From Genetics to Genomics: Ethics, Policy, and Parental Decision-making

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Objective Ethical evaluation of genetic testing in children is traditionally based on balancing clinical benefits and risks. However, this focus can be inconsistent with the general practice of respecting parental decision-making about their children’s health care. We argue that respect for parental decision-making should play a larger role in shaping pediatric genetic testing practices, and play a similar role regarding decisions to use emerging genomic technologies. Methods Genomic testing involves the examination of thousands of DNA markers spanning genes throughout the genome and their interrelationships, yielding virtually limitless interpretations. We presume that parents and providers should proceed cautiously in applying genomic testing in children, as we explore how genomic testing will stress the fault lines of the traditional ethical analysis. Results Empirical data about the psychosocial risks and benefits of genetic testing of children do not reveal serious harms, yet virtually no such data exist yet about genomic testing. Unless empirical social and behavioral data indicate that genomic testing is highly likely to cause serious harms to the children, parental decisions to obtain comprehensive genomic testing in their children should be respected. Once comprehensive genomic testing of children becomes routine, resultant information may be more easily integrated by families than anticipated. Conclusions Research on the social and behavioral impact of comprehensive genomic testing on children and their families is needed to further inform parents, clinicians, and policy makers.

Key words children; clinical utility; decision-making; ethics; genetic testing; genomics; parents; pediatrics; policy.

Introduction

A genetic test provides information about a specific genetic condition, whereas genomics testing involves thousands of DNA markers, spanning genes throughout the genome and their interrelationships, which will yield virtually limitless interpretations (Guttmacher & Collins, 2002). While “whole-genome sequencing” is not yet commercially feasible (Service, 2006), genetic tests have been available over the Internet for greater than 5 years (Gollust, Wilfond, & Hull, 2003) and, currently, websites such as DNA Direct, NavigenicsTM, 23andMe, and deCODEme (Foster & Sharp, 2008), offer an expanding menu of tests for a wide range of medical conditions and/or predictions of future health risks. Despite ongoing debate about whether such services should be regulated or restricted based on evidence of benefits and risks (Burke & Psaty, 2007), we can anticipate further expansion of commercial availability (Javitt, Stanley, & Hudson, 2004) as the platform technologies for conducting genomic analyses evolve and additional genetic epidemiology data are generated that facilitate interpretation. In this article, we examine moral issues regarding whether to permit a broader range of genetic testing in children, including whether to permit whole-scale genomic sequencing.

The ethical evaluation of genetic testing in children is traditionally based on the balance of clinical benefits and risks (American Society of Human Genetics Board of Directors and the American College of Medical Genetics...
Board of Directors, 1995; Andrews, Fullerton, Holtzman, & Motolsky, 1994; Clarke, 1994; Wertz, Fanos, & Reilly, 1994). In the early 1990s, when there were only scant data about children who had received genetic tests results, the presumption was to give greater weight to the potential risks and to restrict testing. However, this criterion is not necessarily consistent with the general practice of respecting broad parental discretion in health care decision-making for and on behalf of their children. In general, parents are the presumed decision makers for their children and their decisions are respected unless they are abusive or neglectful (Buchanan & Brock, 1989; Goldstein, Freud, & Solnit, 1979; Ross, 1998). The tension between assessments of benefits and risks made by health care providers and policy makers, and the procedural respect owed to parental authority will be clearly tested as the ability to conduct and interpret whole-genome sequencing and related technologies gain in momentum.

What limits should be imposed, if any, need to be determined prior to commercial feasibility. In this article, we consider how genetic testing decisions for children have been made traditionally and how the anticipation of comprehensive genomic testing in the near future will stress the fault lines of traditional approaches. The potential for comprehensive genomic testing in children could shift the equilibrium towards expanding or reducing parental discretion, and forces us to reexamine the evidence for our genetic testing policies and practices. We will highlight specific domains where further empirical social and behavioral research is necessary to inform policy and practice.

