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Ethical Issues in Pediatric Genetic Testing and Screening for Current Opinion in Pediatrics

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Abstract

Purpose of the Review—Developments in genetic test technologies enable a detailed analysis of the genomes of individuals across the range of human development from embryos to adults with increased precision and lower cost. These powerful technologies raise a number of ethical issues in pediatrics, primarily due to the frequent lack of clinical utility of genetic information, the generation of secondary results, and questions over the proper scope of parental authority for testing.

Recent Findings—Several professional organizations in the fields of genetics and pediatrics have published new guidance on the ethical, legal, and policy issues relevant to genetic testing in children. The roles of predictive testing for adult onset conditions, the management of secondary findings, and the role of informed consent for newborn screening remain controversial. However, research and experience are not demonstrating serious adverse psychosocial impacts from genetic testing and screening in children. The use of these technologies is expanding with the notion of personal utility of test results is considered sufficient to justify testing.

Summary—Use of microarray and genome sequencing technologies is expanding in the care of children. More deference to parental decision-making is evolving in contexts where information and counseling can be made readily available.

Keywords

genetic testing; genetic screening; pediatrics; predictive testing; newborn screening

Introduction

Advances in genetic technologies have yet to revolutionize the treatment of most children affected with genetic conditions.(**1) The primary fruits of genetic technologies to date include the expanding ability to screen and test embryos, fetuses, children, and adults using accurate and relatively inexpensive tools. The ethical issues in this context arise primarily from this gap between the ability to obtain extensive genetic information and the ability to offer definitive clinical interventions based on the knowledge gained. The purpose of this review is to address two ethical dimensions of genetic testing highlighted in recent literature

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Conflicts of Interest

None to report

and policy developments: the generation of large datasets with testing that confer benefits but also burdens of unwanted information, and the extent the which professionals should defer to parents and older children about whether to screen or test and whether to disclose secondary findings.

Debates over these issues are not new but professional standards are evolving. A joint statement was published in 2013 on the ethical and policy issues in genetic testing and screening in children by the American Academy of Pediatrics (AAP) and the American College of Medical Genetics (ACMG).(2,3) A statement by the American Society of Human Genetics on the ethical, legal, and psychosocial issues in genetic testing in children and adolescents was published in 2015 (**4), and in 2009 statement was issued by the European Society of Human Genetics on genetic testing in asymptomatic minors.(5,6)

Diagnostic Testing

Genetic tests targeting suspected DNA variants or chromosome abnormalities have been used for decades to evaluate children who have congenital abnormalities or who have symptoms suggestive of a heritable condition. In recent years, powerful new platforms have emerged to address circumstances when targeted testing fails to yield a diagnosis. Chromosome microarray analysis and whole exome or genome sequencing are being increasingly used in pediatric clinical care and biomedical research. (**4,7,8) These approaches to testing are examples of multiplex platforms, meaning that a single analysis will produce results on multiple targets. The volume of data produced in testing yields a high sensitivity to detect causative variants, but a price of secondary or uncertain results that also must be managed. A relatively common indication for whole exome sequencing is the child with undiagnosed developmental delay. Recent literature suggests that a genetic explanation can be identified in about 30% or more of such children using tests like genetic microarrays. (9)

While there certainly has been progress in the care of affected children, for the most part, better knowledge of genetic underpinnings of disease has only rarely led directly to targeted therapies. (The CRISPER-Cas9 technology offers exciting possibilities for new therapies when gene replacement in cells or tissues might be effective, although this work has yet to reach clinical trials.(*10)) The ethical issues arising in diagnostic testing are due to two elements: the lack of clinical utility for the identification of a genetic variant associated with the condition, and the possibilities of secondary findings and variants of unknown significance with the use of multiplex testing platforms. A well-established set of criteria for assessing the value of clinical tests includes the notion of clinical utility.(11) In recent years, the notion of “personal utility” has gained traction.(**12) This concept acknowledges the fact that patients and families can benefit from test results in a variety of ways other than clinical interventions. The ethical issue at the policy level is whether tests should be introduced into clinical use if they have potential personal utility but little clinical utility (assuming the test also has analytic validity and clinical validity).

