Disclosing Secondary Findings from Pediatric Sequencing to Families: Considering the "Benefit to Families"

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Introduction

Should children ever have genetic testing for adult-onset conditions? For the last two decades, there have been general recommendations from professional organizations that discourage such testing.[1] Until recently, such testing was only plausible in the context of a family history of a Mendelian condition that might prompt the parents (or an adolescent) to request testing for the adult-onset condition present within the family. In this context there has been a gradual shift in the direction of suggesting parents should have greater discretion to obtain such testing after careful consideration of risks and benefits by the family and the health care provider.[2]

The issue of testing children for adult-onset conditions is also relevant in the context of clinical sequencing, and this context may further challenge the traditional approach of discouraging testing for adult-onset conditions. In 2013, the American College of Medical Genetics and Genomics (ACMG) issued recommendations for incidental or secondary findings in clinical sequencing, stating that clinical sequencing laboratories should search for and report pathogenic variants in at least 56 genes representing 24 actionable conditions.[3] While the 2013 statement recommended that laboratories routinely report these secondary findings, in 2014 ACMG revised its policy to urge that patients be allowed to opt out of receiving this information.[4] This revision was in response to lack of consensus

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about the best approach, including some concerns about the implications for results in children.[5] Six of the 56 genes are for conditions that are exclusively adult-onset (including breast cancer and colon cancer).[6] The ACMG recommendations explicitly did not distinguish between return of secondary findings in children and adults, nor between return of secondary findings in children of different ages. The rationale cited for recommending disclosing secondary findings for adult-onset conditions in children was that there might be benefit to parents or other family members who learned about their own risk through the testing of their child.[7]

This rationale for testing children for adult-onset conditions has challenged the 20-year-old ethical analysis of genetic testing for such conditions in children that supported deferring such testing until children become adults, and instead has emphasized the concept of "benefit to family." In this paper, we consider the "benefit to family" rationale, and whether it is justified. We also explore how providers should discuss this potential benefit with parents who are considering genomic sequencing for their children. We also briefly consider the role of adolescents who may participate in such decisions. Our focus is on clinical sequencing, including research studies on translation of sequencing into clinical use.

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The Traditional Approach to Genetic Testing in Children

One of the first policy statements on the topic of genetic testing in children was the 1995 Points to Consider Statement by the American Society of Medical Genetics (ASHG) and the ACMG.[8] This ASHG/ACMG statement posited two primary potential benefits for genetic testing in children: (1) timely medical benefit to the child or adolescent, and (2) psychological benefits to adolescents in some cases. In the statement, the primary objection raised against genetic testing in children for adult-onset disorders was the potential for psychosocial harm — particularly the potential psychological burdens of knowing about risk of a possible future disease and of being treated as a "sick" child even before onset of symptoms, as well as the potential for alteration in family dynamics between the child tested and his or her parents and siblings. Other writers raised the notion that genetic testing for an adult-onset condition could preclude a child's "right to an open future."[9]

In early 2013, the American Academy of Pediatrics (AAP) and ACMG issued a revised statement on pediatric testing that again affirmed deferring testing for adult-onset conditions, but suggest some additional flexibility.[10] This statement recommended directive genetic counseling to urge that parents defer testing. However, the statement allowed some family discretion when ambiguity imposed psychological burden or the information was valued for life planning decisions. The statement affirmed that the focus should be on the child's interests but also noted that children and family interests are usually intertwined and that parents play an important role in assessing those interests.

The primary objections to testing children for adult-onset conditions remain concern about negative psychosocial impacts and depriving the child of an "open future." Before considering how much weight to give to "benefit to family" as a rationale, we examine these two concerns about testing children.