**Traditional Approaches to Parental Decision-making for Pediatric Genetic Testing**

Although parents generally have health care decision-making authority for their children, decision making about genetic testing in children has been limited by both requirements and restrictions. At one end, there is universal mandatory screening of newborns for a number of rare conditions. Newborn screening (NBS), the most common clinical application of genetic testing in any population, often occurs without parents’ awareness and, in some cases, over their objections (Tarini, 2007). At the other end, testing of young children in high risk families for adult onset conditions or for carrier status is rarely performed because policy statements by numerous professional organizations strongly discourage providers from performing genetic testing in children (American Society of Human Genetics Board of Directors and the American College of Medical Genetics Board of Directors, 1995; Clarke, 1994; Nelson et al., 2001).

These apparently contrasting approaches are linked by an underlying normative claim that the primary justification for genetic testing in children, as with virtually all pediatric intervention, should be the presence of a medical benefit to the child that outweighs the risks. The greater the likelihood and proximity of a medical benefit to the child, the greater the justification for testing, particularly when the risks are low. NBS for phenylketonuria (PKU) is a good example. PKU is a pediatric genetic disorder in which a key metabolic enzyme is lacking and could lead to mental retardation if left untreated. NBS for PKU allows early diagnosis and dietary manipulation and confers preventive benefit. This benefit heavily outweighs the risks caused by false positives and the need for women to refrain from breastfeeding, leading some child advocates, policy makers, and health care professionals to support mandatory testing (Faden, Holtzman, & Chwalow, 1982). As direct medical benefit to the child decreases or becomes more distant, some providers, child advocates, and policy makers argue for restrictions on the grounds that the information is clinically unnecessary, even if desired for non-medical planning purposes. For example, most genetic professionals will not offer, let alone recommend, genetic testing for hereditary breast-ovarian cancer (BRCA cancer gene testing) in a minor-age child because such testing predicts risk for an adult onset condition for which there are no interventions that need to begin in childhood (Borry, Goffin, Nys, & Dierickx, 2008; Duncan, Savulescu, Gillam, Williamson, & Delatycki, 2005).

A child’s right to an open future is the second normative claim used to justify both compulsory NBS and the refusal to test for adult onset conditions (Davis, 1997; Feinberg, 1992; Laberge & Knoppers, 1991). This claim holds that parents have an obligation not to make decisions on behalf of their child that irrevocably limit their child’s future. If a parent refuses NBS and the child has PKU, the resulting mental retardation will have a very significant adverse impact on the child’s life opportunities. In contrast, if a parent tests a young daughter for a BRCA gene mutation, the child is denied the opportunity to decide for herself whether or not to obtain the information as an adult. Since there is variability in the uptake (ranging from 25% to 95% in at-risk adults; Ropka, Wenzel, Phillips, Siadaty, & Philbrick, 2006), parental testing of their child forecloses the child’s choice whether to seek out this information. However, at some point, parents may choose to disclose to the child that the parent carries a BRCA mutation, and thereby the child learns that he or
she is “at-risk.” While this may be necessary for the child to make a decision about testing as a young adult, the disclosure of familial risk itself forecloses a future where a testing decision would not be necessary.

Both the claims of “timely medical benefit” and “open future” can be inconsistent with the standard approach to parental authority and responsibility for their children. There are many medical treatments that have a high benefit-to-risk ratio (e.g., penicillin for strep throat; controller inhalers for asthma) and yet neither diagnosis nor treatment is mandatory. While a diagnosis of PKU clearly benefits the child, the likelihood of harm from a decision to forgo NBS is quite small. In fact, NBS is more likely to result in a false positive result and create undue (albeit temporary) anxiety than a clinical diagnosis (Tarini, Christakis, & Welch, 2006).

