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Target Article

Addressing the Ethical Challenges in Genetic Testing and Sequencing of Children

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American Academy of Pediatrics (AAP) and American College of Medical Genetics (ACMG) recently provided two recommendations about predictive genetic testing of children. The Clinical Sequencing Exploratory Research Consortium's Pediatrics Working Group compared these recommendations, focusing on operational and ethical issues specific to decision making for children. Content analysis of the statements addresses two issues: (1) how these recommendations characterize and analyze locus of decision making, as well as the risks and benefits of testing, and (2) whether the guidelines conflict or come to different but compatible conclusions because they consider different testing scenarios. These statements differ in ethically significant ways. AAP/ACMG analyzes risks and benefits using best interests of the child and recommends that, absent ameliorative interventions available during childhood, clinicians should generally decline to order testing. Parents authorize focused tests. ACMG analyzes risks and benefits using the interests of the child and other family members and recommends that sequencing results be examined for additional variants that can lead to ameliorative interventions, regardless of age, which laboratories should report to clinicians who should contextualize the results. Parents must accept additional analysis. The ethical arguments in these statements appear to be in tension with each other.

Keywords: ethics, pediatrics, exome sequencing, genome sequencing, risks, benefits, interests of child and family, best interests of the child

The debate about predictive genetic testing of children for adult-onset disorders has been cast in a new light by the release of two sets of recommendations, in February and March 2013, respectively, both endorsed by the American College of Medical Genetics and Genomics (ACMG). The first set of recommendations, as part of its overarching consideration of the ethical and legal issues raised by pediatric genetic testing and screening in a range of contexts, addressed whether it is appropriate to test children for a mutation typically associated with adult-onset disease already known to be present in the family and for which there is no intervention in childhood (American Academy of Pediatrics [AAP] and ACMG 2013). This document accompanied a technical report on pediatric genetic testing generally and was issued jointly with the American Academy of Pediatrics (AAP) (Ross et al. 2013) (both hereinafter referred to as the AAP/ACMG statements). One month after the issuance of these recommendations, the ACMG issued a second set of recommendations (Green et al. 2013; hereinafter referred to as the ACMG ES/GS [exome sequencing/genome sequencing] statement), followed shortly by a clarification (Incidental findings 2013), addressing the return of findings from clinical exome- and genome-wide sequencing that are beyond those needed to answer the clinical question for which sequencing was sought. In this article, members of the CSER Pediatrics Working Group, some of whom were involved in developing the documents just described, describe and compare these recommendations and the

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ethical arguments underlying them as they pertain to testing children for adult-onset disorders for which ameliorative interventions are not available during childhood.

The two sets of recommendations on predictive testing, which address somewhat distinct but potentially overlapping clinical contexts, differ in how they approach genetic testing of children for adult-onset conditions. The AAP/ACMG recommendations, affirming previous professional consensus (American Society of Human Genetics Board of Directors and American College of Medical Genetics Board of Directors 1995; Borry et al. 2006; Ethical issues 2001) and citing the best interest of the child, take the position that predictive genetic testing for adult-onset conditions that cannot be ameliorated in childhood—testing that is sometimes requested by parents—generally should not be performed, with rare and carefully considered exceptions when diagnostic uncertainty poses a significant psychosocial burden to the family. While the AAP/ACMG statement did endorse genetic testing for disorders that could occur or be ameliorated during childhood in families known to be at risk, it did not address the appropriateness of looking for or reporting such variants when children are being tested to address another clinical issue.

In contrast, the ACMG exome sequencing/genome sequencing (ES/GS) recommendations proposed that when a child undergoes testing for a specific clinical indication using exome or genome sequencing, the laboratory should also analyze and interpret the child's genomic data looking for known pathogenic mutations—and for certain genes, for variants that are expected to be pathogenic—in 57 (a number since reduced to 56) genes associated with 24 genetic conditions. The 56 genes on the ACMG list were selected because, in the view of the statement's authors, they are associated with phenotypes for which "preventive measures and/or treatments [are] available and disorders in which individuals with pathogenic mutations might be asymptomatic for long periods of time." This recommended analysis, applied irrespective of age, included adult-onset disorders for which measures to modify risk are unavailable during childhood or can safely be deferred to adulthood as well as those for which intervention during childhood is warranted. The ACMG ES/GS recommendations stated that the clinician is "expected ... to contextualize [these findings] for the patient in the light of personal and family history, physical examination, and other relevant findings." The ACMG ES/GS recommended that while patients and parents should have a right to refuse GS or ES, if they do authorize testing, they should not be given the choice to opt out of analysis and reporting to the clinician who ordered the test of identified pathogenic mutations in the 56 genes.

