Should Children and Adolescents Undergo

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In 1993, Tony Holtzman\(^1\) warned that “due in part to shortages of health care professionals with expertise in genetics, primary care physicians will assume a greater role in providing frontline genetic services.” As predicted, the “geneticization of primary care” is occurring. There has been a large influx of genetic tests in pediatrics, although gene therapies lag behind.

In this article, I first give an overview of the range of genetic tests available. Next, using a case-based approach, I examine some of the genetic conditions

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for which testing is available and the ethical issues that such testing raises for the general pediatrician.

**GENETIC TESTING**

A genetic test is "the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes." It can be done for clinical diagnostic purposes or for predictive purposes.

**Diagnostic Testing**

Imagine that, in the delivery room, a child is floppy and has some of the physical stigmata associated with Down syndrome (eg, large tongue, simian creases). The parents are informed of this concern and give consent for karyotyping.

Alternatively, a child is born with meconium ileus. As the child is prepared for the operating room, the parents are told that meconium ileus is almost always associated with cystic fibrosis (CF). The parents consent to genotyping. A positive
test for two mutations will give a diagnosis; without that, a sweat test will probably be needed when the child is a few weeks old.

Karyotyping, genotyping, and sweat tests are all genetic tests, even if the latter does not involve chromosomal or DNA analysis. These tests are noncontroversial in the contexts described: the child is symptomatic, and the tests can lead to a diagnosis, clarify prognosis, and help determine future medical care.

Predictive Testing

Predictive genetic testing, on the other hand, is more controversial. Predictive genetic testing is testing a child for a disease whose presentation may occur in months to years to decades, if it occurs at all. Depending on the condition, the predictive test may be pre-symptomatic (ie, virtually all children with the specific genotype will develop the disease) or predispositional (ie, children with this genotype are at increased risk of developing a particular condition, but not all will). With both presymptomatic and predispositional genetic testing, two children with the same mutation(s) may differ on whether the disease expresses (penetranee) and on how the disease expresses in terms of age of onset and severity (expressivity), even within the same family.

Predictive genetic testing can be done on children to determine whether they are at presymptomatic risk for diseases that present in childhood (eg, Duchenne muscular dystrophy) or for diseases that present in adulthood (eg, Huntington disease); or whether they are at increased predispositional risk for diseases that present in childhood (eg, Type 1 diabetes) or in adulthood (eg, breast cancer). Predictive genetic testing is more controversial than diagnostic genetic testing when it is done on an asymptomatic child for whom there is no medical treatment needed during childhood that can change the course of the disease.

Carrier Testing

Carrier testing is another type of genetic testing. Carriers are usually asymptomatic but are at risk for having a child affected with a particular disorder. Three types of carrier status are relevant for reproductive decisions. The most common type of carrier is a carrier of an autosomal condition (eg, sickle cell anemia, cystic fibrosis). Carriers have one mutant allele and are asymptomatic. If both partners are carriers, each child has a 1 in 4 chance of being affected and a 50% chance of being a carrier.

A second type of carrier is a female carrier of an X-linked condition (eg, Duchenne muscular dystrophy). While the woman is usually asymptomatic, each son has a 50% chance of being affected, regardless of the genotype of her partner. Her daughters will all be healthy, although half will be carriers themselves.

The third type of carrier is an individual who has an unexpressed autosomal dominant allele or a balanced translocation, a rearrangement between nonhomologous chromosomes. Although the individual is asymptomatic, his or her children may not be, regardless of the partner’s genotype. For example, a man with a BRCA-2 mutation is at increased risk of breast cancer compared with men in the general population, although his risk is still only 6.9%. Although the mutation infrequently expresses in men, if these men pass this mutation onto their daughters, the daughters would have up to a 74% risk of developing breast cancer.

Alternatively, a parent with a balanced chromosomal translocation would be healthy, but his or her child would have a 50% probability of having an unbalanced translocation (either too much or too little of one of the chromosomes). Most unbalanced translocations are incompatible with life and result in miscarriage. If the child is live born, it often has multiple disabilities and medical complications.

CASE EXAMPLES

Case #1: Newborn Screening for CF

You receive a call from your state lab that your patient, Baby A, has a positive screen for CF. What is your next step?

