Commentary: Children and Predictive Genomic Testing: Disease Prevention, Research Protection, and Our Future

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Genetic testing offered by direct-to-consumer companies—herein referred to as “predictive genomic testing”—has come under federal scrutiny. Critics claim testing yields uninterpretable and potentially harmful information. Supporters assert individuals have a right to this information, which could catalyze preventive health actions. Despite contentions that predictive genomic testing is a tool of primary disease prevention, little discussion has focused on its use with children. This partly stems from concerns expressed in existing professional guidelines about the potential for psychological and behavioral harm to children engendered by predictive genetic tests for Mendelian diseases. Conducting research to understand the actual benefits and harms is important for policy development and practice guidance and can be ethically justified within the pediatric regulatory framework of research that offers a prospect of direct benefit. Child health psychologists are well poised to contribute to this research effort, and promote the translation of genomic discoveries to improve pediatric medicine.

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such testing lies in its ability to offer at-risk individuals the opportunity to be proactive in reducing their chance of developing disease—a guiding principle of pediatric medicine. Indeed, a majority of the behavioral risk factors for common diseases (e.g., cigarette smoking, diet/nutrition, and physical activity) originate and become established in childhood and adolescence, and often track into adulthood (Tercyak & Tyc, 2006). Therefore, it is critical that any clinical and public health genomics research agenda focusing on the future of predictive genomic testing pay careful attention to children and adolescents—specifically, the opportunities and challenges inherent in building a robust evidence base supporting or refuting the use of these tests with young people, their parents, and families.

Planning for and conducting this type of research requires special consideration of the ethical issues that will inevitably be encountered along the way (Burke & Diekema, 2006; Wade, Wilfond, & McBride, 2010; Wilfond & Ross, 2009). This includes but is not limited to: securing permission from parents and assent from children for participation in genomic research, managing the privacy of genomic test results of adolescent research participants from their parents, minimizing adverse psychological impacts of participation in genetic research, and providing access to effective post-test interventions that may improve children’s and adolescents’ health. The objective of this article is to make the case for the scientific significance and ethical justification for including children in research about the clinical and behavioral impact of genomics tests, thereby encouraging federal agencies to fund such research, professional organizations to support such research, and pediatric psychologists to engage in such research.

The Landscape of Predictive Genomic Testing

Without ever visiting a physician, individuals can now find out whether their genetic code places them at increased risk for developing common chronic diseases. This is a significant change from the 1960s to 1990s, when the primary uses of population-based genetic testing were identifying newborns with rare inherited conditions and adults at risk of bearing children with rare conditions. In both of these scenarios, extensive genetic counseling and physician oversight were involved. Today, it is the confluence of two developments that have created our current landscape of genetic testing (Tercyak, 2009a).

The first development is the expansion to predictive genetic testing, which offers adults tests to assess their risk of developing a disease at a later time in life. This development is epitomized by the testing of specific genetic alleles for breast cancer (e.g., BRCA1 and BRCA2 genes) and Alzheimer’s (e.g., ApoE gene) disease risk (Antoniou et al., 2003; Farrer et al., 1997; Ford et al., 1998; King, Marks, Mandell, & New York Breast Cancer Study Group, 2003; Risch et al., 2001; Slooter et al., 1998). The second development is the advent of genomic technologies that provide the ability to scan large portions of the human genome for subtle genetic changes, which enables statistical disease risk estimation for more commonplace and chronic conditions such as coronary artery disease and diabetes (Feero, Guttmacher, & Collins, 2010; Gollust, Wilfond, & Hull, 2003). The relative risk estimates for these common conditions are far more modest compared to those associated with BRCA1/2 and ApoE because the diseases arise from a complex interaction of genetics and environment versus genetics alone (Manolio, Brooks, & Collins, 2008). Hence, the term predictive genomic testing attends to multiple and subtle changes in genes that act in concert with each other and with the environment to impact health.

The emergence of predictive genomic testing—which is primarily being marketed directly to consumers without physician or regulatory oversight (Gollust et al., 2003)—has sparked debate about whether such tests represent regulated medical tests or personal information to which an individual has an inherent right. Many of the entities offering predictive genomic testing justify their approach under the banner of empowerment and autonomy (Hudson, Javitt, Burke, Byers, & American Society of Human Genetics Social Issues Committee, 2007). They contend that test results provide individuals with important insights into future health risks that may motivate them to adopt preventive health actions. Even in situations where the interpretations of an individual’s genetic code is unclear, DTC companies assert that consumers have a personal right to access information about themselves—especially within the context of wellness and prevention.