A. Concerns about Psychosocial Risks

The ASHG/ACMG statement identified potential risks related to adverse psychological impacts.[11] These risks, such as alteration of self-image, impact on family relationships, and impact on life planning, were extrapolations from clinical experiences of disclosing genetic risk information or from research in other contexts, such as the labeling of children with clinically non-significant findings (e.g., benign heart murmur or newborn jaundice). The analysis in the statement was that in the absence of clear medical benefit to the child from engaging in this testing before the child reached the age of majority, the potential for these psychosocial

risks needed to be considered seriously and were a reason for caution. The statement acknowledged parental authority to make most health care decisions for their children, but also argued that genetic testing for the risk of adult-onset conditions should be regarded as exceeding that authority because such testing would generally not be in the child's interests. However, the statement noted that the deliberative judgment of adolescents, along with their parents' views, should also be considered; if the adolescent and parents wished such testing, it could be justified. This makes sense, as a fully informed decision by an adolescent should be seriously considered and respected based upon ethical norms, even if the adolescent has not yet reached the legal age of majority. The statement concluded by noting that providers have responsibilities to children to encourage testing when the benefits outweigh the risks, to discourage testing when the risks outweigh the benefits, and to elicit the opinion of the older child when appropriate.

The underlying challenge facing the authors of this statement in the mid-1990s was the general uncertainty about adverse psychosocial impact of genetic testing in children and adolescents from the lack of empirical data. Over time, some data have emerged about the impact of carrier testing and predictive testing on emotional states, self-perceptions, and social well-being in children and adults. In a systematic review in 2010, 17 quantitative studies in children and adolescents were identified.[12] The variety of methods used in these studies made generalizations difficult, other than to note that none of these showed clear evidence of harm. Qualitative research contributed some interesting results. One of the more provocative studies, by Fanos and Johnson, described adult siblings at risk of being carriers of the cystic fibrosis gene; in the absence of testing, siblings made assumptions about their genetic status and their uncertainty itself was a source of stress.[13] This was reflected even in conditions with no effective treatment such as Huntington's disease where knowledge of one's status, even if positive for Huntington's, was often psychologically helpful.[14] Fanos and Johnson also pointed out that a benefit of testing even at a young age was the potential for the tested child to incorporate risk status into their identity, just as children do who have clinically diagnosed childhood diseases.[15] Empirical data from controlled clinical trials on adults in the REVEAL Study also contributed to the notion that anxiety, depression, and test-related distress were far less common in the face of genetic risk information than had been previously assumed.[16] Taken together, these studies suggest the psychological impact of testing children may be less severe than anticipated, albeit still somewhat uncertain. As consequence, we would argue these data justify allowing some familial discretion. At the same time we acknowledge that further research is warranted.

We acknowledge that the concept of the "right to an open future" is indeed important for parents to consider in making decisions about genetic testing. Parents may not have considered this before, and in some contexts, this consideration may influence their decisions about having their children tested. In considering whether to receive secondary results for adult-onset conditions, parents should not only assess the impact on foreclosing future testing choices by the child, but also the possible impact on the child's potential insurability and employability.

B. Concerns about an "Open Future"

In 1997, Davis argued that parents should not be able to request testing of their young children who might be at risk for Huntington Disease (HD).[17] She borrowed the concept of a "right to an open future" from Feinberg, who had considered the concept of "an open future" as an example of a "rights-in-trust." These are rights that must be preserved for a child so the rights can be exercised as an adult.[18] Davis suggested that testing a child at a young age precluded the future option that these individuals could choose to decline testing once fully able to consider the decision.[19] Data at that time suggested that while most adults at risk of HD indicated a willingness to be tested, only a small fraction actually acted on that choice.

Over the years, the "right to an open future" has often been used to justify prohibitions in testing children for adult-onset diseases.[20] Yet, parents make many decisions that foreclose options and shape the

direction of a child's life as an adult, and indeed, parents are expected to make decisions that will impact a child's future.[21] Further, it is difficult to predict how parental decisions about their children will be viewed by those children when they become adults. For example, some parents make decisions to encourage their young children to focus on becoming extremely competitive athletes, artists, or academic achievers. The parental motivations for extreme childhood achievement are complex. While they may be motivated by their perceptions of the child's interests, sometimes the motivation may be more related to value to the parents or other family members, including fame and financial gain. These decisions may be appreciated by some of these children, once they are adults. But sometimes those grown children will attribute hardships to these types of parental choices and conclude that the parental choices limited their future.[22]

We acknowledge that the concept of the "right to an open future" is indeed important for parents to consider in making decisions about genetic testing. Parents may not have considered this before, and in some contexts, this consideration may influence their decisions about having their children tested. In considering whether to receive secondary results for adult-onset conditions, parents should not only assess the impact on foreclosing future testing choices by the child, but also the possible impact on the child's potential insurability and employability. However, these adverse impacts of testing children for adult-onset actionable conditions such as hereditary breast and ovarian cancer, remain hypothetical. Unless it is clear that parents are harming their children,[23] parental discretion to obtain such results has weight.

