Genetic Testing in Children

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Increasing availability of DNA based tests in clinical practice has lead to widespread debate on the ethical issues involved. The wider usage of these tests in children has raised many questions regarding the ethics, validity of the request and its effects on child's psychosocial well-being. Though there have been much discussion with many studies attempting to address the issue, there is no consensus. Formulation of guidelines has been hampered by the diversity of tests available for varied indications and lack of research studying the effects of testing in children over a time. Some tests have valid indications with proven benefits over harms while others have less clear justification. We attempt to address this issue with the intent to sensitize the caregivers regarding various aspects to be considered before offering any genetic tests in children.

Keywords: *Child; Genetic testing; Guidance Ethics; Utility.*

Tests based on DNA technology are increasingly becoming available and have found tremendous applications in clinical practice. These tests play an important role in diagnosis of the disease, carrier detection and pre-symptomatic as well as prenatal diagnosis. DNA based tests are not only technically challenging, but also present many ethical dilemmas with regard to the indications, interpretation and implications for the patient and family. One such ethical issue that needs to be addressed is genetic testing of children.

It is beyond doubt that the testing which can make a difference in the management of a patient in the immediate future is essential, whatever may be the age of the patient. However, the situation in many clinical scenarios is different and complex, e.g., the request of parents of a child with Hemophilia A or Duchenne Muscular Dystrophy to test their 7-year-old daughter for carrier status of the disease. They might argue that they are anxious to know her carrier status, though it will not be of any significance to her till she attains reproductive age and wishes to start her family. On the contrary, the request of a father with multiple endocrine neoplasia II to test his children for mutation in RET oncogene is justified as there is a 50% chance for each of his offspring to inherit the mutation. Medullary thyroid carcinoma has been reported as early as by 3 years of age in carriers of *RET* gene mutation. Knowing the carrier status can help in planning prophylactic thyroidectomy. Another example that can be considered is the request from a family of Huntington disease to test their children for the mutation. At present there is no treatment which can change the course of the disease even when detected pre-symptomatically. Testing for such untreatable, late onset disease in children has many ethical, legal and psychological implications. Hence the issue of genetic testing in various situations has to be assessed from the perspectives of the child, the parents and the geneticists.

ISSUES TO BE DISCUSSED WHILE TESTING CHILDREN

Benefits and harms of testing

As with all forms of investigations, DNA testing also has its own benefits and potential harms.

Potential benefits

Medical benefits: DNA testing plays a major role in arriving at definitive diagnosis in diseases such as spinal muscular atrophy, Friedreich ataxia, Fragile X syndrome, Leber optic atrophy, Leigh disease. A confirmed diagnosis helps with counseling and offering prenatal diagnosis to prevent recurrence in the family. Accurate diagnosis is necessary to predict the prognosis of a condition, especially if there is genotype-phenotype correlation. In Myotonic dystrophy, severity of the disease correlates with the number of trinucleotide repeats.

Identifying patients with increased susceptibility to diseases such as cancer by molecular testing helps in surveillance. This makes pre-symptomatic diagnosis

possible and provides adequate time to take steps for preventing the progression. In MEN II, prophylactic thyroidectomy protects against medullary thyroid cancer. In a child diagnosed with unilateral retinoblastoma, adequate surveillance is needed to prevent involvement of the other eye if the child is a germ line carrier of *RB1* mutation gene. Similarly, unnecessary and unpleasant procedures such as colonoscopies in familial adenomatous polyposis can be avoided if the genetic test is reported to be negative. Effective measures can be instituted to modify the course of a disease if there is clarity in the diagnosis. Using appropriate drugs in familial hypertrophic cardiomyopathy can prevent arrhythmias. Dietary restrictions have been beneficial in diseases such as familial hyperlipidemia [1].

Psychological issues: The report can reduce the uncertainty and offer emotional relief if negative. A positive result is also helpful in preparing for the future as in planning education, managing finances and allows time to adjust and avoid emotional problems.

Reproductive issues: DNA tests may not directly benefit the tested children as it will only be useful in reproductive or family planning decisions. But such testing can be utilized by parents to undergo prenatal diagnosis or consider other reproductive options to avoid recurrence of the disorder in the family.