The two sets of recommendations differ somewhat in their audiences. The AAP/ACMG recommendations on predictive genetic testing are directed primarily at clinicians who are considering whether to order a single gene test for a child with a positive family history. The ACMG ES/GS recommendations address both laboratories and clinicians regarding a secondary analysis of an exome or genome sequence that was ordered to diagnose a disorder in the child. These sets of recommendations therefore raise two questions: (1) How does each set of guidelines characterize and analyze the locus of decision making as well as the risks and benefits of testing? (2) Are the guidelines in conflict, or have they come to different but compatible conclusions because they consider different testing scenarios?

The discussion presented in this article proceeds in two parts. First, we lay out the AAP/ACMG recommendations about pediatric genetic testing and the ACMG's more recent recommendations about genomic sequencing and analysis of 56 additional genes, along with the justifications provided, relying heavily on the documents' language. Second, we present a side-by-side comparison of issues raised by AAP/ACMG and ACMG ES/GS statements, identifying questions for further discussion in light of this comparison. The authors of this article hold widely divergent views about whether the two sets of recommendations can be reconciled (and if not, about which represents the more appropriate approach). This article thus does not seek to draw conclusions about which sets of recommendations, or which parts of which sets, are preferable, but rather to elucidate the range of frameworks, assumptions, and values in the two documents as a prelude to further discussion.

THE TWO SETS OF RECOMMENDATIONS AND THEIR ETHICAL JUSTIFICATIONS

AAP/ACMG Recommendations

There has been a long-standing consensus that the primary and strongest justification for genetic testing of children exists when the results will clarify the cause of current symptoms, when the onset of the condition may occur during childhood, or when the information will be used to embark on a course of care that must start during childhood to prevent or ameliorate later symptoms (American Society of Human Genetics Board of Directors and American College of Medical Genetics Board of Directors 1995). The last, for example, is the justification for newborn screening. The broad consensus has been that minors who are known to be at risk of adult-onset disorders should not undergo genetic testing for a condition unless the results would lead to altered medical management during childhood that improves outcome (e.g., familial adenomatous polyposis), in part so that these young people can make their own choices about testing once they reach adulthood. Although at-risk adults are more likely to refuse predisposition genetic testing when no therapeutic or preventive interventions for the condition in question exist, some decline testing even when such interventions are available (de Snoo et al. 2008; Glenn, Chawla, and Bastani 2012; Kinney et al. 2006; Melnyk and Shepperd 2012; Ramsoekh et al. 2007). The February 2013 statement of the ACMG and AAP concluded that

> Predictive genetic testing for adult onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might

> be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing.

In the accompanying technical report, "The AAP and ACMG continue[d] to support the traditional professional recommendation to defer genetic testing for late-onset conditions until adulthood," citing more than two dozen previous statements by national and international professional organizations. They went on, however, to state that

> Predictive genetic testing may be appropriate in limited circumstances. [cit. om.] In deciding whether a child should undergo predictive genetic testing for late-onset conditions, the focus must be on the child's medical best interest; however, parents and guardians may also consider the potential psychosocial benefits and harms to the child and the extended family. [cit. om.] Extending consideration beyond the child's medical best interest not only acknowledges the traditional deference given to parents about how they raise their children [cits. om.] but also recognizes that the interest of a child is embedded in and dependent on the interests of the family unit. In some families, the psychosocial burden of ambiguity may be so great as to justify testing during childhood, particularly when parents and mature adolescents jointly express interest in proceeding. Some parents may seek predictive genetic testing for adult-onset conditions even when children are unable to participate in the decision-making process because of immaturity or cognitive impairment. After careful genetic counseling, it may be ethically acceptable to proceed with predictive genetic testing to resolve disabling parental anxiety or to support life-planning decisions that parents sincerely believe to be in the child's best interest. [cits. om.]

