Session 15. Genetic Testing and Screening of Children

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Overview
Every year, approximately 4 million children undergo genetic testing as part of newborn screening. This is the most common form of genetic testing in the entire population. Other children undergo genetic testing as part of a diagnostic workup for clinical problems (from progressive muscle weakness to developmental delays) or as part of research protocols or family linkage analyses. With the completion of the human genome project, there are hopes that genetic medicine will evolve into personalized medicine and become an integral part of medical practice. The expansion of genetic testing and screening in pediatrics raises ethical issues about the limits of parental autonomy, whose consent is needed, and what rights to privacy, if any, do children have with respect to their parents.

Participants will discuss the issue of mandatory consent in newborn screening and whether such a policy can persist in light of expanded screening; the benefits and risks of carrier genetic testing and under what circumstances it should be encouraged, permitted, or discouraged; and the benefits and risks of predictive genetic testing and under what circumstances it should be encouraged, permitted, or discouraged.

Instructor’s Guide
- Case Summary
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Case Summary
Parents come to see you, their pediatrician, prior to the birth of their first child. They are hoping to have a natural delivery and want to minimize the “medicalization” of their baby’s birth. They ask you about the benefits and risks of refusing newborn screening. They are also concerned that the blood spot may be used for research purposes without their knowledge.

Alternate Case
Shari, a 15-year-old, comes to your office with her mother. Her younger brother, Bob, had an abnormal newborn screen for cystic fibrosis (CF), but a sweat test result was negative, indicating that he does not have CF. Bob was found to have one CF mutation (delta F507, the most common mutation). Both parents were screened and found to have delta F507. Shari is very healthy and tall and her parents and physicians are not concerned that she has CF, but her parents
wants to know if Shari can be tested for being a carrier. Also, her mother, 2 maternal aunts, and maternal grandmother all had breast cancer in their early 30s. They have been tested and found to have BRCA mutation. Shari’s mom wants Shari tested for the BRCA mutation so that if she is a carrier, she will get appropriate screening. There is no breast cancer in her father’s family. Shari is ambivalent about genetic testing.

**Learning Objectives**
1. Be familiar with the history of newborn screening practices and policies.
2. Be aware of the controversies surrounding newborn screening in the United States today.
3. Understand when carrier identification of minors occurs and the risks and benefits of this identification.
4. Be able to discuss under what circumstances carrier identification of minors is or ought to be encouraged, permitted, and discouraged.
5. Understand the risks and benefits of predictive genetic testing for adolescents.
6. Be able to discuss under what circumstances predictive genetic testing of minors is or ought to be encouraged, permitted, and discouraged.

**Suggested Reading for Instructor**
[http://aappolicy.aappublications.org/cgi/content/full/pediatrics;107/6/1451](http://aappolicy.aappublications.org/cgi/content/full/pediatrics;107/6/1451). Accessed May 16, 2011


**Further Reading**


Case Discussion

What conditions are included in newborn screening?
The first condition included in newborn screening was phenylketonuria (PKU), an autosomal recessive condition that if left untreated, leads to mental retardation. Treatment entails dietary therapy. Screening began in the 1960s with the development by Robert Guthrie of a simple assay that could be performed on blood collected on filter paper. Hypothyroidism (which may or may not have a genetic basis) and galactosemia were added in the 1970s and 1980s. Expansion occurred slowly because each condition required a separate test, and it was expensive. In 1986, a study found that penicillin reduced morbidity in newborns with sickle cell disease, and most states quickly incorporated hemoglobinopathy screening into their newborn screening programs. However, the largest expansion in the number of conditions included in state newborn screening programs has occurred in the past 10 years with the adoption of tandem mass spectrometry (a platform technology) that allows for screening for many conditions with one sample at one time, including conditions for which there are no therapies and conditions about which the natural history is poorly understood. Virtually all of the conditions included in newborn screening are autosomal recessive, meaning that both parents must be carriers to have an affected child.

There is also newborn screening beyond the blood spot. Hearing screening is now universal in the United States and data are being collected to show the benefits of pulse oximetry screening to detect some cardiovascular and pulmonary conditions.

Can parents refuse newborn screening?
In all states except Wyoming and Maryland, newborn screening is mandatory, meaning that it can be done without parental permission, even without parental notification. However, in all states except Nebraska and South Dakota, parents have the right to refuse newborn screening.