Benefit to Family

The 2013 ACMG statement on secondary findings suggested that in addition to benefits to the child, the potential benefit to the family is important. In particular, in the context of sequencing without a family history of a Mendelian condition, the discovery of adult-onset penetrant autosomal dominant genes in children is potentially relevant to the parents and other family members, who may not appreciate their own risk.

The concept of "benefit to family" involves an important distinction. In the 2013 ACMG statement on secondary findings, benefit to families was primarily conceived as a derivative of the benefit the child. The argument is that any benefit to the family that might be gained by identifying a parent who, for example, is at risk for hereditary breast and ovarian cancer, is also a benefit to the child because of the potential for the information to improve the parent's health and thus their ability to support the child. Alternatively, benefits to family can be conceived as being independent of a direct benefit to the child or in some cases may even be counter to the interests of the child. Parents routinely balance competing interests of family members and make decisions about how to prioritize them. But the distinction is important because in the first conception, the parent will need to consider whether this information will or will not be in the child's interest. In the alternative conception, the parent needs to balance the child's interest versus the family interests.

We believe that disclosing secondary findings in minors for adult-onset disease can be justified by either conception. First, children may indirectly benefit by the sharing of unexpected and possibly life-saving secondary research findings relevant to the health of their parents. This is based upon the assumption that that preserved parental health will be in the child's interest. The parent may consider the presence of extended family available to support the child if the parent's health is compromised, or the lack of such relatives, when making a decision about the importance of the parent's health to the child.

Under the second conception, the parent may consider testing the child to benefit the parent even if these results are not clearly in the child's interest. It may not be necessary to claim that the information benefits the child to justify testing the child in order to benefit the parent. It can be sufficient for the parent to claim that the information is not likely to cause more than minimal harm the child. The "harm threshold" used for decisions about social interference in parental decision making and the "minimal risk" threshold used in pediatric research allow children to bear some risk.[24] It is not clear that providing information that will more immediately benefit the parent will be sufficiently harmful to the child to preclude testing. There are no data indicating that many children will grow up to be adults who look back and consider that sharing of their personal medical information as a child to aid a family member as a negative outcome. Further, there are data that many adults would consider sharing their own significant, actionable research results with family as the correct thing to do.[25]

This becomes more complicated if the child is old enough to express preferences, and does not agree with parents about testing and disclosure of such results. If a child prefers to defer testing, then test results regarding adult-onset conditions should not be disclosed to benefit others. It is hard to know how often children will weigh their "right to an open future" over the preservation of the health or life of a parent and claim that disclosing this information is a net harm to them. We are aware of no data that that are relevant to

this assessment. In the unlikely event that such preferences are explicitly expressed, parents can actively pursue their own direct testing.

Our point is that parents should be given the option to receive their child's genetic results regarding adult-onset conditions, unless the child is old enough to express their wishes and does not want this. The potential benefits to families and the lack of clear harms points to physicians allowing families to make these decisions. There may be reasons that some parent might choose to not receive such results. The most typical applications of pediatric sequencing currently are in the context of cancer, other serious illness, or intellectual disabilities.[26] In these contexts, some parents may prefer to defer learning about their own future risk to maintain their focus on the underlying disease or condition in their child. Particularly if the child's condition is likely to be profoundly life-shortening, the parents may decide the information will not have a direct and immediate benefit to the child and will distract the parent from their child.