In contrast, critics worry that information gained through predictive genomic testing is, at best, uninterpretable and, at worst, may actually be harmful. There is concern that testing may prompt individuals to make decisions based on faulty or conflicting data since test results have been shown to vary depending upon which companies perform the testing (Hamburg & Collins, 2010; Ng, Murray, Levy, & Venter, 2009). Moreover, receiving ambiguous information about one’s lifetime risk for a common disease may create unnecessary and regrettable psychological stress or distress, alter one’s self-image, or lead to health behaviors that have not been shown to improve health (i.e., taking unproven treatments...
or supplements) or are actually unhealthy (e.g., initiating tobacco and substance use). It is also possible that persons may adopt fatalistic thinking about their health, erroneously concluding that it is “all in their genes,” and not seek to make improvements to their health because “nothing they do matters.” In our view, the more recreational the aims of the test (e.g., determining ear wax type), the less concerning is the potential for harms. CONVERSELY, given the current uncertainties about the accuracy of risk information and health impact, the potential for harm is greater with more specific health claims (e.g., cardiovascular disease risk) (Government Accountability Office, 2010).

To date, concerns about the utility and harm of predictive genomic testing have been largely speculative rather than factual because few data exist. Most of the evidence that does exist comes from a few prospective clinical trials of individuals who have had testing for a single gene variant because of their family’s disease history. For example, the REVEAL (Risk Evaluation and Education for Alzheimer’s Disease) Study, one of the largest studies of the psychosocial and behavioral effects of genetic susceptibility testing—and among the few to use randomized controlled methods—was conducted with first-degree relatives of those with Alzheimer’s disease. The researchers have not yet found evidence of serious psychological harm in persons receiving results for ApoE4, a genetic variant that increases one’s risk for Alzheimer’s (Green et al., 2009). More than a decade’s worth of studies have also been conducted to provide results of BRCA1/2 genetic testing for breast cancer risk. These studies have also shown limited adverse impact (Vadaparampil, Miere, Wilson, & Jacobsen, 2006).

Important caveats here are that all of these studies have recruited adults who were motivated to obtain information about a specific disease—often by significant family history of disease—that study participants were often supported through genetic counseling, and that they were closely monitored afterwards for potential untoward psychosocial side-effects. A study of everyday consumers’ reactions to information about genetic susceptibility to multiple, common diseases is currently underway (McBride, Wade, & Kaphingst, 2010). This study, which primarily used a website and online decision aids to inform adult participants about the potential risks and benefits of personal genomic testing, also suggests these tools are helpful in supporting adults’ decisions about testing (Kaphingst et al., 2010). To date, the single largest and most comprehensive study on this topic failed to show any adverse psychological effects associated with adults’ use of personal genomic tests and did not demonstrate impact on their preventive health behaviors or healthcare utilization (Bloss, Schork, & Topol, 2011). Whether and how such test-related decisions and outcomes might be different for parents and/or their children remains to be seen.

**The (Baby) Elephant in the Room: Children and Predictive Genomic Testing**

Despite the recent controversy, it is unlikely that predictive genomic testing will disappear anytime soon—if ever. Furthermore, given the aspiration for the utility of predictive genomic testing for disease prevention (including primary prevention among unaffected, healthy young people) (Haga & Terry, 2009), examining the potential risks and benefits of such testing in a pediatric context is an important next step in the translation of this research into clinical and public health practice (Tabor & Kelley, 2009). It should be recognized that predictive genomic testing is already available to parents who would like their children tested through online avenues. For example, one online DTC company defers decisions about personal genomic testing in children to parents, who then control access to information about the child’s genotype until the child reaches the age of 18 years—at which point the child is given control (23andMe, 2010). Unfortunately, we do not know how many parents utilize this testing for their children because this information is proprietary and research in this area is lacking.

Despite this backdrop, the potential use of predictive genomic testing in children for multifactorial, preventable conditions (e.g., obesity, type 2 diabetes) has been relatively absent from much of the ongoing discourse (McGuire, Diaz, Wang, & Hilsenbeck, 2009). A recent American Society of Human Genetics policy statement on personal genomic testing did not address its use in children for adult-onset disorders (Hudson et al., 2007). However, several studies suggest that many parents have some interest in predictive genomic testing for their child (Tarini, Singer, Clark, & Davis, 2010; Tercyak et al., 2011). Additionally, other studies describe parents’ interests in learning about their children’s risks of developing adult-onset hereditary cancers, and the presumed intent of predictive genomic tests—to identify disease long before it starts and to promote preventive and risk-reducing measures including lifestyle and behavior changes (Bradbury et al., 2010; Peshkin et al., 2009).