How should a pediatrician respond to parental refusal?
The first step is to understand why they are refusing. Parents may refuse because they misunderstand the risk. If a parent says, “But those conditions do not run in our family,” the correct answer is that it is rare for individuals to know that an autosomal recessive condition runs in the family because carriers are asymptomatic and often not identified. Alternatively, a parent may say that they would prefer to wait to see if symptoms develop. These parents must be educated that such an approach may be too late; by the time a child is clinically symptomatic, irreversible changes may have occurred.

Some parents refuse because of religious or cultural beliefs about blood testing; others because of concerns about the medicalization of the birth process. These parents should be counseled that the probability of a missed diagnosis is low, but it can be devastating. In most states, parental refusals are respected on the grounds of parental authority (often referred to in the bioethics literature as parental autonomy); parents have the right and responsibility to make health care decisions for their child, unless their decision is abusive or neglectful. Given the low likelihood of a missed diagnosis (less than 1 in 3,000), the refusal does not qualify as neglectful.
Why is newborn screening mandatory?
Bob Guthrie developed the bacterial inhibition assay screening test and the filter paper that made newborn screening for PKU feasible and acceptable. Three factors coalesced to garner widespread interest and support for a program that promised to be able to screen, diagnose, and prevent at least some causes of intellectual disability. First, President John Kennedy had a special interest in intellectual disabilities partially due to his sister, Rose Marie. A second key factor was the growing strength of the National Association for Retarded Children (NARC), now known as The Arc of the United States, a parent advocacy group that was keen on preventing disabilities. Third was Robert MacCready, the state laboratory director for Massachusetts. MacCready, as chair of the NARC Public Health Service Committee, lobbied for mandatory legislation in Massachusetts because he thought uptake was not fast enough and was instrumental in encouraging Guthrie and NARC to support and advocate for mandatory legislation nationally.

Are there reasons to reconsider the need for parental consent for newborn screening?
The main argument in support of voluntary consent is based on the great deference that our society gives to individual decision-making about health care matters and, in the realm of pediatrics, the deference given to parents about how they raise their children. In 1994, the Institute of Medicine report, Assessing Genetic Risks, supported voluntary consent for newborn screening. In 2001, the American Academy of Pediatrics statement on genetic testing of children also supported voluntary consent.

Three empirical facts support voluntary screening. First, in states where newborn screening is voluntary, the data find high uptake (greater than 99% in Maryland). Even when optional screening is offered, uptake is very high (greater than 98% in Massachusetts when tandem mass spectrometry was offered as a research program).

Second, the expansion of newborn screening to include conditions like sickle cell disease and CF has led to the identification of carriers. Traditionally, the identification of genetic carriers has required strict informed consent in part because of the eugenics movement in the first half of the 20th century, culminating in the extermination of those declared “unfit to breed” in Nazi Germany and numerous sterilization laws in the United States. The early modern genetic counseling programs of the 1970s insisted that genetic testing be voluntary and that genetic counselors provide information in a nondirective fashion to distinguish modern-day genetics from the eugenics movement earlier in the century.

The early history of sickle cell screening actually reaffirms the need for voluntary programs and informed consent. Sickle cell screening began as a population screening program in the early 1970s using a solubility methodology known as Sickledex, which did not distinguish between sickle cell trait (being a heterozygous carrier with minimal health implications) and sickle cell disease. Like the test itself, the screening organizers, physicians, and the general public were confused about the difference between trait and disease. Not surprising, then, that the program was a serious failure clinically (because of the clinical limitations of the Sickledex test itself) and sociopolitically (because of the clinical misunderstandings by physicians and the public and the poor psychological and educational preparation of the African American community about the benefits and risks of screening). Despite good intentions, the program led to discrimination in health insurance and employment (including the military) and eventually was considered an attempt at “genocide against those of African ancestry.” The unintended adverse consequences
of sickle cell population screening gives further justification for requiring voluntary and informed consent for wide-scale carrier identification in newborn screening hemoglobinopathy programs.