Potential Harms

Genetic tests may prompt further investigations and unnecessary treatments with no proven benefits thus causing distress and escalating the cost. A child found to be unaffected runs a risk of rejection by the family, especially when many other members are affected. A positive test may cause unwarranted anxiety about the possible early signs of the disorder before any genuine manifestations actually set in. Testing at an early age deprives the child's right to decide about pre-symptomatic diagnosis as an adult. Revealing the results can impair the self-esteem and lead to discrimination in education, employment, insurance etc. The reports can adversely affect the relationship with future partners and lead to coerced decisions.

Decision Making Capacity of the Child

Consent for any test requires competence to make independent decisions after completely understanding, communicating and reasoning out. Decision-making capacity is not entirely dependent on age, with some children having attained this ability by 12 or 14 years of age. Therefore it is important to individualize each case and assess the capabilities of the child in concern.

Advocating on Behalf of the Child

One should evaluate whether a request made by parents for a particular test is appropriate after considering the relative benefits and harms to the child. It is the major responsibility of the geneticist to see that the interests of the child get priority.

Psychological and Emotional Effects on Child

It appears logical that genetic testing is likely to have psychological effects on the child. However, studies till date have not demonstrated any impact on the emotional state with either the carrier or predictive testing of children. There seems to be no significant effect on the child's self-perception, self-image or self-esteem [2]. However, more research to evaluate the impact of genetic testing using more sensitive and appropriate assessment tools to detect changes over time is needed.

TYPES OF GENETIC TESTING

Diagnostic Testing

DNA based tests have an important role in diagnosis of patients as these are the confirmatory or the only diagnostic tests available for some genetic disorders. Testing for dystrophin gene deletions is now the preferred confirmatory investigation for Duchenne muscular dystrophy when clinical signs and symptoms suggest the diagnosis. Similar is the case of spinal muscular atrophy, Friedriech ataxia, Fragile X syndrome and many more monogenic disorders. In other diseases such as sickle cell anemia, hemophilia and thalassemia, though the diagnosis can be made by other investigations, genetic testing is an important additional option as it makes prenatal diagnosis possible. DNA based diagnosis plays an important role in the management of cystic fibrosis, especially when the sweat chloride test is equivocal. Pharmacogenetic testing for choosing the safest drug and its dose can be ordered whenever needed and has the same legal and ethical implications as that of any other diagnostic test. Though genetic tests for conditions such as disorders of sexual differentiation are very important in establishing the etiology and initiating appropriate management, they are likely to have major emotional and social impact on the tested child as well as the entire family. As diagnosis of disorders of sexual differentiation is a medical and social emergency, use of DNA based and other genetic tests in a neonate or child has the same implications as any other type of diagnostic tests [3]. Genetic tests help in counseling and prenatal diagnosis without causing any harm to the family [4].

Carrier Testing

This type of testing is usually requested when a relative is

affected with an autosomal recessive or an X-linked disease or when parents are carriers. Testing may allow the carriers to be well prepared to choose their partners and take appropriate reproductive decisions. There is consensus among geneticists and pediatricians that children should not be tested for carrier status. However, the evidence that such testing causes any emotional or psychological harm is weak.

Presymptomatic Testing

For early onset disorders: It would be prudent to test children for diseases which have an early onset or for conditions wherein the early institution of preventive and intervention measures can affect the prognosis. A good example would be juvenile hemochromatosis which is caused by mutations in any of the two genes HFE 2 (90% of cases) and *HAMP* (10% of cases). As the disease is inherited in an autosomal recessive manner, each sibling of an affected individual has a 25% chance of being affected. All the family members of an affected individual should be tested for the mutations identified and be followed from early childhood with annual ferritin and transferrin iron saturation. Treatments such as regular phlebotomies can prevent or reverse many of the complications from organ damage if the disease can be detected early [5]. Similarly, pre-symptomatic diagnosis of Wilson disease and retinoblastoma in childhood greatly helps in medical management of at risk child. This is also the case with *RET* mutation in the offspring of a parent with MEN II.

For late onset disorders: Pre-symptomatic diagnosis of each of the adult-onset conditions presents a different sort of complexity. While it can help in planning for the future, availing life insurance, and making reproductive decisions, testing for conditions such as Huntington disease are known to pose many psychological, ethical and legal dilemmas. The pre-symptomatic testing for late onset, untreatable disorders like Huntington disease and Spinocerebellar ataxias even in adults need pre-test counseling and a period of decision making. Huntington disease guidelines recommend against pre-symptomatic testing of children [6]. However, testing an adolescent for gene associated with a 100% risk of colon cancer or an 18-year-old girl with a family history of breast cancer can provide relevant information to help surveillance and take preventive measures.