Likewise, the prohibitions of predictive genetic testing and carrier testing can be inconsistent with the standard approach to parental authority, particularly when the benefits and harms are contested or based on values and preferences. The psychosocial risks of genetic testing including stress, anxiety, and social stigmatization are often ambiguous and subjective. Whether a child’s knowledge of their risk status for an adult onset condition is worse than the child knowing their family history of risk and not knowing their own risk status is debatable. There is some evidence suggesting that children may be better able to incorporate genetic risk status into their self-identities and self-concepts than do adults (Duncan et al., 2008). In fact, other data support the position that the benefits of certainty outweigh the harms of ambiguity, even when a genetic test result is positive and confirms risk or diagnosis (McConkie-Rosell, Spiridiglozi, Melvin, Dawson, & Lachiewicz, 2008). Additional studies find that children raised in high risk families often know that they face increased genetic risk. For these children, the future is not open and, in fact, they might believe they carry predisposing disease genes even when they do not (Fanos, Davis, & Puck, 2001; Fanos & Johnson, 1995). In this setting, genetic testing may “open their future,” or relieve the distress of uncertainty. These studies suggest that some of the predictions of adverse consequences of predictive genetic testing for late-onset diseases are overstated, and that testing may be more beneficial than previously anticipated. However, more research in this area is needed to better understand these issues.

There is also a more fundamental criticism towards these normative claims against pediatric genetic testing. Both deviate from the moral position that parents should have the authority to decide which medical interventions are appropriate for their children (McConkie-Rosell & Spiridiglozi, 2004; Pelias, 2006; Rhodes, 2006; Robertson & Savulescu, 2001). It is not necessary to argue that parental authority is limitless or unconstrained for this consideration to gain moral traction; it is only necessary to show that genetic testing is consistent with the types of health care decisions that typically belong to parents (Ross, 1998). Further, respecting parental authority does not imply that providers should refrain from making explicit directive recommendations to parents about health care decisions.

Consider that 47 states in the US have mandatory NBS, which is “justified” because of the significant benefits and minimal risks. The lack of respect for parental decision-making is perplexing when one realizes that when parental permission is sought, refusals are quite rare (Faden, Chwalow, Holtzman, & Horn, 1982), even when the tests are considered “experimental” (Atkinson et al., 2001). Moreover, parents are not mandated to read to their children, although there are no risks and the benefits of literacy are significant and correlate with academic success and improved health metrics (Paasche-Orlow & Wolf, 2007). Parental discretion is also permitted when the risks of harms are much more significant than forgoing NBS. For example, parents are permitted to teach their children to ski and to play football (Caine, Caine, & Maffulli, 2006; Meyers, Laurent, Higgins, & Skelly, 2007).

There is also an inconsistency between the restrictions regarding genetic testing of children and the policies permitting prenatal testing for these same conditions. Although parents are discouraged from testing their young children for adult onset conditions, pregnant women are allowed to test their fetus, and providers may be reluctant to discourage them from doing so out of respect for reproductive freedom. In the prenatal context, providers are traditionally “nondirective” and “offer options,” rather than explicitly recommending which tests to undergo, or what actions to take based on the results. Consider, then, an expectant couple who seeks prenatal testing for Huntington disease (HD; an autosomal dominant cause of early-onset dementia) because one partner carries the gene associated with HD. Although it was historically assumed that parents would test a fetus for a condition like HD and then terminate an affected pregnancy (International Huntington Association [IHA] and the World Federation of Neurology [WFN] Research Group on Huntington’s Chorea, 1994), a small number of parents do not terminate at-risk fetuses (Simpson et al., 2002). In light of current pediatric practice that proscribes testing of children,
prenatal testing is the only option for parents who really want to know if their child has inherited the risk for HD, even though the medical risks of amniocentesis are greater (and therefore less desirable) than collecting a blood sample from a small child.