ACMG Recommendations Regarding Results of Additional Analysis of Genomic Data

Genome-based tests, such as genome and exome sequencing, which make it possible to assess variants in nearly all genes, are now beginning to be used in all age groups for refining cancer diagnoses and therapies. Of particular relevance to pediatrics is the growing importance of these approaches for ascertaining the causes of previously undiagnosed genetic conditions, particularly neurodevelopmental disorders and multiple congenital anomaly syndromes. Often these studies are done on parent–child trios to facilitate analysis of inheritance for recessive disorders and to identify de novo mutations. As the use of these technologies increases, a great deal of sequence data on children (and their parents) is being generated, raising the question of which parts of the data, if any, need to be analyzed and reported beyond that needed to answer the presenting clinical question. The ACMG ES/GS recommendations identified 56 genes that have pathogenic mutations that can be acted on, at times well into the future, to prevent or mitigate later symptoms. They recommended that laboratories analyze these 56 genes, and interpret and report identified pathogenic mutations to the ordering clinicians, for both adult and pediatric patients. The ACMG ES/GS statement reaffirmed prior ACMG guidance (Points to consider 2012) that informed consent should be sought for genomic testing after appropriate pretest counseling, including discussion of the possibility of findings from additional analysis, but "did not favor offering the patient a preference as to whether to receive" the findings of additional analysis.

A major driver of the ACMG ES/GS recommendations was concern that patients and their parents, and by extension other family members, would not otherwise learn about these mutations, since genome-wide tests are not currently broadly available. A related motivation was the possibility that these mutations may be present even in the absence of a positive family history that might prompt targeted diagnostic testing. The authors of the recommendations explained that

> at this moment in the evolution of clinical sequencing, an incidental finding relevant to adult disease that is discovered and reported through clinical sequencing of a child may be the only way in which that variant will come to light for the parent. . . . The Working Group also felt that the ethical concerns about providing children with genetic risk information about adult-onset diseases were outweighed by the potential benefit to the future health of the child and the child's parent of discovering an incidental finding where intervention might be possible.

In a subsequent clarification, the ACMG reasoned that identifying pathogenic mutations in children would benefit the children by enabling their parents to obtain medical management for the risk to their own health, as well as providing the children with information about a predisposition about which they might not otherwise learn at any point prior to the development of clinical manifestations. They further reasoned that any risk of altered parental nurturing as a result of receiving information is outweighed by the increased ability of the child to recognize the need to obtain medical care in the future. The ACMG in its clarification stated:

> The ACMG affirms its recommendation not to perform diagnostic testing for an adult-onset condition in children but believes that reporting an incidental finding of a severe, actionable, pathogenic mutation falls outside this recommendation.

In comparing the two documents, questions remain about whether these sets of recommendations do in fact conflict and if so, to what extent their differences can and should be reconciled.

POTENTIAL DIFFERENCES BETWEEN THE SETS OF RECOMMENDATIONS

Nature of the Test and the Reason It Is Performed

In the scenario contemplated in the AAP/ACMG statements, parents request that their child undergo predictive testing for a mutation associated with adult-onset disease known to be present in the family but for which effective early intervention in childhood is not available. The only question is whether to do the test or not, and these organizations concluded, as have many before and since (Points

to consider 2012; van El et al. 2013), that such tests should be discouraged because they fail to protect and promote the child's best interests. Although few data are available regarding the impact of such tests on children, either for good or for ill (Malpas 2008; Mand et al. 2012; Wade, Wilfond, and McBride 2010), the rationale is that children may be harmed during childhood by being tested for adult-onset disorders. The harm of such testing that has raised the greatest ethical concern is foreclosure of the child's ability to decide for him- or herself about whether and when to be tested after reaching adulthood—an opportunity loss that is relevant since some adults who know they are at risk choose not to pursue testing (de Snoo et al. 2008; Glenn, Chawla, and Bastani 2012; Kinney et al. 2006; Melnyk and Shepperd 2012; Ramsoekh et al. 2007). If testing is deferred, then assuming that their parents share the risk information with them in an appropriate and understandable manner and they are referred to competent providers (Aktan-Collan et al. 2011), children will be able to make their own decisions about testing on reaching adulthood. The AAP/ACMG statements acknowledged that it may be appropriate in some cases to proceed with testing during childhood, but only after detailed conversations between the provider and family that take into account the family's motivation, context, and understanding.