Statements from professional organizations intended to guide clinical practice have discouraged genetic testing in children for adult-onset diseases (Clarke, 1994; Guidelines for genetic testing of healthy children, 2003; Nelson et al., 2001). One of the first of these statements was a joint report from the American Society of Human...
Genetics and the American College of Medical Genetics published in 1995, who wrote: “If the medical or psychosocial benefits of a genetic test will not accrue until adulthood, as in the case of carrier status or adult-onset diseases, genetic testing generally should be deferred.” (American Society of Human Genetics Board of Directors & American College of Medical Genetics Board of Directors, 1995). This more than 15-year-old statement focused primarily on genetic testing for Mendelian disorders (i.e., disorders that come from the mutation of a single gene, and often with little or no known environmental influence [e.g., BRCA1/2 genes]), many of which were severe and did not have effective interventions (e.g., early-onset breast/ovarian cancer).

In contrast, predictive genomic testing may be able to identify an individual’s risk for developing common, treatable, and possibly preventable disorders which can promote environmental modifications, such as lifestyle and health behavior changes. For example, one could envision testing obese children to see whether have an elevated genetic risk of developing diabetes, in addition to their current clinical risk factor (obesity). Such testing could provide additional motivation for lifestyle change in those children who are at greatest risk (i.e., those with clinical and genetic risk factors). Another example might be identification of adolescents at elevated genetic risk for smoking initiation (such as those with ADHD), which could allow for the development of targeted smoking prevention programs (Swan, 1999; Wilfond, Geller, Lerman, Audrain-McGovern, & Shields, 2002). In fact, a recent study by Herbert et al. demonstrated that a substantial proportion of adolescents with ADHD might be interested in such testing (Herbert, Walker, Sharff, Abraham, & Tercyak, 2010).

Admittedly, it remains to be determined whether earlier knowledge (including information acquired during childhood) of one’s risk of an adult-onset condition improves medical outcomes with minimal psychosocial and behavioral burden. It is possible that a parent’s or child’s knowledge of this genetic predisposition could lead to a fatalistic perspective or diminished self-esteem (Malpas, 2008); however, empirical evidence supporting or refuting this supposition remains sparse (Wade et al., 2010). The existence and scope of such a fatalistic reaction to predictive genomic testing is unknown and should be explored rather than assumed.

In keeping with these concerns, the American Academy of Pediatrics cautioned in 2001 that “genetic testing of children and adolescents to predict late-onset disorders is inappropriate when the genetic information has not been shown to reduce morbidity and mortality through interventions initiated in childhood” (American Society of Human Genetics Board of Directors & American College of Medical Genetics Board of Directors, 1995; Nelson et al., 2001). However, this recommendation, as well as the ASHG/ACMG statements discussed above, address clinical applications of genetic testing and not research. Yet research is necessary to determine the benefits and risks before decisions about clinical applications can be made. The limited research that has been done suggests that risks may not be as great as we once feared (Wade et al., 2010). If so, then the challenge lies in how to gather additional data about the utility of predictive genomic tests in children in the context of a professional ethos about clinical testing that may indirectly discourage necessary research by citing lack of evidence and concerns about significant harms. This reasoning is circular: we can only understand the benefits and risks of testing if we do research.

**Research Ethics of Filling the Evidence Gap in Predictive Genomic Testing for Children**

Given the increasing presence of predictive genomic testing in our society and the potential extension of this testing to children to aid disease prevention efforts, it is important to conduct such research in children (Moore, Khoury, & Bradley, 2005; Tercyak, 2009b). A comprehensive clinical and public health genomics research framework must include well-designed research studies focused on children’s health—with close monitoring to assess the risk/benefit profile. Testing within the context of research studies will ensure the review and oversight needed to maximize benefits and minimize harms.

