Pediatric Professionals' Attitudes about Secondary Findings in Genomic Sequencing of Children

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Objectives To evaluate the attitudes of pediatric professionals towards the March 2013 statement of the American College of Medical Genetics and Genomics that whenever genomic sequencing is ordered, the laboratory must look for 56 genes known to be highly penetrant in high-risk groups, and these results must be reported to the clinician regardless of patient age or consent.

Study design E-mail and postal survey sent to 332 members of the American Academy of Pediatrics (AAP) Section on Bioethics (SOB) (n = 183), Section on Genetics and Birth Defects (n = 148), and 1 member of both groups regarding the mandatory search and reporting of secondary findings from genomic sequencing performed on children.

Results Of 332 potential participants, 12 asked to be excluded and 181 partially or completely responded (181/320, or 56.6%). Two were subsequently excluded (179). More than 80% believed that patients and parents (guardians) should have the right to refuse to be informed of secondary findings. Only 34.7% of AAP SOB members supported the American College of Medical Genetics and Genomics proposed mandatory search policy in contrast with 70.8% of Section of Genetics and Birth Defects members ($P < .01$). Approximately 30% of both groups thought that parents should not have access to information about adult-onset conditions in their children. AAP SOB members were less likely to support testing a child for parental benefit (34.5% vs 79.7%, $P < .01$).

Conclusions There is broad consensus that parents should have the right to opt out of receiving secondary findings. There is no consensus about the ethics of justifying disclosure on the basis of parental benefit. *(J Pediatr 2015;166:1276-82)*.

To address the rapid evolution of sequencing technologies and other genetic tests in the past few years, the American College of Medical Genetics and Genomics (ACMG) has put forth a number of policy statements and practice guidelines regarding sequencing.[1-4] The reporting back of "incidental findings" from clinical whole-exome sequencing (WES) and whole-genome sequencing (WGS) was presented at its annual meeting in March 2013. In this policy statement, the ACMG stated that whenever WGS or WES is ordered in the clinical setting, the laboratory must also look for 56 genes known to be highly penetrant in high-risk groups, and these results must be reported to the clinician. The ACMG recommendations "did not favor offering the patient a preference as to whether or not to receive the minimum list of incidental findings described," arguing that there is a "fiduciary duty to prevent harm by warning patients and their families about certain incidental findings and that this principle supersedes concerns about autonomy." By the time the report came out in print in July 2013,[2] controversy existed about its recommendations, with criticism focused on the mandatory search and reporting of 56 genes regardless of participant consent or age.[5-12]

An issue related to the controversy was whether the ACMG recommendations conflicted with its most recent update on the genetic testing and screening of children. One month before the annual meeting, in February 2013, the ACMG updated its policy on the genetic testing and screening of children in collaboration with the American Academy of Pediatrics (AAP), with the copublication of a policy statement and technical report in the journals *Pediatrics* and *Genetics in Medicine*, respectively, but did not address WGS/WES.[13,14] The joint AAP/ACMG statements asserted that genetic testing and screening should promote the child's best interest. In that vein, the statements recommended against predictive genetic testing of children for adult-onset conditions.[13,14]

In August 2013, the ACMG published a clarification to its March 2013 recommendations. The clarification asserted that disclosure of pathogenic mutations in adult-onset conditions was justified in pediatric samples for 2 reasons. First, it gave information not only relevant to the child proband but also possibly about

AAP	American Academy of Pediatrics
ACMG	American College of Medical Genetics and Genomics
SOB	Section on Bioethics
SOG	Section on Genetics and Birth Defects
WES	Whole-exome sequencing
WGS	Whole-genome sequencing

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a parent. In a family in which this risk may not have been previously suspected, this information benefits the child "by potentially preventing a severe adverse health outcome in a parent."[3] Second, the ACMG argued that the policy does not contradict the AAP/ACMG policy against predictive genetic testing of children because the AAP/ACMG joint policy focused on high-risk families where there are expectations that the child will be offered testing as an adult. In contrast, the ACMG policy focuses on the identification of mutations in families without a family history.[3] The ACMG acknowledged that this information may have adverse psychosocial implications but argued that "the ability to identify a significant medical risk for the child that could avoid future morbidity takes precedence over this possible risk." It asserted that this policy was "in the child's best interest."[3]