The practice of proscribing carrier testing of children is also contradicted by current mandatory NBS strategies that obtain carrier information even when the parents do not seek it. For example, NBS for sickle cell disease identifies all carriers, and depending on methodology, NBS for cystic fibrosis identifies a subset of carriers. Although policy statements by professional organizations recommend not offering carrier testing in childhood, there is a consensus to disclose to the family (on behalf of the child) when the information is obtained incidentally (Andrews et al., 1994). Thus, while parents cannot request carrier testing of their children, they may be required to learn about the carrier status of their child that was obtained in mandatory NBS (Lewis, Curnow, Ross, & Massie, 2006).

While these criticisms of both “compelled” NBS and “restricted” testing of young children for adult onset disorders have not yet resulted in significant changes in clinical guidelines or public health practices, the debate about parental discretion will intensify as comprehensive genomic testing becomes more economically accessible. As professional organizations develop policy statements related to comprehensive genomic testing in children, they should first reconsider their current policies and practices related to genetic testing of children based on available empirical data. These data do not show significant harms caused by predictive testing for adult onset conditions in childhood (Duncan & Delatycki, 2006). The application of policies to clinical practice recommendations, based on considerations of “timely medical benefit” and the “open future,” should be influenced by these empirical data and permit greater parental discretion. The empirical data to date also suggest that where incomplete data about benefits and risks persist, policies should be revised to be more deferential to parental authority. While the data, and in some cases, the lack of data, may direct clinicians towards an explicit directive recommendation for or against testing, parents should generally be given final decision-making authority.

Ethical Considerations in Developing Policy for “Comprehensive” Genomic Testing

In the near future, genomic testing is likely to become more accessible and will provide both information about the risks of common conditions such as heart disease, diabetes, and hypertension as well as predictions about individual responses to specific pharmaceuticals and other medical therapies (Aspinall & Hamermesh, 2007). Over time, the number and range of conditions for which such testing is available is likely to expand to include more behavioral traits, ranging from information about anxiety and depression, to attention and addiction (Rothstein, 2005).

As these new technologies and approaches emerge and become commercially feasible, the clinical and policy decisions about when they should be made more widely available and how they should be regulated will be based, to some extent, on the evidence of clinical validity and clinical utility (Burke et al., 2002). While clinical validity and utility have traditionally been the primary criteria for genetic testing policies, the evaluations by researchers and policy makers may differ greatly, and professionals may interpret the clinical value of a genetic test quite differently from the general public or from members of at risk families (Ravitsky & Wilfond, 2006). Even when there is agreement that the clinical validity and utility of a test is limited, some argue that any personal meaning that the information conveys to individuals should be sufficient to justify allowing them access to the information (Shalowitz & Miller, 2005).

The health-related information about a person that will become available from comprehensive genomic testing may potentially influence an individual’s clinical and personal decisions, and these decisions may improve his or her health and quality of life. Alternatively, the health-related information may be misunderstood and misinterpreted and could lead to adverse clinical or personal decisions. The balancing of potential risks and benefits has been the mainstay in decision making about new genetic tests, and highlights the importance of adequate education and counseling of patients and the public at large about the benefits and limitations of genetic tests (Andrews et al., 1994; Wilfond & Nolan, 1993).

Comprehensive genomic testing will increase the scope of potential information beyond health to include information about behaviors and other genetically influenced traits including predictions about ancestry, weight gain, sports performance, musical talent, and aging (Goddard et al., 2007; Janssens et al., 2008). Information about these genetically influenced traits may be requested because they have personal meaning related to identity or lifestyle choices, or they may be requested out of simple curiosity. Some such genetic tests are already commercially available.
When considering a competent adult’s decision to seek out nonclinically relevant genetic information, it may be comparable to the decision to undergo psychological testing and counseling, or even astrological guidance, to both predict and plan for the future. Although the validity and utility of each service varies, all such services are permissible under the proviso of *caveat emptor*. In fact, it is likely that the initial quality of comprehensive genomic information will be modest at best because of limited genotype–phenotype correlations (Khoury, Little, Higgins, Ioannidis, & Gwinn, 2007). This may frustrate health care providers who would prefer that the information not be available until clinical utility and validity are achieved. We encourage health care professionals to develop means to share the ambiguity and impreciseness of the information because the commercial availability of new genomic tests is not likely to be limited by regulatory bodies, such as the U.S. Food and Drug Administration (Lesko & Woodcock, 2004). The rise and fall of whole body CT scans in shopping malls suggests that providers and the public can make assessments of value (Burger, Kass, Sunshine, & Siegelman, 2008).