Testing for Balanced Chromosomal Translocation

Testing for balanced chromosomal translocations is purely of reproductive significance, and is probably best avoided during childhood. Potential harms are the psychological consequences with stigmatization as having undesirable characteristics, genetic discrimination and adverse effects on self-image.

Cancer Susceptibility Testing

Requests for such tests usually come from parents who are carriers of a cancer susceptibility gene or had cancer as a child to know the risk of second malignancy. Scientists may seek such tests to identify children at increased risk of primary or secondary malignancies to enter them into research protocols. The fact that most cancers have multifactorial etiology and genetic susceptibility accounts for a small percentage of cancers complicates testing. In some forms of familial cancers, genetic testing of children or adolescents is justified as it offers effective prevention or early diagnosis by surveillance. In familial adenomatous polyposis, genetic testing can identify children in the families who are not at increased risk and thus be relieved of the burden of annual colonoscopies. Although prophylactic resection of the colon is usually done after 16 years, screening with annual sigmoidoscopies beginning by 10 years allows for early removal of polyps and careful follow up. Genetic testing of childhood survivors of unilateral retinoblastoma is effective as carriers of the altered *RB1* gene have a 50% chance of developing a secondary cancer, identification of whom can aid in surveillance [7]. For some conditions in which early interventions in childhood will definitely lead to favorable medical outcome, testing can be done without considering the minor's right to decide in future.

On the other hand, there seems to be no justification for childhood testing in certain familial cancers. Inheriting a mutation in *BRCA1/2* gene confers almost 80% risk of developing breast cancer and a child of an affected parent has a 50% chance of inheriting a mutated copy. But currently there is no justification for *BRCA* testing in children, as there are no methods effective in early detection or prevention of cancer and there is no clear role for prophylactic surgery in children. Recommendations state that *BRCA 1/2* testing should not be available to children with or without their parents' consent as it carries substantial risks for psychological, familial and social well-being of those tested [8]. In case of Li-Fraumeni syndrome, which is a familial cancer susceptibility syndrome, screening a child for p53 mutation is controversial. There are no effective screening methods available apart from the regular physical examination and immediate investigation of symptoms and these can be done even without genetic testing [9].

Newborn Screening and Prenatal Diagnosis

Though newborn screening programs have been in place for over five decades in developed countries, they are still in the infantile phase in India. As the number of conditions

covered have gone up to 30 and new technologies are being incorporated, there is a pressing need to address the ethical issues and their impact in future [10].

Effectiveness of newborn screening for disorders such as phenylketonuria where the benefits of early treatment clearly outweigh the risks has been proved beyond doubt [11]. There are no ethical or legal dilemma about including such disorders in the screening panel. Newer techniques such as tandem mass spectrometry, genomic screen, microarray, next generation sequencing are likely to reveal disorders with uncertain natural history and novel genetic variants with unknown significance, thus paving the way for fresh controversies [12]. Carrier status of neonate for recessive conditions such hemoglobino-pathies and cystic fibrosis are also expected to be diagnosed more often and there is a consensus that this should be reported to parents keeping in mind the future recurrence risk. Although most of the newborn screening programs provide information to the parents, these are usually complex to understand, incomplete and at times misguiding. This leaves the family clueless about the diseases covered, their natural course, therapeutic options and the costs involved.

In India there are no well-defined population-based screening programs though newborn screening tests are being done on a pilot basis. A written consent is not mandatory and tests are offered unscrupulously by private laboratories. Some screening panels include more than a hundred rare disorders many of which are untreatable. There is also a dearth of experts who can interpret these reports and advice appropriate management. Confirmatory tests and medications as well as special diets required to manage the disorders are not easily available. There are no uniform guidelines for storage and disposal of dried blood samples which can be very valuable in program evaluation and research. Thus it is important that as newborn screening takes its root in India, appropriate guidelines are formulated and well regulated screening services are provided.

Commercial testing

With the increased availability of commercial/direct to consumer testing, there is emerging concern that the genetic testing of children may be ordered by parents without involving the health care personnel or the child in decision making. Information and counseling regarding appropriateness of the test, benefits and harms may not be disseminated adequately. These concerns apart, people may prefer commercial testing because of the autonomy and anonymity it provides in matters such as availing life insurance. Such testing may also be preferred by people who are concerned about a particular condition but are for some reason unable or unwilling to obtain testing through the normal routes. There is no assurance that corporations will carry out the tests after considering the likely age of onset of the condition. As these tests are available over the counter there will be no one

CONSENSUS AMONG PEDIATRICIANS AND GENETICISTS WITH REGARD TO GENETIC TESTING OF CHILDREN

(*a*) Medical benefits, if timely is a primary justification to conduct the test. This includes diagnostic testing in symptomatic children and also pharmacogenetic tests.