It is critical to realize that the absence of such research will not prevent the eventual use of predictive genomic tests in children. On the contrary, in the absence of such research, predictive genomic testing will likely diffuse into the pediatric arena without systematic analysis of the type and magnitude of various harms or benefits. A case in point has been the expansion of newborn screening in the last decade that was primarily technology driven, without adequate research (Borkin et al., 2006). Clinical uses of pharmacogenomic tests are emerging (Becquemont, 2009; Sheffield & Phillimore, 2009), and extension to other populations, such as children, is only a matter of time (Wilfond & Ross, 2009). It seems more prudent, therefore, to both observe and deliver interventions of uncertain benefit/harm, such as pediatric predictive genomic testing, as a research endeavor rather than as a clinical one (Freund, Clayton, & Wilfond, 2004).

Institutional review boards (IRBs) and funding agencies may be reluctant to support research studies involving
predictive genomic testing in children. This may be related to general concerns about genomics research or about the appropriateness of clinical genetic testing in children. Some might even rely on the professional organizational statements about predictive testing in children for late onset Mendelian conditions in their deliberations. However, it should be recognized that these statements focus on clinical test use rather than research per se.

To facilitate research that provides reliable and valid data about pediatric benefits and harms (or lack thereof), professional organizations should update these statements and make a clear distinction between the uses of such tests for clinical versus research purposes (including the return of test results to parents and/or children and issues surrounding individual vs. collective harms and benefits). The Secretary’s Advisory Committee on Genetics, Health, and Society recently weighed in on this issue, noting the important role of children as subjects in large population studies on genes and health and that the ethical issues related to inclusion can be addressed within the research regulatory framework (Office of Biotechnology Activities & National Institutes of Health, 2007).

Of course, support for and approval of a study of predictive genomic testing in children would require that standard ethical criteria be met (Emanuel, Wendler, & Grady, 2000). IRBs could potentially approve such studies as either research involving “greater than minimal risk but presenting the prospect of direct benefit to the individual subjects” (45 CFR 46.405) (U.S. Department of Health and Human Services, 2009) or research involving “greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject’s disorder or condition” (45 CFR 46.406) (U.S. Department of Health and Human Services, 2009). A key distinction between these two regulatory categories is whether there is a prospect of direct benefit to the individual.

A prospect of direct benefit is not just any possible benefit, but a benefit that has a reasonable chance of occurring. This means that for any specific benefit (e.g., a favorable change in behavior, a clinical outcome, or a psychological benefit), an estimation of the likelihood of that benefit occurring must be made based upon data from related research or on a normative determination that a benefit is a reasonable prospect. Admittedly, some study designs could make the prospect of direct benefit impossible. For example, an observational study that does not provide for the return of genomic test results to the health care provider, family, or child does not offer a prospect of direct benefit. Studies that provide results to families and providers may offer a prospect of direct benefit. The sort of preliminary research that might support this determination includes prospective studies of parent–child behavioral responses to pediatric genetic testing for hereditary cancer syndromes (e.g., Familial Adenomatous Polyposis, Li-Fraumeni Syndrome, and Multiple Endocrine Neoplasia) and behavioral analog studies (e.g., laboratory assessments using scenario-based depictions). In addition, observational studies of parent and child uptake and outcomes of DTC genomic testing can also provide additional information.

Importantly, for both 45 CFR 46.405 and 45 CFR 46.406 research categories, there are two additional risk/benefit considerations beyond the prospect of direct benefit. First, the risk must be justified by the anticipated benefit to subjects. As described earlier, much of the risk of predictive genomic testing in children is speculative at best: the sparse empirical data that exist do not suggest great risk (Wade et al., 2010). This recent systematic review of the psychosocial impact of genetic testing in children found 17 articles, of which most found no statistically significant difference in any of the following outcomes between those who tested positive and those who tested negative: depression, anxiety, general psychological well-being, dispositional optimism, or behavioral problems. Only two studies addressed the effect of genetic testing on self-esteem, self-perception, or health-related well-being, and neither study found any statistically significant differences between children with positive or negative tests. Clearly, balancing risk and benefit in this context will be influenced by normative judgments about their relative meaning. Researchers have an obligation to articulate why they believe the risks justify an anticipated benefit for a particular study. In turn, the IRB also has an obligation to consider that assessment in good faith and not presume that the risks can never justify the anticipated benefits for predictive genomic testing research among youth.

The second additional criterion is the “relation of the anticipated benefit to the risk (must be) at least as favorable to the subjects as that presented by available alternative approaches.” An alternative approach to predictive genomic testing in children might be taking a detailed family history and providing disease risk predictions based on those results to the parent and/or child (U.S. Department of Health and Human Services, 2010). Family history often conveys as much (if not even greater) information about future disease risk than genetic test results. Data from prior work on the impact of genetic information on children, including the experiences of parents and siblings who are affected by serious health conditions, suggest that benefits and risks to a particular child are difficult to anticipate in advance (Tercyak, 2010). As long as the risk/benefit ratio
for genomic testing is as favorable, such research could be approved under 45 CFR 46.405.