The availability of comprehensive genomic testing will also change the impact of genetic information for individuals and their families (Foster & Sharp, 2008). Concerns about disclosure of “incidental” genetic information (Kohane, Masys, & Altman, 2006) by providers to individuals or sharing genetic information between family members (Offit, Groeger, Turner, Wadsworth, & Weiser, 2004) may be attenuated when each person has potential access to “all” the information contained in his or her genomic sequence. Anyone who desires his or her “own” information will not need to rely on a provider or family member to disclose the information, as is currently the case. Alternatively, intra-familial disclosure may become more necessary because of the need to correlate phenotypes and genotypes both to improve the personal predictions of one’s own health status and to improve the predictive value of testing more generally.

Empirical data about adults who undergo comprehensive genomic testing should be collected to understand the level of interest in such tests, the level of recipient understanding regarding the genetic data it provides, how the information impacts their lives at different stages of the lifecycle, and what impact the information has on different relationships. These are complex areas of inquiry that will require the input of researchers, clinicians, and scholars from many different disciplines, including the social and behavioral sciences.

**Ethical Considerations for Comprehensive Genomic Testing in Children**

Once testing an individual’s entire genome becomes feasible, interest in using this technology with children can be anticipated. There are already proposals, based primarily on technical feasibility and potential public interest, for expanding NBS to include conditions for which early and effective treatments are not yet available (Alexander & van Dyck, 2006). Health-related information from comprehensive genomic testing in children raises the same concerns about clinical benefits and risks that have been associated with “traditional” genetic testing. However, the range of health information will be much broader and will include information about adult onset conditions and carrier status. The concerns about how parents will use this information and how it will impact children’s self-identity, self-concept, social and behavioral functioning, and lifestyle choices need to be empirically studied. Child health psychologists, in particular, have much to contribute to this process in light of their background and training in child development, clinical assessment, and the relationship between health and behavior.

Likewise, information about behavioral and other personal traits raises ethical, social, and psychosocial concerns. There are legitimate questions about how parents may use the latter information, and how such “predictions” may become “self-fulfilling prophecies.” And yet, parental hopes and fears already influence how parents raise their children and what their children achieve and aspire towards. Parents currently have the prerogative to test their child’s intelligence and academic achievement and to make educational decisions based on the data. They can obtain radiographs of bones to predict their child’s adult height and seek out therapies to alter the predicted height (Allen, 2006; Ross, 2007). Parents can also have their children assessed for a range of social and behavioral disorders, and seek out treatment to better their children’s functioning. To reiterate, parents have (and should have) broad discretion in childrearing practices and their decisions generally should not be proscribed unless their actions are abusive or neglectful.

To the extent that “personal meaning” gains wider acceptance as a legitimate criterion for expanding the availability of new tests and applications of genomic technology, the current policies and practices of restricting some genetic testing of children and mandating other tests will need to be reevaluated. There will be some parents who will find the information that becomes available through new technologies and data useful in shaping their parenting practices, while others will be more skeptical of
their value. These disparate parental judgments may be independent of professional assessments of clinical validity and utility. Extrapolating from the empirical data about predictive genetic testing of children in at-risk families discussed earlier, we speculate that once comprehensive genomic testing of children becomes routine, the information may be more easily integrated by families than might be predicted.