(*b*) Tests that benefit the family in preventing recurrence without causing harm to the tested child as in thalassemia and spinal muscular atrophy are justified.

(*c*) If neither the medical nor the psychological benefits accrue till adulthood as in late onset diseases then it is better to defer the test.

(*d*) If there is uncertainty regarding the benefits or harms of a test then the decision of competent adolescents and their family should be given due credit after a thorough discussion.

(*e*) The rationale for genetic testing is the same whether the child is biological or adopted into the family.

(*f*) Genetic tests for carrier status with reproductive implications should not be done in children at parent's request but the same may be offered to an adolescent planning to start a family.

(*g*) Predictive genetic testing for childhood onset diseases may be done after obtaining parental consent. But such tests for adult onset disorders may be deferred unless an early intervention is indicated. Caution should be exerted while offering these tests to minors without the involvement of parents.

(*h*) Tissue histo-compatibility testing of a minor acting as a potential stem cell donor is permissible.

(*i*) Direct –to-consumer testing of children is strongly discouraged [13].

independently advocating on behalf of the child. The American Academy of Pediatrics and American Academy of Medical Genetics strictly discourage direct-to-consumer and home kit genetic testing of children [13].

CONCLUSIONS

The implications of genetic testing in children are similar to any other diagnostic investigation. However, there are many issues unique to childhood testing for genetic disorders that needs to be addressed before applying them in this age group. There is no dilemma in applying the test in children when benefits are very clear. These tests can confirm the diagnosis, forecast a prognosis and help formulate a treatment plan. Molecular tests also play an important role in providing genetic counseling and prenatal diagnosis to the family. There is a need to discuss in detail, avoid taking hasty decisions and provide adequate care to safeguard the interests of the child.

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REFERENCES

1. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. Points to consider: Ethical, Legal and Psychosocial implications of genetic testing in children and adolescents. Am J Hum Genet. 1995;57:1233-41.
2. Wade CH, Wilfond BS, McBride CM. Effects of genetic risk information on children's psychosocial wellbeing: A systematic review of the literature. Genet Med. 2010;12:317-26.
3. Öçal G. Current concepts in disorders of sexual development. J Clin Res Pediatr Endocrinol. 2011;3:105-14.
4. Burke W. Genetic testing. N Engl J Med. 2002;347:23.
5. Goldberg YP. Juvenile hereditary hemochromatosis. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews (Internet). Seattle (WA): University of Washington, Seattle; 1993-2013. 2005 Feb 17 [updated 2011 Aug 11]. From http://www.ncbi.nlm.nih.gov/books/NBK1170. Accessed 15 April 2013.
6. Huntington Disease Society of America. Guidelines for Predictive Testing for Huntington's Disease. The Huntington disease society of America, New York, 1989.
7. Moline J, Eng C. Multiple endocrine neoplasia type 2: An overview. Genet Med. 2011;13:755-64.
8. Koenig BA, Greely HT, McConnell LM, Silverberg HL, Raffin TA, Members of the Breast Cancer Working Group of the Stanford Program in Genomics, Ethics, and Society. Genetic Testing for BRCA1 and BRCA2: Recommendations of the Stanford Program in Genomics, Ethics, and Society. J Women Hlth. 1998;7:531-45.
9. Li FP, Correa P, Fraumeni Jr. JF. Testing for germline p53 mutations in cancer families. Cancer Epid Biomarkers Prev.1991;1:91-4.
10. Tarini BA, Goldenberg AJ. Ethical issues in newborn screening in the genomic era. Ann Rev Genomics Hum Genet. 2012;13:1-13.
11. Wilcken B. Expanded newborn screening: reducing harm, assessing benefit. J Inherit Metab Dis. 2010;30:S205-10.
12. Lantos JD, Artman M, Kingsmore SF. Ethical considerations associated with clinical use of next-generation sequencing in children. Pediatr. 2011;159:879-80.
13. American Academy of Pediatrics, Committee on Bioethics, Committee on Genetics; American College of Medical Genetics, Social, Ethical, and Legal Issues Committee. Ethical and Policy Issues in Genetic Testing and Screening of Children. Pediatrics. 2013;131:620-22.