The parents themselves, in contrast to their pediatricians, are typically in the best position to decide how much to value the benefit to themselves and the family from receiving their child's secondary results about adult-onset conditions, and how to weigh the child's interests in making these decisions. Such decisions are similar to the many decisions that parents make that involve balancing competing interests. For example, parents who have an extremely premature infant hospitalized in a NICU for 3-4 months will face decisions about dividing their time between being at their baby's bedside, working, and caring for other children. Parents in that context are given significant latitude to make treatment decisions, even in opposition to physician recommendations. Providers can only override parental decisions when those decisions will clearly harm their children. In the context of returning secondary results for adult-onset conditions, there are not sufficient empirical data to suggest that likelihood of harm to children is high enough to preclude parents from learning information that potentially could extend their own life and ability to be a parent by taking actions based on the information.

Advice to Providers about How to Counsel Parents

Parents will need counseling from health care providers in order to make a decision on whether to receive secondary findings about adult-onset conditions in their child from genome sequencing, whether in a research or clinical context. The impact of testing for the *BRCA1* and *BRCA2* genes, for example, will be same regardless of whether this is done in a clinical context or in a research context where the goal is to learn about appropriate integration of sequencing into clinical care. We support the approach that, in general, the option of receiving secondary findings from their child's sequencing, including secondary findings that predict adult-onset conditions, should be offered to parents with a careful discussion of the risks and benefits of receiving this information, and parents should be given the option of receiving or declining such findings. Providers and parents should also involve children in such decisions, to the extent the child is able to participate.

Pediatricians are accustomed to engaging with parents and acknowledging that parents are often faced with balancing their child's interests with family interests. Decisions about infant day care are an example of this; a physician may support a decision for early placement that is in the family's financial interests, even if not in the infant's interest, as there is greater opportunity for children to avoid viral infections by remaining at home. However, for some families, the value to the parent of working outside the home outweighs the benefits of staying at home, even when the child has a chronic illness that may be exacerbated by day-care exposure. Pediatricians will often support or even encourage families to makes such choices, based on their knowledge of the family. Similarly clinicians can suggest to the parent that receiving results concerning actionable adult-onset conditions is a reasonable thing to do because it could be beneficial to the parent, and indirectly to the child. Particularly when the results are limited to small number of conditions that are clinically actionable, so that knowing these results may benefit the parent's health, such secondary testing is likely to be valuable to the family in the long run.

This argument for family benefit is speculative. Further research will be needed to establish if families do indeed benefit from being offered results on these adult-onset conditions found in children who have sequencing done for clinical reasons. We would distinguish between discussing this benefit with a particular family and using this rationale to propose population screening of newborns or young children for the same conditions. There are no serious calls at present for routine population sequencing in newborns or children to include adult-onset conditions. This is because a positive balance of benefit to harms and costs has not yet been established to support population-wide sequencing. However, valuable data may be collected from parents deciding to receive their child's results on adult-onset conditions. Evaluating the impact on these families may support further evidence-based

decisions about newborn or pediatrics sequencing at a population level.

Because the benefit to families remains speculative, discussions by pediatricians with parents who are considering requesting secondary findings in children for adult-onset conditions should be balanced. Pediatricians should point out to parents the reasons that some may not want this information and discuss the alternatives. These alternatives could include not requesting these results from their child's sequencing, allowing the child to decide at adulthood whether to be tested for adult-onset conditions, and the parents choosing to have themselves tested separately for actionable conditions of concern. As mentioned earlier, the specific context for sequencing their child (for example, an advanced cancer diagnosis in the child) might be a reason that some parents would prefer to defer knowing information that is not medically needed in childhood. Additionally, some parents will prefer to focus on the medical issues facing the child.

Many parents may decide to receive secondary information on adult-onset conditions that are actionable for the parents, for a variety of reasons. Their reasons may include interest in their own health, curiosity, or belief in the value of this information for the child. In other contexts, evidence suggests that people value information for its own sake and are confident the information will be useful to them.[27] It will be important to collect data to learn from parents' decisions and experiences. Such data will allow a better understanding of the concept of "benefit to family" as a justification for disclosing results from pediatric genome sequencing. This concept could also have implications for other contexts of genetic testing in children, such as newborn screening, where there have already been proposals to extend the general criteria for adding conditions in order to diagnose the child (even if no treatment is available), thereby avoiding a diagnostic odyssey and so conferring benefit on the family.[28] Thus, data from the experience of decision making for children about the receipt of secondary results from clinical sequencing may have relevance to later policy decisions on newborn screening and other forms of population screening.

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