Pediatric Issues in Return of Results and Incidental Findings: Weighing Autonomy and Best Interests

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Nowhere are the ethical issues in genomic research more complex than in pediatrics. Balancing the sometime conflicting autonomy of the parent and the child, and the best interest of the family and the child, brings up many challenging issues. Addressing this balance, especially in the context of the child's developing maturity and comprehension, requires deep analysis and discussion. Issues discussed include the impact of genetic information on the family, parental versus the child's autonomy, the best interests of the child versus the family, potential limitations on the parents' right to know or not know information about their child, and changing role of the developing child in return of research results. Finally, a dynamic model will be proposed that takes into consideration the child's evolving role in consenting and return of results that can be adapted in different national contexts.

Keywords: consent, ethics, pediatrics, return of genomic results

Introduction

MEDICAL RESEARCH INVOLVING children benefits everyone. Not only are there many diseases that affect children but also many diseases that affect primarily adults have their antecedents in childhood. Both the NIH, in their 1998 “NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects” (NIH, 1998), and the Medical Research Council (Medical-Research-Council, 2004) address the importance of medical research that involves and benefits children. It is particularly important to include children in genomic research. In children, the genetic contributions to diseases are the greatest, and many complex diseases with genetic and environmental components have their origins in childhood, including asthma, diabetes, cardiovascular disease, and obesity. In addition, predictive genetic testing is consistent with anticipatory guidance, a guiding principle of pediatric medicine.

However, there are several key differences in conducting research in a pediatric versus adult population. For one, a third party mediates the relationship between the researcher and participant: the parent. This parent–child–researcher triangulation adds complexity from the consent process to the return of results. This triangulation is further complicated by the children's evolving capacity to make decisions that reflect their preferences and desires, from early childhood when the parents act as a full proxy in decision-making for their child to the age of

majority when the child becomes an adult with full autonomy around decision-making. In addition, the difference in capacity between any two children of the same may be quite different.

In genomic research, the ethical issues around the return of individual research results and incidental finding to participants and families are arguably the most complex. The return of individual results from genomic research studies has been widely debated (Fabsitz *et al.*, 2010; NCI, 2010; Knoppers and Levesque, 2011; Bledsoe *et al.*, 2012; Clayton and McGuire, 2012; Dressler *et al.*, 2012; Johnson *et al.*, 2012; Wolf, 2012, 2013; Wolf *et al.*, 2012; Jarvik *et al.*, 2014; Kocarnik and Fullerton, 2014; Knoppers *et al.*, 2015) and, although ethically desirable, may not be feasible (Fernandez *et al.*, 2003). Clearly, the policy and options for receiving individual results need to be clearly outlined in the consent form (Presidential-Commission-for-the-Study-of-Bioethical-Issues, 2013). If results are to be returned, ethical frameworks for the return of results in children have been proposed (Avard *et al.*, 2011; Holm *et al.*, 2014; Knoppers *et al.*, 2014; McCullough *et al.*, 2015; Senecal *et al.*, 2015). Here we outline the issues around return of individual genomic information to children and their families.

Ethical Principles of Beneficence and Respect for Persons

Two important and, sometimes conflicting, ethical principles to consider in the return of genomic information are

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“beneficence,” acting in a person’s best interests and “respect for persons,” the right of self-determination or autonomy (Beauchamp and Childress, 2012; Presidential-Commission-for-the-Study-of-Bioethical-Issues, 2013). Both best interests and autonomy are complicated in the case of decision-making regarding children (Ross, 2013; Zawati *et al.*, 2014; McCullough *et al.*, 2015). Researchers have a duty to act in the best interests of their participants and to hold to professional standards; parents have a duty, and are granted the authority, to make decisions that are in the best interests of their child; and children have an evolving capacity to make decisions for themselves (Zawati *et al.*, 2014). Children also have an evolving capacity for autonomy, and although they do not have full autonomy, they will have autonomy in the future as adults. This leads to the “child’s right to an open future” (Feinberg; Davis, 1997), the notion that children will have the ability to exercise self-determination once they reach the age of majority, and that parents would preserve that opportunity by making decisions that will allow their children the greatest ability to make their own decisions once they are adults. Best interests and autonomy are person dependent: the parents’ view of what is in the best interest of their child and themselves, and their autonomy and authority to make decisions for their children; the researchers’ view of what is in the best interest of the child and the family, and their professional obligations to standards and their research; and the child’s growing and future autonomy.