The value of identifying a genetic “explanation” for a condition has been shown to be important for parents beyond clinical responses or reproductive planning, both because

knowing a cause seems intrinsically important and because many parents need to feel they have explored every avenue for information.(*13) Early-stage research also suggests that parents learn to cope with results of uncertain significance.(*14) More research in this domain needs to be done but, to date, the data and experience suggest that parents receive benefits in the absence of clinical responses and without serious risks. However, a move away from clinical utility to personal utility could greatly expand the number of tests that might be considered indicated in various circumstances. All of the professional statements emphasize the importance of carefully counseling parents about the complexities and limitations of genetic testing using these tools.(**4)

Secondary Findings

The disadvantage of multiplex platforms is that results of uncertain significance are generated and incidental findings arise that may have clinical significance. The question of how to manage secondary findings has been one of the most hotly debated topics in genetics in recent years. In 2013, the ACMG published recommendations for clinical medicine that suggested that when genome scale sequencing is used, regardless of the indication, a set of 56 variants known to be associated with significant and medically-actionable conditions should be routinely assessed and reported by the laboratory.(15) As examples, variants including BRCA1 for adult-onset breast and ovarian cancer and Long QT syndrome are on the list. The ACMG suggested that these variants should be assessed whether or not the patient (or parents of a child) consented to such testing beforehand. Further, they suggested that secondary findings regarding adult onset conditions should be reported to the parents of children.

A recent analysis of sequence data from 6503 unselected individuals indicated that if the ACMG list is used, 0.7% of European ancestry individuals and 0.5% of African ancestry individuals would have returnable results.(16) This group analyzed a larger set of 112 medically actionable genes and found returnable findings in 2.0% of individuals of European ancestry and 1.1% in those with African ancestry. So actionable secondary findings are uncommon but not rare. Therefore clinicians must be prepared to manage this information when microarray or sequencing is considered.

This set of recommendations by the ACMG proved to be contentious, both because informed consent was not required for secondary results and because, for children, the disclosure of results for adult onset conditions seemed contrary to long-standing tradition of allowing children to decide for themselves about genetic testing when they became adults. (17) However, there are important differences between disclosing a secondary finding in a child and choosing to test a child for an adult-onset condition in a known high-risk family. In the former, if a child is found to have on sequencing a BRCA1 mutation, his or her family members may not be aware of a BRCA1 mutation in the family. In this case, failure to disclose the child’s results will prevent other family members from obtaining testing and pursuing preventive or early detection measures. This situation is distinctly different from a decision to test a child for BRCA1 when others in the family are already aware of the genetic risk in the family. The 2015 ASHG report made several recommendations in this context. They suggested that, when possible, testing should be targeted as much as possible,

based on the clinical context, in order to reduce the possibility of secondary findings.(**4) This includes the possibility of a targeted or selected analysis of sequence data. Disclosure of secondary findings for adult onset conditions is appropriate but parents should be informed and provide consent for disclosure. One exception is when a secondary finding has urgent and serious implications for the child's health, at which point the ASHG recommends that results should be disclosed to parents regardless of their previously stated wishes regarding disclosure.

Predictive Testing for Adult Onset Conditions

In the 1990's, many of the major professional societies for genetics and pediatrics took a firm stand against predictive genetic testing in children for adult onset conditions when there is no clinical action to be taken in childhood.(5) The justification was several-fold. First, the pros and cons are complex and children cannot make autonomous decisions. It is relevant that many adults who are at risk for a heritable condition choose not to be tested.(18) Second, we are uncertain about the psychological and social implications of knowing about risk status at a young age. Might children be psychologically harmed by stigma, discrimination, or changes in body image by family awareness of increased risk status for a child? The prevailing opinion held, therefore, that children and clinicians should wait until the child reaches adulthood to make a decision about testing.

While a robust literature is lacking, studies to date suggest that most children and families manage this type of predictive information without significant adverse impacts.(19) We must also acknowledge that uncertainty about an individual's risk status can be quite burdensome for some adolescents and families and, of course, many individuals tested will be found not to be at increased risk. In addition, there is growing support for the ability of parents to make thoughtful and appropriate decisions for their child in these types of circumstances.(3, **4) The emerging position is one of greater flexibility, illustrated by the recent professional statements that demonstrate a softening of the stance on this issue. In the situation where parents and an informed adolescent are requesting testing and adequate counseling has been performed, testing may be appropriate and consistent with the child's best interest. Predictive testing of young children for adult onset conditions is still discouraged. This stance also indicates that such testing in a research context can be ethically justifiable, which will enhance our knowledge of when predictive testing in children is most appropriate.

