample wording below*);

Where consent or re-consent is infeasible or impracticable, a rationale should be provided.

Sample Consent Document Language:

The following is an example of possible consent form wording. It should be edited to fit the context and requirements of the study that is being submitted for review.

Genetic Testing or Genetic Research

Cells in your body contain a type of molecule called deoxyribonucleic acid, or DNA for short. DNA is what your genes are made of. Your cells also contain another type of molecule called Ribonucleic acid (RNA for short) that works closely with your genes. Changes in genes or RNA may affect a person's chance of developing certain diseases. These changes may be inherited (i.e. passed on in families from parents to children) or they may be somatic (arising in a single body cell at some point during life and generally cannot be passed on to children). "Genetic testing" or "genetic research" is a type of research that studies these changes, and will hopefully provide a better understanding of the links between the genetic changes and specific diseases, and eventually develop new ways to prevent, detect and treat these diseases.

Incidental (Unexpected) findings and Genetic Research

It is possible that genetic testing may discover a finding that the researchers were not looking for, such as a genetic change being present that indicates that you (or a family member who may carry the same genetic change) are at greater risk for developing a condition for which

screening or prevention strategies are available or which presents an important risk to your health. This is called a “clinically relevant incidental finding”.

If an incidental finding of this type is discovered, you have the right to know but you may choose whether or not you want to know. At the end of this consent document, you will be offered the option of being told if an incidental finding of this type is discovered. Whatever your choice is now, you may change your mind at any time by telling the study doctor or another member of the research team (for example, study nurse or genetic counsellor). If your choice now is to be told, then if such an incidental finding is discovered, you will be asked at that time whether or not you would like to hear more details of the finding. If you choose to know the details, you will be given information about how to proceed, including information about receiving genetic counseling. If you choose not to know the details of the incidental finding, you may change your mind in the future and ask that the details be given to you. Please note however, that if you choose not to learn the details at the time you are told that there is an incidental finding, and change your mind later, there is a possibility that the information may no longer be available.

Risks Related to Genetic Testing and Incidental Findings

When you donate your blood or tissue for genetic testing or research, you are sharing genetic information, not only about yourself, but also about biological (blood) relatives who share your genes or DNA. While the risk of your information being accidentally released is estimated to be extremely small, disclosure of genetic research data could result in discrimination by employers or insurance providers toward you or your biological (blood) relatives. This is because there is currently no law in Canada that specifically protects against genetic discrimination. For example, no law prevents an insurance company in British Columbia from requesting information about the result of a person’s genetic test as part of the process of assessing risk to determine whether to grant coverage and to set premiums. When you apply to an insurance company for new insurance coverage, it is possible that the personal results of any genetic testing performed in connection with this study could be requested by that insurance company, particularly if the results are shared with you or your physician. If you wish to participate in this study and do not already have insurance coverage in place, you may wish to seek some advice about whether participation could affect your insurability. You might consider applying for and obtaining insurance before participating in research that could return genetic information to you. Even if you already have insurance in place, results from genetic testing could have implications for your ability to renew your coverage if, for example, you try to change the terms of your insurance coverage or if your policy reviews eligibility after set periods of time.

If you become aware that you have a disease-related genetic change, this knowledge may provide you or your family with important information that could be used to either prevent the disease (if possible) or to inform other health care decisions related to the finding. However, there is also a risk that simply having this knowledge may cause anxiety or distress and alter your decision to have a child or other lifestyle decisions for you or a family member who may have the same genetic change.

Every effort will be made to protect your privacy and the confidentiality of these results. Because technology changes so quickly, the potential future use of genetic information is unknown and therefore the potential future risks also are unknown. You should be aware that genetic information cannot be protected from disclosure by court order.

Incidental findings that are found during participation in a research study will usually be confirmed in a laboratory that is not associated with the research study before they are used for your health care and other important decisions. In this situation, it is not always clear who is responsible for covering the cost of the confirmation tests or the costs of genetic counselling that you may have as part of the process of finding out the results. Please know that these services may not be covered by your provincial health care plan and may only be available if you pay for them. In such instances, the confirmation testing would only be done with your permission and the total cost to you for the testing and genetic counselling may be more than \$1000.

Signature Page Checkbox Sample Wordings:

I understand that clinically relevant incidental findings may not be discovered for many months or even years following the collection of my blood or tissue sample. If and when such incidental findings are discovered:

1. I do NOT want to be notified about incidental findings and I understand that I may change my decision at any time by contacting the principal investigator.
2. I DO want to be notified about incidental findings and I understand that I may change my decision at any time by contacting the principal investigator.
 - 2a) I want to be notified about incidental findings as soon as they are discovered.
 - 2b) I want to be notified about incidental findings, but not until after _____ (date)
3. In the event that incidental findings are discovered after I die, I DO NOT want this information to be shared with my next of kin;
4. In the event that incidental findings are discovered after I die, I DO want this information to be shared with my next of kin: _____ [Name/Contact] _____