Eight states have CF screening programs mandated by legislative or execu-
tive actions (two have not yet implement-
ed the program); four other states offer
CF screening routinely with parental con-
sent or at the discretion of the provider
and the hospital with parental consent.6
The states use different methodologies.
All begin with screening for immunoreac-
tive trypsinogen (IRT), a test for the pres-
ence of the protein trypsin, which is
derived from the pancreas and is present
in high concentration in the blood of
infants with CF.
In some states and
countries,7 those in the highest percentiles
(the specific percentile varies) are tested
for DNA mutations. If the sample has two
mutations, the child has CF; if the sample
has one or no mutations, the child may
still have CF, and depending on the state,
some or all are sent for sweat tests.
In other states and countries, DNA
testing is not done on the first sample.
Rather, a second sample is obtained from
children in the highest percentile (again,
the specific percentile varies).7 Those
samples in which the blood IRT level is
still elevated are considered to have a pre-
sumptive positive screen and need to
undergo diagnostic testing (ie, sweat test,
genotyping, or both). Thus, in part, the
next step depends on a state’s screening
protocol.
Informing the family is necessary. In
virtually all states, the public health
department contacts the physician regard-
ing positive neonatal screens, and he or
she is supposed to contact the family in a
timely manner. If a condition is acutely
life threatening (eg, congenital adrenal
hyperplasia or maple syrup urine disease),
and no physician is designated, then the
public health department will contact the
family directly.
In this case, the mother, Ms A, is
reached at home and she is surprised. She
states that she did not even know that the
child had been tested for CF. This is not
surprising. In 48 states, newborn screen-
ning is mandatory, but even if consent is
not required, there is no justification not
to inform parents about what is being
done to their child. Parents often are given
pamphlets about newborn screening when
they are admitted to the hospital, but this
is too little, too late for most parents who
want and need education prenatally.8,9
Ms. A then asks for what other condi-
tions her child was screened. Again, the
answer varies by state. The National
Newborn Screening and Genetics
Resource Center web site, a cooperative
agreement between the Maternal and
Child Health Bureau Genetic Services
Branch and the University of Texas
Health Science Center at San Antonio
Department of Pediatrics, maintains an
up-to-date listing of the testing program
in each state.6
Newborn screening is changing rapid-
ly with the introduction of tandem mass
spectrometry (MS/MS), which consists of
two spectrometers that separate and quan-
ify ions based on their mass/charge
ratios. MS/MS can measure many differ-
ent types of metabolites, and is therefore
useful to screen infants for a large number
of amino and organic acid metabolism
disorders with one sample. It has revolu-
tionized newborn screening because of
the negligible increase in cost for each
disorder added.10 However, that benefit is
slightly misleading, because screening
involves not only the initial screening test
but also the diag-
nostic testing and a
system to ensure follow-up.11
Pediatricians need to be cognizant of
the policies in their states regarding
whether screening is mandated or
requires consent, what conditions are
being tested for, and the methodologies
being used, which affects the rate of false
positives and false negatives. Pediatrici-
ans should also work with their obstetri-
cal colleagues in educating expectant
families and new parents about newborn
screening.8,9

Case #2: Prenatal Versus Postnatal
Genetic Testing in High-risk Families
When Early Treatment is Available

Baby B comes in with his parents. A
family history shows the father had
retinoblastoma as a child, so you recom-
mand genetic testing of the child. The par-
teins refuse. What do you do next?
The first thing to do is to explore the
reasons for their refusal. This reveals that
Mrs. B’s obstetrician referred them to
genetic counseling, but they refused prenatal testing because of the risk it would pose to the fetus. Amniocentesis increases the risk of miscarriage by 1%; it also carries a 5.5% risk of skin marks and a less than 2% risk of other injuries.\textsuperscript{12}

However, postnatal testing is different from prenatal testing. While both tests inform the parents of the child’s genetic risk of developing retinoblastoma, prenatal testing often is done to allow parents to decide whether or not to continue the pregnancy, and if it is continued, to be prepared for the testing. Some may refuse because of fears of insurance discrimination, others because they equate genetic testing with “playing God,” and others because they do not want to put their child through the pain of phlebotomy. All of these parents must be told that, unless the child’s risk status is clarified, the child will be assumed to be at risk, as were all children before genetic testing became available. This means that the child will need to undergo ophthalmologic examination every 3 months. This may seem noninvasive at age 3 months, but some older infants and toddlers require general anesthesia for the examination, which has its own attendant risks. The genetic blood test can obviate these risks for 50% of children.