In December 2013, members of the Clinical Sequencing Exploratory Research Consortium Pediatrics Working Group published a comparative analysis of the ACMG report and clarification with the joint AAP/ACMG recommendations. The analysis revealed tension, if not outright conflict, between the 2 sets of recommendations with regard to predictive genetic testing of children for adult-onset conditions and about whose best interest—family's or child's—should be considered when genetic testing of a child is performed.[15]

In this study, we queried members of the AAP Section on Bioethics (SOB) and the AAP Section on Genetics and Birth Defects (SOG), the 2 AAP authoring committees of the joint statement, to examine their perspective of the new ACMG recommendations. Our hypotheses were: (1) that both the AAP SOB and the AAP SOG would object to the lack of consent requirement for the reporting of these 56 genes; but (2) that AAP SOG members would be more supportive of the mandatory search and reporting. After the study was completed, in April 2014, the ACMG modified its policy to allow for patients and their parents (surrogates) to opt-out of receiving information about the 56 genetic conditions when they or their child had clinical sequencing performed.[16]

Methods

Between January and March 2014, we contacted 332 members of the AAP SOB (n = 183), SOG (n = 148), and 1 member of both organizations to participate in a survey. Respondents were excluded if they did not reside or practice in the US or did not have an e-mail address.

Physicians were contacted a maximum of 4 times to complete the survey. The first, second, and fourth attempts were sent electronically through SurveyMonkey (http://www.surveymonkey.com). The third attempt was made via the US Postal Service and included a 2-dollar incentive.

The survey consisted of 10 attitudinal questions about sequencing and about the ACMG recommendations and 10 demographic questions. Several questions were stated in the negative to reduce bias in the tone of the survey. First, participants were asked which secondary findings should be offered to be returned to parents and whether there were some secondary findings to which parents should not have access. Participants also were asked what secondary findings they should be offered about their own child. Secondary findings were characterized into 4 groups: carrier status (X-linked and autosomal recessive), adult-onset cancer predispositions, adult-onset disease predispositions (noncancer), and disorders or conditions that present in childhood.

Participants were then asked to state the degree to which they disagreed or agreed with 6 ethical statements for or against the ACMG recommendations and 2 statements related to the mandatory search for secondary findings using a 4-point Likert scale (1 = strongly disagree; 2 = moderately disagree; 3 = moderately agree; 4 = strongly agree). Participants also were asked whether they support or oppose the practice of mandatory testing for 56 genes every time WGS/WES is performed and whether they thought reporting these results would be in a child's best interest.

Participants were also given a 4-point Likert scale to describe familiarity with the ACMG statement (1 = very familiar; 2 = moderately familiar; 3 = have heard about it, but have not actually read or discussed the statement; and 4 = not familiar). Participants were given a 5- point Likert scale to describe their frequency of ordering genetic tests excluding metabolic newborn screening (1 = frequently [daily]; 2 = often [at least 1 × per week]; 3 = sometimes [at least 1 × per month]; 4 = rarely [several times per year]; and 5 = almost never). Demographic data also were collected. Three free-response areas for comments were provided. The complete survey can be found in the **Figure** (available at www.jpeds.com).

Quantitative data were analyzed using SPSS 22.0 for Macintosh (IBM, Armonk, New York). Significance was set at $P < .05$. χ^2 analyses were performed, grouping strongly and moderately oppose (disagree) and strongly and moderately support (agree). For test ordering, the responses "frequently," "often," and "sometimes" were combined and compared with the responses "rarely" and "almost never." χ^2 analyses compared those who belonged to the AAP SOB vs the AAP SOG (excluding those who self-reported dual membership to both), those with and without children, by sex, and by age (<40 and ≥40 y). Mean age was compared with the independent-samples t test. Qualitative comments were coded for themes by both authors and consensus was reached in all cases. The University of Chicago Institutional Review Board exempted the research and waived the requirement for written informed consent.

Results

Of 332 potential respondents, 1 had previously opted out of SurveyMonkey surveys, 3 asked to be excluded by e-mail, 1 was found to be a nonphysician before giving a response, and 7 self-excluded by mail. Of 320 potential respondents, we received partial or complete responses from 181 (56.6%). Two surveys were excluded from analysis because they came from nonphysicians. Of the 179 valid survey responses, 101 respondents stated they were AAP SOB members, 74 were AAP SOG members, and 4 stated they were