Parental Decision-Making about Newborn Screening

Newborn screening is conducted by state-based programs in all states. Targets of bloodspot screening include metabolic, endocrine, genetic, and infectious diseases for which early detection will improve outcomes in comparison to the clinical diagnosis of symptomatic children. Other screening modalities include hearing screening and pulse oxymetry screening for critical cyanotic congenital heart disease. Newborn screening (NBS) is considered one of the most effective public health programs of the 20th and 21st centuries.

Two ethical issues are part of the national dialogue about NBS in recent years. There are long-standing debates over whether such screening should be conducted as part of

"mandatory" public health programs or whether the informed consent of parents is appropriate. Second, the debate over parental permission had a major impact on NBS in 2015 with the passage of federal legislation requiring permission for the retention and research use of residual NBS bloodspots.

Newborn screening programs are a little over 50 years old and the question of whether these programs should be mandatory or voluntary emerged in the early years of these programs. The first condition targeted by NBS was PKU (phenylketonuria) and the notion was that the benefits of NBS are so dramatic for this condition that parents need not provide permission for screening. Most states permit parents to opt-out of screening, but very few parents are adequately informed about this option so only a tiny fraction of parents choose to opt-out of these programs. In the 1990's, the Institutes of Medicine published a report on newborn screening that supported informed consent from parents for screening.(20) The AAP in 2000 recommended additional research to determine the feasibility of consent in this context.(21) These opinions and others had little impact on public policy with virtually every state continuing to screen without parental consent. In fact, Maryland, that for many years was one of the few states to require written consent for newborn screening, changed their policy recently to a mandatory screen with the ability of parents to opt-out. Two excellent articles have been published recently with contrasting opinions on the ethical issues in parental consent for newborn screening.(**22, **23)

From the perspective of professional organizations, the AAP/ACMG recommendations from 2013 supports parental permission for screening, although they stopped short of recommending use of a signed consent form as documentation.(2) The ASHG statement supports the continued use of the "opt-out" approach for screening, albeit with improved parental education so that parents are more aware of screening and their prerogatives.(**4) The ASHG justification is primarily that a consent process in the hectic and short post-partum period is unlikely to be meaningful and the failure to obtain or document consent due to practical challenges for staff could negatively impact these valuable programs. One alternative approach under recent discussion is the implementation of a two-tiered system whereby tests are mandated for conditions for which substantial benefits are clear, but consent is obtained for tests of less certain clinical utility.(*24)

The management by state programs of residual newborn screening bloodspots has been highly controversial for several years. Many states retain bloodspots after clinical testing is complete for several purposes including quality improvement, forensic purposes, and biomedical research. These bloodspots are valuable because they represent they entire newborn population of a state and research can be performed with these spots including genetic analysis, detection of infectious agents, and detection of potential environmental toxins. However, because parental permission is not obtained for clinical screening, retention and research uses of residual bloodspots traditionally was conducted without parental knowledge or permission. Such research uses are consistent with the federal regulations governing human subjects research if the bloodspots are de-identified to the investigator.

Two state programs were sued by parent groups in 2009, Minnesota and Texas, due to the lack of consent.(*25). The controversy led to federal Congressional action in 2014 when a

section was added to the Newborn Screening Saves Lives Act of 2014 that requires parental permission for the use of residual newborn screening bloodspots.(26) This law went into effect in 2015 and covers all federally funded research using newborn screening bloodspots. Such a requirement is consistent with the wishes of the majority of the general public.(27) However, the lack of a pre-existing consent infrastructure in this context has meant that valuable research using these resources has been suspended across the country. The ethical conflict between the value we place on parental authority and the value we place on research for children and families will be challenging to resolve.

Conclusions

Genetic testing using powerful tools such as microarray and whole exome sequencing are emerging into pediatric clinical care despite limited clinical utility and a burden of secondary findings and uncertain results. Research to date suggests that parents identify personal utility in test results and are not unduly burdened by uncertain results. Clinicians must be prepared to counsel parents about the range of results anticipated with use of these test platforms. In the context of newborn screening, public demands for more knowledge and choice, primarily over the management of residual bloodspots, has highlighted a long-standing conflict between our traditional respect for parental authority and the need to conduct screening programs through efficient and effective means.

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Key Points

- Genetic testing using multiplex platforms is becoming more widely used in pediatric clinical care
- Genetic testing often yields results of limited clinical utility but of meaningful personal utility to parents
- Secondary findings and uncertain results from sequencing and microarray testing are challenging to manage and support the need for careful pre-test counseling
- Screening approaches create barriers to effective parent education and choice that must be addressed in the near future