In the scenario contemplated in the ACMG ES/GS statement, by contrast, the child is undergoing genome-wide or exome-wide sequencing in order to address a current medical problem such as cancer or an undiagnosed genetic disorder. The ACMG ES/GS recommendations are predicated on the assumption that the family whose child is undergoing testing would be unaware of their child's and their family's risk for an additional condition that could be uncovered by further analysis of the sequence data (in some cases, however, the family may already be aware of the familial risk of one or more conditions being evaluated by additional analysis). The ACMG concluded that mutations in the 56 genes are "incidental findings [that] are inextricably part of exome and genome analysis, and that such results should be returned to clinicians" who can then "contextualize" the results for patients and families as noted in the following. The existence of these data—data that are not obtained in order to answer the question for which sequencing was ordered—led the ACMG to recommend that sequence information be analyzed for pathogenic mutations in these 56 genes, and to conclude that failure to do so may even be "unethical" (Incidental findings 2013). In recommending that these genes be analyzed, the ACMG was influenced by the fact that genome sequencing and exome sequencing are at present not widely available. In addition, if the family of a child with a pathogenic mutation in one of these genes is unaware that its members are at risk, family members likely will not otherwise have reason to seek to learn whether they have one of these mutations, precluding or delaying the possibility of seeking appropriate medical management for the child's relatives, even if no intervention was warranted for the child prior to adulthood.

Whose Interests Are to Be Taken Into Account?

The ACMG/AAP documents focused on the best interests of the child, with the family's interests being pertinent primarily insofar as they affect the child. While the ACMG ES/GS recommendations similarly addressed the interests of the child, they also considered the potential health benefit to parents or other family members as a factor in deciding which results to seek and disclose to the clinician. The ACMG ES/GS authors argued that disclosure will benefit the child both directly and indirectly—directly by learning of a significant health risk that she or he may choose to address as an adult, and indirectly by having parents and other biological relatives who might be healthier by virtue of having been given an opportunity to address their own, perhaps previously unsuspected, risk.

Weighing Risks and Benefits

The potential benefits of testing just described are categorized differently in the two sets of recommendations and are also weighed differently against the potential risks to the child. In assessing the impact of predictive genetic testing for an adult-onset disorder for which the child is known to be at risk, the AAP/ACMG statements focused on averting the risks to the child of learning that he or she is at risk, including the risk that the parents may treat the child differently. They identified as relatively minor the benefit of reducing uncertainty through testing of the child, and as major the benefit of deferring to permit the child to make a decision after reaching adulthood. By contrast, the ACMG, in its recommendations about reporting the specific results of additional analysis of genomic data, placed a higher value on the benefit to the family and to the child of identifying and reporting these mutations, which in the ACMG's view outweighs the child's interest in making his or her own decision in the future based on the information available at that time.

Who Decides What?

Finally, the sets of recommendations diverge in who is involved in decision making and the roles they play. The details of these differences are set forth in Table 1 and summarized here. The AAP/ACMG recommendations established a strong presumption that, unless ameliorative interventions are available during childhood, children should not undergo testing for predispositions to adult-onset conditions and clinicians should generally decline to order testing. The recommendations did, however, allow for circumscribed exceptions to this presumption, and accorded decision-making discretion to the child's clinician and parents (and, if appropriate, the child, especially in adolescence). In the context of clinical sequencing, by contrast, the ACMG recommended which types of mutations laboratories should report to clinicians, with parents and clinicians given the choice only between sequencing plus reporting findings in 56 additional genes or forgoing sequencing

Table 1. Roles of Potential Decision Makers

Potential decision makers	AAP/ACMG pediatric genetic testing for adult onset disorders	ACMG ES/GS Results of additional analysis of genomic data
What is the scope of parental decision making?	Parents may ask clinician to test the child for a mutation known to exist in their family	With acceptance of ES/GS for the primary indication, parents accept analysis of the additional 56 genes
What is the role of the adolescent?	Greater presumption for testing if desired by both adolescent and parents	Not addressed
What is the scope of decision making for clinician?	Clinicians should decline to test children for adult-onset disorders unless preventive or therapeutic interventions are available during childhood. Testing after careful counseling may be permissible in unusual cases to relieve anxiety or permit life planning.	Clinicians working with families are responsible for contextualizing results or making referrals; "clinicians . . . have a fiduciary duty to prevent harm by warning patients and their families" about these findings.
What role do professional organizations play?	Set forth ethical guidance for decision making by parents and physicians, including strong presumption against genetic testing of minors for predisposition to adult-onset condition unless ameliorative interventions are available in childhood.	Define list of genes that must be analyzed by laboratories with pathogenic and predicted-to-be-pathogenic mutations returned to clinicians; provide ethical arguments for their recommendations.

