Paediatric research and the communication of not-so incidental findings

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Paediatric research may well be the first field in which the ethical implications of next-generation sequencing (NGS) will be appreciated. Allowing as it does for the revelation of much more than just the disease gene being researched, the advent of NGS will require careful consideration of the return of research results and incidental findings to parents. In contrast to the choices offered to adults with regard to the return of both research results and incidental findings, the same does not hold true for children. Parents must act in their 'medical' best interests. Current policy guidance on this issue in Canada is unclear.

Key Words: *Ethics; Incidental findings; Next-generation sequencing; Paediatrics; Research results*

The recent introduction of next generation sequencing (NGS) into genetic research is spawning much discussion on the return of results, because there well may be incidental findings (IFs) (1). In the past, international and national ethical guidance was largely confined to clinical trials where there could be some certainty of individual research results (IRRs) and perhaps, some IFs. The advent of whole genome (or exome) sequencing has catapulted the issue of the return of IRRs and now not-so-incidental findings onto centre stage, and creates issues particular to the context of paediatric research.

In Canada, the December 2010 Tri-Council Policy Statement 2 (TCPS2) does not address the issue of the return of IRRs, other than to state that researchers should present a plan for ethics review outlining the measures to be undertaken for dissemination of genetic research results (section 13.2). In contrast, for IFs (ie, "unanticipated discoveries made in the course of research"), "[r]esearchers have an obligation to disclose to the participant any material incidental findings discovered in the course of research" (section 3.4). The TCPS2 goes on to broadly define material IFs as those "that have been interpreted as having significant welfare implications for the participant, whether health-related, psychological or social". To understand the implications of this guidance for Canadian paediatric research and for the clinic, a brief review of international norms on return of results provides the background to our discussion of the return of IRRs and IFs.

International norms have long distinguished between different contexts concerning the 'duty' to return IFs and IRRs. For clinical biomedical research in general, the Council for International Organizations of Medical Sciences (CIOMS), in its 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects, provided that "individual subjects will be informed of any finding that relates to their particular health status" (3). CIOMS also stated that "subjects have the right of

La recherche en pédiatrie et la communication d'observations pas si fortuites que ça

La recherche en pédiatrie est peut-être le premier domaine dans lequel on ressentira les conséquences éthiques du séquençage de prochaine génération (SPG). Puisque le SPG peut révéler beaucoup plus que le gène de la maladie recherchée, il faudra évaluer attentivement la manière de transmettre les résultats de la recherche et les observations connexes aux parents. Les choix qui sont offerts aux adultes à l'égard de la manière de transmettre les résultats de la recherche et des observations connexes ne le sont pas aux enfants. Les parents doivent agir dans l'intérêt de leur enfant sur le plan médical. Les politiques d'orientation sur la question ne sont pas claires au Canada.

access to their data on demand, even if these data lack immediate clinical utility" (3). These sweeping statements were somewhat tempered, however, in their 2009 International Ethical Guidelines for Epidemiological Studies:

In light of contemporary standards for informed consent [...] epidemiologists should make subjects aware of findings that are clinically relevant to their individual health. When (eg, because of the scale of a particular study) an investigator does not plan to do so, he or she must obtain approval from the ethical review committee. In all cases, the extent to which findings will be disclosed to subjects as a group or as individuals should be clearly conveyed in the informed consent material (Guideline 5) (4).

Regarding genetic disease research in particular, "international policies are converging towards an ethical duty to return individual genetic research results to subjects, provided there is proof of validity, significance and benefit" (5,6). Indeed, the IFs issue was already acknowledged by the international community in the mid-1990s by the International Human Genome Organization (HUGO). HUGO's 1996 Statement on the Principled Conduct of Genetic Research (7) declared that "choices to be informed or not with regard to results or incidental findings should be respected".