This is not meant to imply that whatever information parents want about their children should be provided carte blanche. Clearly, education and counseling will be crucial to ensure that families understand the limitations of the information. However, restrictions and mandates should be based on a criterion of risk of serious harm (Diekema, 2004). Given the lack of data confirming harm and the related data that indicate children may fare better than anticipated, such restrictions and mandates cannot be justified. Policies and practices will also need to clarify the role of the older adolescent in the decision-making process, although the issues related to balancing and assessing parental and adolescent interests and preferences goes beyond the focus of this article.

This is also not meant to ignore the professional and moral obligation to educate parents and to help parents make good decisions on behalf of their children. It is morally appropriate for providers to strongly recommend particular tests in infancy and young childhood (i.e., PKU testing), and to strongly discourage other tests (e.g., ApoE testing of children for adult onset Alzheimer disease and heart disease because ApoE is not predictive but only provides an increased relative risk and has limited sensitivity and specificity) (Roberts, Cupples, Relkin, Whitehouse, & Green, 2005). Selective and directive recommendations are a routine aspect of pediatric practice. However, it will become increasingly important for professional organizations to begin to reconcile their support for mandatory genetic testing for some conditions and their support for restrictions for other conditions with the broad discretion that parents have and need in the health care arena in order to promote their children’s well-being.

A restrictive approach also might not be realistic in the near future as new genomic technologies are likely to be implemented in children out of clinical experience. Eventually, it may be less expensive and more efficient to perform whole-genome testing than to obtain particular genetic information at various decision points. For example, improved pharmacological dosing based on patient genotype for metabolizing certain drugs is already available (de Leon, Susce, & Murray-Carmichael, 2006). As individualized pharmacological dosing becomes available for more pharmaceuticals, it may be less expensive to “run the whole genome” and store the genomic information for retrieval at a later point in time when clinical practice demands it, rather than to sequence particular genes in acute situations (Robertson, 2003). Once comprehensive genomic testing is performed, genetic information beyond a specific clinical question becomes available for review later on.

Given the lack of accuracy in genotypic–phenotypic correlations, the current interpretations provided to parents about the additional genetic information that is knowable from comprehensive genomic testing may be no more useful than the knowledge that can be gleaned from a self-constructed family history (Yoon, Scheuner, & Khoury, 2003), though this is apt to change as our genomic understanding grows. The accrual of genotype–phenotype correlations will require extensive knowledge about environment, diet, and social stresses and how these factors influence genetic expression. It will also require greater understanding of gene–gene interactions. The National Children’s Study is one research program aimed at providing such correlations (Sapienza, Corbie-Smith, Keim, & Fleischman, 2007). The National Children’s Study is designed to examine the effects of environmental influences on the health and development of more than 100,000 children across the US, following them from before birth until age 21. It is designed to help us distinguish the impact of genomic information from the broad range of social, environmental, cultural, and economic influences on child development. Such research will be critical for the effective and valid interpretation of comprehensive genomic data. The complex ethical issues raised by longitudinal genomic research on children are significant (Wilfond, 2007).

Conclusion

While it is important to acknowledge potential harms when developing policy, one of the lessons of our recent genetic testing social history is that it has been neither the “best of times, nor the worst of times.” To date, the positive impact on population-based clinical practice has been less than imagined, but many concerns about adverse side-effects have also turned out to be overstated. Respect for parental decision-making implies that the primary justification to restrict parents from obtaining genomic data would be that the harms clearly outweigh the benefits. Given that such data are lacking, the presumption should be to respect parental discretion. Parents will need advice and guidance about the potential benefits and limitations of
such information, and health care providers should be proactive about engaging parents in these discussions.

The increasing availability of comprehensive genomic testing may influence the public and parents’ world views about the relationship between genomic information and life expectations in ways that we cannot easily predict. As we move from single gene diagnostic testing to predictive and comprehensive genomic testing in the pediatric setting, it is important to collect social and behavioral science data about the extent to which parents are interested in genomic information that is not directly related to specific clinical decisions. It will also be important to evaluate how parents use the broader expanse of genetic information, whether they communicate this information to their children, how children respond to the information, and the short- and long-term impact of such testing and knowledge on children and their families.

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