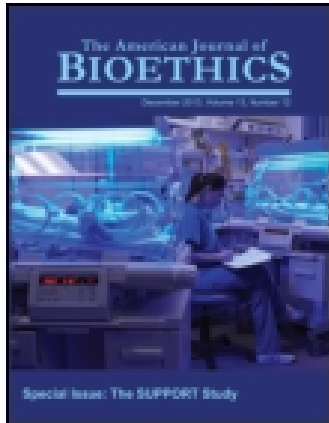


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### Genetic Testing of Children: The Need for a Family Perspective

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# Genetic Testing of Children: The Need for a Family Perspective

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It has been proposed that two recent guidelines, both endorsed by the ACMG, are in tension with each other because they result in opposing outcomes with respect to genetic testing of children for adult onset diseases. We argue that if they are viewed from a family, rather than individual, perspective they are consistent with each other. Although new genome technologies are often described as facilitating personalized medicine, they can often only do so in the context of familial information. Individual and family approaches need to be combined when considering genetic testing in children for adult onset diseases.

Clayton and colleagues (2014) conclude that the ethical justifications behind two recent sets of U.S. guidelines—both endorsed by American College of Medical Genetics and Genomics (ACMG), and both released in 2013—are in conflict with each other. We agree that there is apparent conflict between them, because one argues that children's genetic test results should be communicated even if they are not of medical significance until adulthood, while the other recommends against genetic testing for adult onset conditions taking place in childhood.

We believe, however, that ethical justifications for the guidelines are consistent if viewed from a family perspective and if account is taken of the different circumstances in which each is intended to apply.

The first set of guidance is from the American Academy of Pediatrics (AAP) and was released jointly with the ACMG: the AAP/ACMG guideline. In common with many other guidelines internationally (summarized in the British

Society of Genetic Medicine report [2010]), these guidelines recommend deferral of genetic testing in children for adult onset diseases until the child is in a position to make a decision for him- or herself, arguing there is no medical benefit to such testing in childhood. The guideline is intended to apply in situations where a particular genetic mutation in a family is already known and where the request is for a test to be carried out on a (young) child many years (or even decades) before the likely onset of symptoms or utility of ameliorative treatments or screening. An example might be a request by a parent for childhood testing in a family with a BRCA1 or BRCA2 gene mutation known to have been inherited by either the mother or father of the child in question. Because the risk of cancer associated with the mutation does not become relevant until adulthood, the AAP/ACMG guidance concludes that predictive genetic testing should be deferred until such time that the child is old enough to decide for herself if and when she wants such testing.

The second set of recommendations, referred to by Clayton and colleagues as the exome or genome sequencing guidelines, or the ACMG exome sequencing/genome sequencing (ES/GS) statement (Green et al. 2013), is not specifically concerned with childhood testing. It addresses the question of which results—in addition to those that provide an answer to the clinical question that prompted the use of genomic testing—should be disclosed. It recommends that when such untargeted technologies are used, certain genetic variants should be analyzed and reported regardless of the reason for the test. As a minimum set, 56 variants have been

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listed as those that lead to disorders for which preventative measures and/or treatment are available. The list includes variants that will not manifest in disease during childhood. What this means in practice is that in situations in which genomic approaches are used to test a child for a childhood onset condition but the test, incidentally, generates information relevant to additional adult-onset conditions, the guidelines recommend that this should be fed back. This is clearly, in practical terms, in conflict with the recommendations of the AAP/ACMG guidance that such testing should be deferred until adulthood.

The reasoning used in favor of disclosing these variants by the ES/GS guidelines is that disclosure could be of medical benefit to the adult family members of the child in which the mutation is found incidentally or unexpectedly. Thus, while in the BRCA1 or BRCA2 example the child under investigation would not benefit from receiving these results now, her mother may harbor a mutation without her knowledge, and she might well benefit from preventative or therapeutic interventions were she aware of her risk.

The circumstances envisaged by the ES/GS guidelines are therefore very different from those of the AAP/ACMG guidance. In one, a clinically useful test in a child produces information that is of current relevance for the parents (in addition to being of future relevance for the child). In the other, a test that is not currently clinically indicated is requested in a child because of its potential relevance when she is an adult.

Exome sequencing/whole genome (ES/WG) testing is increasingly used in the care of children to increase the diagnostic yield in developmental delay by comparison with more targeted genetic tests. Importantly for this discussion, an integral part of the interpretation in such testing is comparison with parental samples. The sequences of these so-called trios are compared to see whether an abnormality is *de novo* or segregates with a phenotype. What this means is that genomic investigations in children therefore take place on a family, not just on an individual child, and the health professional might then reasonably feel a responsibility to this family unit, which includes, but is not limited to, the child. Furthermore, the parents have a legitimate interest in hearing about any abnormalities found in their samples. This highlights the fact that in such situations a range of additional morally significant factors are present in the situations envisaged by the ES/GS guidelines. These added factors promote more emphasis on a need to alert family members to their risks, whereas the AAP/AMCG statement places more emphasis on preserving a child's future choice. The circumstances to which both apply are different: In the AAP/ACMG guidance the child's future choice is independent of family members' awareness of their risks. The example in Box 1 illustrates that there are circumstances, nevertheless, where both set of recommendations could result in the same outcome and would not be in conflict.