Nevertheless, both types of findings remain the source of much debate on the international level (8). To use but one biobanking example, "[i]mposing the return of results that is applicable in disease research or in clinical trials into the broader resource mission of population biobanks will undermine their longitudinal goals (to say nothing of the creation of untoward legal liability). Most importantly, it would create unrealistic expectations and harm the credibility and transparency of population biobanks" (5). As stated in the Organisation for Economic Co-operation and Development

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2009 Guidelines for Human Biobanks and Genetic Research Databases (HBGRD's), "[n]on-validated results from scientific research using an HBGRD's human biological materials and data should not be reported back to the participants and this should be explained to them during the consent process" (section 4.14) (9).

Today, with the advent of NGS, scientific criteria to determine what results to return are being proposed for both the clinical (10) and the research (11) settings. Generally, renewed focus is being brought to bear on requiring scientific validity and clinical utility, the latter being further interpreted as a clinically significant result that is 'actionable' (ie, treatment or prevention is available) (11). Alongside this 'clinically actionable' criterion, however, remains the duty to return life-saving data revealing imminent harm of death or grave injury (5). But what of information affecting reproductive choices? What will happen to the 'no return' policy of longitudinal, population biobanks, such as the United Kingdom Biobank or the Canadian Partnership for Tomorrow Project, as researchers accessing them for disease-specific research begin to use NGS? Must a researcher consult with an ethics review committee (or its equivalent) for every determination? Moreover, what about paediatric genetic research, particularly now that momentum is growing in the search for rare diseases (12)?

Most importantly, this brief background reveals the absence of any discussion of the paediatric context by either international bodies or the TCPS2. This is crucial, because while adults can exercise their autonomy by refusing any return of results that are offered (the 'right not to know'), the same cannot be said for parents who, by law, must always exercise their authority in the best interests of the child (13). Hence, it could be argued that where there exists the possibility that research may reveal an IRR or an IF that is medically significant and clinically actionable during childhood, the option to refuse the communication of such a finding should not be offered to the parents.

Thus, the TCPS2 position cited in the introduction is troublesome in several regards. First, its scope extends well beyond clinical significance to 'welfare' and psychosocial considerations. Second, the 'actionable' criterion is absent. Third, while researchers are advised to consult with their ethics review committee if necessary for determination on a case-by-case basis, the practicality of interpreting such an open-ended obligation in the face of NGS is not discussed. So ethics committees as well are left in the dark.

In Canada, the Finding of Rare Disease Genes in Canada (FORGE) project (14) is studying more than 70 childhood genetic disorders. Using NGS, it includes children and families in the discovery of rare disease-causing genes. FORGE maintains that clinically actionable findings that directly impact the care of the child during childhood must be communicated. This is consistent with the supplemental guidance on the TCPS2 that is offered by the Canadian Institutes of Health Research's Best Practices for Health Research Involving Children and Adolescents (16) currently nearing completion. It proposes that "[i]ndividual results should be communicated if they have significant implications for the health of the child. Incidental findings should also be communicated to the competent child or, if incompetent, to the parents if the findings have significant implications for the child... Researchers should respect the wish of the child and/or parents regarding the return of research results. However, when the health of the child may directly benefit from the communication of results, researchers may, with REB approval, override a refusal to receive results". Since such best practices are meant to be complementary to TCPS2, perhaps the obligation to return IFs that are clinically significant and actionable for the health of the child

during childhood is clear. But in the interim, it could be argued that the TCPS2 is creating an extremely broad and more substantive obligation to return findings for both children and adults due to its 'welfare' and 'psychosocial considerations'. Furthermore, even in the case of adults, were an individual to exercise the right not to know and waive any communication of future IFs and IRRs, can such a refusal be truly informed considering the imprecise and limitless nature of this new 'obligation' to return under the TCPS2 (15)? The TCPS2 provides policy guidance, but such an ethical norm could easily be transformed into a legal one. The three funding Councils (ie, the Natural Sciences and Engineering Research Council [NSERC], the Social Sciences and Humanities Research Council [SSHRC] and the Canadian Institutes of Health Research [CIHR]) that drafted the new TCPS2 may wish to reconsider the ramifications of creating such an ambiguous 'obligation' for researchers, their institutes and their ethics review committees, to say nothing of research participants.

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