The pediatrician must ensure that ophthalmologic screening is done. Parental unwillingness to comply with ophthalmologic screening in at-risk children is medically neglectful. If family compliance cannot be achieved through counseling and discussion, the family may need to be referred to child protection services.

Case #3: Predictive Genetic Testing for a Childhood-onset Condition When Treatment is Not Available

Your next patient, Baby C, a boy, comes in for a routine 6-month check-up. Ms. C is teary-eyed. Her sister’s 4-year-old son was just diagnosed with Duchenne muscular dystrophy (DMD), an X-linked, recessive condition. DMD is a progressive neuromuscular disorder, causing boys to lose ambulation in childhood. It is largely lethal in the child’s late teens or early 20s. Ms. C asks about the chances that her son will have the disease. She requests testing of the child immediately. How do you respond?

The first question is whether Ms. C’s sister has been tested. While two-

birth of a child with particular needs. In contrast, newborn testing is done to influence the course of medical treatment. If the father has a known mutation, and the child tests negative, then the child is not at risk of retinoblastoma. If the child tests positive, on the other hand, the child will need to undergo ophthalmologic examinations every 3 months for several years to detect any tumor growth at an early stage, when it is curable.

The physical risk of the genetic test to the child is phlebotomy. There are other concerns, including potential insurance issues, particularly if the parents tried to change jobs after a positive result (eg, the fear that retinoblastoma would be viewed as a “pre-existing condition”).

Given the risks and benefits, some parents may decide against genetic testing. Some may refuse because of fears of insurance discrimination, others because they equate genetic testing with “playing God,” and others because they do not want to put their child through the pain of phlebotomy.

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matic for several years. Although some centers are treating presymptomatic and early symptomatic boys with steroids, this is not now standard of care and is associated with significant morbidity. Ms. C understands this but requests testing for planning purposes; the family is considering moving and want to know if they should buy a house with stairs or a ranch house. She would also like this information to help her decide the timing of a second child.

One reason to support a parental right to predictive genetic testing of children for early-onset conditions is that parents may have valid reasons to want to test. In families with a positive family history, parents may want to know because it eliminates the anxiety of not knowing. Data show ambiguity can be more stressful than either a positive or negative result. If the test is negative, the parents can raise the child free from this particular threat; if it is positive, the parents can plan for the child’s future needs. The information can also be useful for parental reproductive planning. Parents can decide whether to have additional children and how to time the next pregnancy, given the child’s risk status. Parents specifically may choose to accept the risk, conceive naturally, and avoid testing, or they may choose to use donor gametes, to pursue prenatal testing or preimplantation diagnosis, or to adopt. The information can also influence other parental life-planning decisions (eg, distance from a tertiary care facility, choice of insurance). Lastly, if the test is negative, parental guilt can be assuaged; and if the test is positive, parents can prepare both emotionally and financially.

Arguments against predictive genetic testing for conditions that present in childhood are also important to consider. First, there is the concern that these parents will seek unproven interventions. Many parents do seek alternative medicine for their children, particularly those with chronic and life-threatening illness. They need to understand that even if a wide range of tests were done, there is no guarantee that the child will be healthy.

It is also important to distinguish predictive screening for DMD in families with a known proband versus population genetic screening as is done in several countries. The difference is that the at-risk families may already have an understanding of the disease and are aware of their risk status. In predictive population screening, by contrast, individuals and couples may not know what DMD is or about its genetic inheritance. To these individuals, the decision to test may be a test to confirm a healthy child, and they may not be prepared for the results that follow, even if they consented to testing.
Case #4: Predictive Genetic Testing for an Adult-onset Condition

Ms. D brings in her 12- and 14-year-old daughters, Donna and Debbie, for genetic testing for breast cancer. Ms. D underwent a mastectomy for breast cancer 10 years ago and is doing well. Her sister also had breast cancer and was recently diagnosed with ovarian cancer at age 45. Her sister’s physician recommended genetic testing, and her sister was found to have a BRCA-1 mutation. Her sister’s children (24-year-old-twin daughters and a 26-year-old older sister) were tested for the gene, and only the oldest is a carrier. Ms. D was tested, and she carries the same mutation. She would like to have her own children tested. What should you do?