altogether. According to the ACMG ES/GS statements, "The rationale for our recommendations was that **not** reporting a laboratory test result that conveys a near certainty of an adverse yet potentially preventable medical outcome would be unethical." (There is ongoing debate in the genomics community about whether all 56 of the conditions included in the ACMG's list reach this evidentiary standard, but that topic, which will require additional research to resolve, is beyond the scope of this article.) The ACMG stated that the child's clinician should "contextualize" the additional results, but also said that "clinicians and laboratory personnel have a fiduciary duty to prevent harm by warning patients and their families about certain [results of additional analysis of genomic data] and that this principle supersedes concerns about autonomy" (Green et al. 2013, 11). (Some readers may argue that the ACMG recommendations technically do not direct clinicians to disclose results to patients or parents, but rather, only recommend that laboratories report those results to clinicians, who then may then separately decide whether or not to report them to patients. However, once the results have been placed in a medical record, as will occur in many medical practices, it may realistically be difficult to prevent the patient or parent from seeing them, especially given the mandate of the Health Insurance Portability and Accountability Act (HIPAA) and the new requirements of meaningful use of electronic health records (EHRs), which gives patients a legal right to access to their own medical records. A full discussion of this issue, however, is also beyond the scope of this article.). Table 1 lays out in parallel the positions in the documents about the roles of various participants in decisions about testing.

In summary, our reading of the AAP/ACMG and ACMG ES/GS recommendations supports the conclusions that their ethical justifications differ and appear to be in tension with each other and that therefore the statements differ with regard to whose interests should be taken into account, how benefits and risks should be weighed, and the decision-making roles of clinicians and parents. Additional deliberation involving a broad range of stakeholders that carefully considers some of the issues identified here and the many nuances that they raise points to the need for additional research in this area. This research, over time, should lead to the development of ever more sophisticated, comprehensive, internally consistent, and ethically sound guidelines for genetic testing of children.

Language From ACMG Clarification regarding Incidental Findings

> We believe, however, that the disclosure of incidental findings such as a *BRCA1* gene mutation is justified for the following reasons: 1) If the child carries a pathogenic mutation there is a high probability that one parent does as well. Given that this is an incidental finding, it is fair to assume that the presence of this variant in the family has not been previously recognized based on clinical findings or family history. In this circumstance, and since only medically

actionable variants highly likely to be pathogenic would be reported, the child does benefit by potentially preventing a severe adverse health outcome in a parent. 2) The recommendation that children not be tested for an adult-onset disorder is typically invoked in circumstances where there is a known family history of risk, with the expectation that the child will be offered testing at an age when he or she can make an informed decision about testing. If there are no other clinical or family history indications, as might be the case for an incidental finding, that opportunity may not occur, potentially until the child is affected. 3) There is also some concern that the nurturing of the child might be adversely affected by the parent's knowledge of the child's future risk and the need to decide when to reveal that to the child. We believe, however, that the ability to identify a significant medical risk for the child that could avoid future morbidity takes precedence over this possible risk. ACMG affirms its recommendation not to perform diagnostic testing for an adult-onset condition in children, but believes that reporting an incidental finding of a severe, actionable, pathogenic mutation falls outside this recommendation.

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One co-author (L.S.F.R.) was the lead author of the joint American Academy of Pediatrics/American College of Medical Genetics and Genomics policy statement and technical report on the Ethical and Policy Issues in Genetic Testing and Screening of Children (AAP and ACMG 2013; Ross et al. 2013) and another co-author (L.G.B.) was a co-author of ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (Green et al. 2013).

Ellen Wright Clayton wrote the first draft of this article and made all revisions in response to comments and suggestions made by members of the Clinical Sequencing Exploratory Research (CSER) Consortium Pediatrics Working Group. She approved the final article as submitted.

Laurence B. McCullough, Leslie Biesecker, Steven Joffe, Lainie Friedman Ross, and Susan M. Wolf made substantial contributions to the article's analysis; they reviewed and revised it critically for important intellectual content, and they ultimately approved the final article as submitted. ■

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