In the ideal world, and in many if not most cases, the best interests of all parties coincide, and the autonomy of all parties is preserved. But this may not always be the case. There may be limits to parental autonomy if their decisions are not in the best interest of the child. If there are results for conditions that are serious or life threatening, of childhood onset, and are treatable or preventable (“clinically actionable”), then the medical best interests of the child may override the parents’ autonomy to opt out of receiving such results, analogous to refusing to treat their child’s cancer. In this case, it would be the researcher’s duty to act in the best interest of the child and overrule the parents’ right not to know.

On the flip side, there may be limits on parents’ right to know information about their child. The disclosure of results for conditions that solely have their onset in adulthood, and have no treatment or prevention, may infringe on the child’s future right to decide if he or she wants this information. In this case, it is in the best interest of the child to protect his or her future ability to decide if he or she wants to learn this information, and thus the child’s future autonomy overrides the parents’ right to know this information. This approach is consistent with the practice of medical genetics for many years.

Finally, the most complex scenario is when there are results for adult onset conditions that are treatable or preventable, and for which the intervention/s to prevent the condition would not be implemented until adulthood. In this case, the child’s future autonomy would suggest that these results should not be disclosed and the child, once an adult, should have the option to decide on disclosure. However, the children do not exist in isolation—they are part of a family. And knowing the result in the child may be beneficial to family members who may be at risk for the condition. Most of the

genetic conditions that are of adult onset, serious/life threatening, and treatable/preventable are inherited in an autosomal dominant manner, and in most cases pathogenic variants in these genes usually do not arise *de novo* (although of course they can). That means that a child with the pathogenic variant in a gene for one of these conditions likely inherited that variant from a parent. Thus, by returning the result on the child to the parents, the parents are afforded the opportunity to find information important to their health. In this case, negating the child’s future right-not-to-know or to decide whether to be tested—that is, violating the child’s future autonomy—may be in the best interests of the child, as it may enable the child to have parents who are alive and healthy.

Consent and Return of Genomic Results

As already discussed, although return of individual genomic information may be ethically desirable, for a number of reasons it may not be feasible in the research setting, and the policy toward return of results should be spelled out clearly in the consent form. If return of results is possible, many agree that participants should have an option to decide if they want results back, and, if possible, designate their preference regarding types of results to receive (Kohane and Taylor, 2010; Harris *et al.*, 2012; Parker, 2012; Bennette *et al.*, 2013; Wright *et al.*, 2014; Holm *et al.*, 2014, 2015; Sapp *et al.*, 2014; Ziniel *et al.*, 2014; Bacon *et al.*, 2015). This information is gathered through the consent process. Thus, the consent process is key—not only are the policies and governance of the research explained, but if there are choices to be made, participants make them at this time.

A major difference from adults is that children do not give consent, and instead parents provide “proxy” consent (Helgeson, 2005; Hens *et al.*, 2011a, 2011b). Parents represent their child and decide what is in the best interest of the child, and the child can participate as able through the assenting process. During the consent/assent process, the choices and boundaries should be laid out for families, as much as possible. Thus, delineating what results will be returned (highly actionable childhood onset conditions), what will not be returned (adult onset not treatable), and where there are choices will result in a truly informed consent process.

A Model for Return of Research Results in Pediatrics

Returning research results and incidental findings to participants and families engages them in the research enterprise (Kohane *et al.*, 2007). In pediatric research, this is a dynamic process requiring, at the least, a process that allows for assent as appropriate and re-consent at the age of majority. Ideally, engagement allows for the participation of older children, 13–17 years, in designating choices (along with their parents) for results to receive from the research. In one “preference-setting” model (Holm *et al.*, 2014), parents set preferences for results to receive if their child is <13 years. In children 13–17 years, results are returned in accordance with parental and participant preferences (adolescent and parental preferences must agree). Cases in which adolescent and parental preferences do not agree would be considered on a case-by-case basis, with the default being the fewest results returned. Such a model takes into account the growing autonomy of the child, yet the responsibilities of the parents.

Conclusion

There are a number of ethical challenges in the return of research results to families in the pediatric setting. These can be easily overcome with a clear and thoughtful approach to the consent process, by educating families on the types of results they may receive, and by engaging the children themselves as much as possible in the research process.

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