Finally, the appropriate age for enrolling children in research involving predictive genomic testing must be considered. While assent from children who are developmentally capable of assent is necessary for research participation, assent does not require that children have the same understanding of the benefits and risks that is expected of parents who provide permission (American Academy of Pediatrics Committee on Bioethics, 1995). In fact, we should assume that even children who are old enough to obtain assent (i.e., 5–7 years) will have limited understanding of all the relevant information involved in deciding whether to join such a study and be tested. Nevertheless, it will be important to engage children in an age-appropriate fashion, as we would for a clinical intervention, to ensure they have appropriate expectations for future tests and interventions. Equally important is that a research study utilizes advances in behavioral and risk communication science to develop education and counseling protocols for families and children to maximize benefits and minimize risks.

In summary, the current pediatric regulations support the involvement of children in predictive genomic testing research. Rigorously designed studies with sound methodology would provide important information to guide clinical practice and policy recommendations. Until results from these research studies are available, the use of predictive genomic testing with children and adolescents in a clinical context remains problematic and should not be routinely provided or encouraged by healthcare providers. It is important that pediatric health care providers help parents who may inquire about predictive genomic testing on their child’s behalf understand that data about the benefits and risks to children and families is incomplete. Parents interested in this information could be encouraged to join a research study that might offer this testing—in a well-controlled and -monitored setting. Healthcare providers should also remind parents that healthy behaviors such as consuming a well-balanced diet, engaging in sufficient physical activity, and avoiding tobacco use are important for everyone—regardless of their genomic profile.

A Role for Pediatric Psychology

In the future, predictive genomic testing is likely to become a routine part of primary care medicine, including pediatrics. Along with family history and other clinical information, testing will be used to help identify persons at increased risk for some of the most challenging and vexing diseases of our time, including cancer, cardiovascular disease, diabetes, and obesity. However, reservations about the clinical utility of some tests offered directly to consumers on the Internet should not preclude the conduct of all research on this topic, especially research with healthy young people in controlled settings. We think it vital that we conduct research about predictive genomic testing in children and adolescents so that we can better understand the actual benefits and risks to them, and to the practice of pediatric medicine more broadly (Tercyak, 2009b). Specifically, research will need to assess the effectiveness of genetic testing on the success of a child’s lifestyle modification efforts as well as the success of programs directed at preventing unhealthy behaviors (e.g., smoking) and to examine the impact on self-perception and emotional well-being.

Social and behavioral research, especially research with children, adolescents, and their families, is essential to help accelerate the translation of genomic discoveries from bench to bedside (McBride & Guttmacher, 2009). Child health psychologists are uniquely poised to facilitate research in this area. Given their background and training in child development, experimental research methods, child behavioral assessment and behavior change, as well as their deep understanding of the role of behavior in health, they are positioned to contribute significantly to interdisciplinary genomic research teams. These teams could construct rigorous and informative research studies that utilize reliable and valid research tools to track both harmful and beneficial social and behavioral outcomes (McBride & Guttmacher, 2009). Child health psychologists are concerned about the early influence of lifestyle and behavior on children’s health and development, and it is critical for those in this field to become conversant about genomics (Patenaude, 2003). For child health psychologists lacking expertise in genetics and genomics, this knowledge can be acquired through a number of sources, including didactics and continuing education opportunities for health professionals (Patenaude, 2003).

Pediatric psychology researchers and others engaged in this enterprise will need to address a number of ethical issues. As outlined herein, the primary issue is assessing the potential risks and benefits of testing and communicating this assessment as part of informed consent processes with children and their parents. In our view, study investigators and IRBs can work together within the existing regulatory framework to meet standard ethical criteria.

The translation of genomic discoveries into child health applications will be more rapid if conversations about ethical concerns are supported or refuted by social and behavioral data. This provides a new opportunity for child health psychologists to work alongside pediatricians, geneticists, bioethicists, and other clinical and public
health specialists to develop model research protocols in personal genomic testing that incorporate questions of an ethical and psychosocial nature. In an ethically sound and controlled research environment—as opposed to the unregulated free market—thoughtful and important questions such as these may be asked and answered to the collective benefit of society.

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References