The main arguments used against predictive testing of young children for late-onset diseases are that they ignore the child’s right, as an adult, to make these decisions for himself or herself; they ignore the child’s right to confidentiality with regard to the decision and the health care information, and they ignore the fact that there are no medical indications for testing prior to adulthood. Women who test positive for a BRCA mutation should be encouraged to begin regular mammography in their 20s or early 30s, depending on the age that breast cancer presented in their family members. They also should be informed about, and offered the option of, elective bilateral mastectomy and prophylactic bilateral salpingo-oophorectomy, which have been shown to be effective in reducing the risk of cancer. However, nothing can or will be done in childhood. This raises the concern that parents of children with a BRCA mutation will seek nonvalidated treatments.

In this case, the daughters, although minors, both are mature and express their own opinions in support of genetic testing. Debbie states that if she knew she had the mutation, she would get married and have a family early on, rather than delay child-bearing. Donna states that she already considers herself at risk, such that the testing only has benefits: if she tests negative, she can stop worrying; if she tests positive, she knows that she will need frequent surveillance.

The question remains whether physicians should permit teenagers to be tested. The consensus statements are unanimous against predictive genetic testing of children for late onset conditions. The overriding belief is that “predictive testing for an adult onset disorder should generally not be undertaken if the child is healthy and there are no medical interventions established as useful that can be offered in the event of a positive test result.”

Empirical data, however, show parents believe that they have a right to test their adolescent daughters and some doctors are willing to provide these services. The case would be different if Debbie and Donna disagreed with their mother and did not want testing. In that scenario, it would be surprising if Ms D could find a physician willing to take a blood sample, forcibly if necessary, to perform this test, given that there are no medical indications.

The case would also be different if Debbie and Donna were younger, perhaps ages 5 and 7. Here, one could imagine the physician trying to encourage the parents to delay testing until Debbie and Donna could give a mature assent. However, the parents may be unwilling to wait, on the grounds that the older child’s dissent may be dispositive.

Finally, the case would be different if Debbie and Donna sought testing for “life-planning purposes” and asked the physician not to inform their parents because they feared that their parents would be against testing. Debbie and Donna might explain that their parents would feel guilty of having passed on this “death sentence” and that they would not want to burden them with this. Given that genetic information is difficult to understand because of its probabilistic and ambiguous nature, clinicians encourage adults to bring in social supports (eg, spouses, siblings, parents) when considering testing. To empower adolescents to procure testing without adult (parental) involvement implies greater competency, which is not the case. It also denies that parents may have valid reasons not to want their children tested, including fear of insurance discrimination for themselves, the children, and other family members; parental right not to know their own status; and parental right to privacy from their own children.

Case #5: Carrier Testing

Your last case of the day is a teenager, Ellen, who comes in with her mother requesting carrier testing for hemophilia. Ellen has a brother with hemophilia and is concerned that she may be at risk of having an affected child. Ellen denies being sexually active and denies any plans for procreation in the near future. She is a straight-A student who aspires to become a physician. She wants to know because she has understood for some time her own risks and argues that ambiguity is worse than knowing. Her parents initially tried to dissuade her, but they are convinced by her arguments. What do you do?

Here again the case is simplified because the family is in agreement and Ellen’s arguments sound mature and convincing. Even so, the medical community has been against carrier testing of children when it has no immediate reproductive purpose. Parents, however, believe that they have a right to test their children for carrier status. The literature shows that adolescents perceive their own health to be worse and at least one study found that a small percentage (less than 10%) of adolescents who learned that they were carriers believed that the information had an adverse effect on self-image. Still, parents argue that this is important infor-
tion that is best shared at “teachable moments” and not at the time of marriage or preconception counseling when the results may cause an even greater threat to self-image.31

SUMMARY

Genetic testing comes in many shapes and sizes. The decision to undergo genetic testing must involve consideration of the medical, psychosocial, and reproductive benefits and risks of testing. The evaluation of risks and benefits varies significantly both between and within families. Pediatricians should keep up with the rapid advances in genetic medicine and the myriad of tests that are being developed and marketed. They also need to be familiar with the psychosocial risks and benefits that these new tests generate for individuals, families, and communities.

In some situations, genetic testing is merely another diagnostic tool; in other situations, genetic testing offers information about the risks for future diseases. Pediatricians need to be knowledgeable about tests that are indicated clinically and their potential psychosocial implications to best serve children, adolescents, and their families.

REFERENCES

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