The publication of the ES/GS guidelines has generated heated debate on a range of issues: about whether analysis of the ES/GS variants represents opportunistic screening; about whether such screening would satisfy Wilson and

Jungner criteria; and about whether parents would in practice be free to decline to receive the results of the 56 variants (Burton and Zimmern 2013). Here we limit our argument to the question of whether these guidelines are in ethical conflict with the AAP/ACMG. It is our view that it is not necessarily the case that there is inconsistency between the two guidelines, even though they might result in different outcomes for a particular child.

Somewhat similar debates were rehearsed in the 1990s on the introduction of newborn screening programs for recessive genetic conditions such as hemoglobinopathies or cystic fibrosis. A by-product of diagnosing newborns with recessive conditions is finding asymptomatic carriers of the condition. This has no health implications for the newborn carrier, but may imply a future reproductive risk for the parents. Most neonatal programs disclose carrier status to parents even though guidance would recommend deferring targeted carrier testing till a child could choose for herself (Human Genetics Commission 2006). Finding carrier status is an incidental finding of the investigation, much as the 56 variants in the ES/GS guidance are. By contrast, specific requests for carrier status, for example, testing of healthy older children in the light of a family history, would fall under the AAP guidance. Healthy older children have already shown themselves not to have inherited the condition, and discovering whether they are carriers or not can be deferred when they near reproductive age.

Although both exome and genome sequencing are often "sold" as examples of personalized medicine, we would argue that their effective and appropriate use more broadly should also be thought of as examples of familial medicine. In order to interpret the results of testing in one person, other relatives are tested, which must in turn establish some duty of care to interpret and disclose pertinent health information to these additional "patients" (Crawford et al. 2013). Furthermore, if testing of relatives is necessary to interpret results in one person, ethical questions may rise as to what actions are justified in case relatives decline to participate (Ashcroft et al. 2005). We have argued elsewhere that overly individualistic approaches to good practice in genetic testing may not be appropriate in situations where the result may be relevant to other family members (Lucassen and Parker 2010; Parker and Lucassen 2004).

We believe that adopting a family perspective on the types of issues raised in genetic practice, while at the same time taking into account the specific context in which testing takes place (Lucassen and Fenwick 2012), will help to better understand and interpret both sets of recommendations and their lack of conflict with each other.

### Box 1: Variant Panel in ES/GS and AAP Guidelines

A boy with developmental delay is investigated with ES/GS technologies and a BRCA1 mutation is found. This mutation is already known about in the boy's family—his father has it. It is not relevant to the boy's health care now and the adults in the family already know about it. Anticipation and communication of the possibility of such an incidental finding

(Presidential Commission for the Study of Bioethical Issues 2013) could allow for the boy's result not to be communicated until a later time. This would satisfy both the ES/GS and the AAP recommendations. ■

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# The "Right Not to Know" in the Genomic Era: Time to Break From Tradition?

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The target article by Clayton and colleagues (2014) helpfully lays out the differences between two recent sets of genetic testing guidelines, referred to as the "AAP/ACMG" (American Academy of Pediatrics [AAP] and American College of Medical Genetics and Genomics [ACMG] 2013; Ross et al. 2013) and "ACMG ES/GS" (exome sequencing/genome sequencing) (Green et al. 2013; Incidental findings 2013) statements. These statements differ markedly in their respective positions on the testing of children for adult-onset disorders that cannot be treated during childhood. While AAP/ACMG generally discourages such testing, ACMG ES/GS requires analysis of some gene variants that could predict adult-onset disorders in children.

This difference reflects a dramatic shift in the priority granted to a person's "right not to know" genetic information. ACMG ES/GS explicitly acknowledges that its support

for generating genetic results for adult-onset conditions in children is a departure from previous recommendations. Its authors argue that the interests of other parties, including the child's parents, must be taken into account: "To mask or withhold the incidental finding is to state that the child's right not-to-know supersedes the parent's opportunity to discover a life-threatening risk factor" (Green et al. 2013, 572; Incidental findings 2013). This stance has been met with significant criticism; some argue that the ACMG ES/GS recommendations contradict ethical clinical practice by failing to preserve a child's future choice about genetic results (All-lyse and Michie 2013; Wolf, Annas, and Elias 2013), and others argue that these recommendations are also problematic from the parents' perspective, impinging on their right to refuse information and even lifesaving treatments based on that information (Burke et al. 2013).

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