Third, the widespread adoption of tandem mass spectrometry and identification of conditions for which treatments are not known to be effective represent a paradigm shift in newborn screening. Traditionally, the justification for using the state’s public health powers to mandate screening depended on meeting the Wilson and Jungner criteria, which include such requirements as the condition being an important health problem, the natural history of the condition being well understood, and there being a suitable test acceptable to the population as well as an accepted treatment and an agreed-on policy on whom to treat as patients. The expansion to include conditions identified by tandem mass spectrometry, for which the effectiveness of treatment, need for treatment, or duration of treatment are unknown, represents a shift from a focus on public health emergencies to the provision of a public health service, making the justification for a mandatory program even more tenuous. Proponents of a mandatory program traditionally argued that the benefits of newborn screening for a condition like PKU are so strong that one would not want any parent to refuse, but adoption of tandem mass spectrometry means that this no longer holds for all of the conditions identified.

**What is done with newborn blood spots after screening is completed?**

Policies and practices vary by state. However, the Guthrie cards have been described as “a national treasure.” The potential use of residual blood spots for research was realized early in the history of newborn screening, and these residual samples have been used over the past 4 decades for de-identified population research on environmental exposures, infectious diseases, and genetics.

Parental concern about the use of residual blood spots for research, however, is growing. In 2009, parents went to court in Minnesota and Texas about the use of these samples for research when they were collected without parental consent. The desire to use the residual blood for research is another argument in favor of seeking parental consent for newborn screening.

**Alternate Case**

**What is Shari’s risk of being a CF carrier?**

Both parents are carriers, which means that with any pregnancy, they have a 25% chance of having an affected child, a 50% chance of having a child who is a carrier, and a 25% chance of having a child who is healthy. Given that Shari does not have CF, her risk of being a carrier is 2 in 3.

**What are the pros and cons of knowing that one is a carrier for an autosomal condition?**

The most common reason for carrier testing is for reproductive planning. Because ideally reproduction only occurs in adulthood, most professional statements discourage carrier testing in childhood. These statements give a variety of reasons for deferring carrier testing until adulthood, including the minor’s right to privacy, the fact that many adults choose not to be tested, and the unknown risks and benefits of screening for genetic information that will not be needed for a long time. Concern has been expressed that carrier identification of minors may lead to labeling and stigmatization; that it may be misunderstood, leading to medical mismanagement; or that it may lead to vulnerable child syndrome and increased anxiety.
The statements seem to ignore that some children will know their carrier status because it was identified as part of newborn screening. Newborn screening programs have been identifying carriers of sickle cell for 20 years in many states and the data do not show that it has been harmful. And now newborn screening programs are identifying carriers of CF, even though there are methodologies for identifying CF in newborn screening programs that would not identify carriers (repeated immunoreactive trypsinogen measurement). Other children know their carrier status because parents had prenatal testing or because they were tested when a sibling was found to be affected. Psychological data about getting this information in childhood are generally reassuring. There is some evidence suggesting that children may be better able to incorporate genetic risk status into their self-identities and self-concepts than adults and some data to 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. Another benefit of carrier testing in childhood is that at least some minors will screen negative and they and their parents can be reassured that they are not at risk for having a child with this particular genetic problem. And there are some studies in which adults have stated that they wished they had known at a younger age.

The data to date do not necessarily confirm that the best time for carrier testing is adulthood. First, there are some data to show that there may be health implications of being a carrier; for example, there are data to show that being a sickle cell carrier may place one at greater risk for exertional sickling, and that being a carrier for Duchenne muscular dystrophy increases one’s risk of cardiomyopathy. But even if knowledge about carrier status is mainly focused on reproductive issues, the data are not clear when is the best time to learn this information. In several countries around the world, carrier programs have been developed in high schools to ensure that individuals have this information before marriage and reproduction. There are concerns about the voluntariness of screening programs that take place in the schools. It is also not clear whose consent would be needed in the United States for a minor to participate. One could argue that carrier information is about reproduction and should be covered by specialized consent statutes that allow adolescents to consent for themselves. One could argue on the other hand, however, that such genetic information is more complex and has familial implications, such that parental involvement should be required.

What role should Shari play in deciding about CF carrier testing?
In general, the guidelines discourage carrier testing during adolescence even if Shari is eager for this information, unless she needs it for reproductive decision-making. Clearly if such testing is going to be offered to adolescents, the adolescent should have a say in the decision-making given that the information is purely elective. Whether the adolescent should be able to get testing alone is more controversial. Currently, parental permission is needed outside of the reproductive context. However, parental consent should not necessarily be definitive in that the child’s dissent should be heard. What role the adolescent should play may depend on whether there are health risks of being a carrier. Given that we know of no health benefits for CF carrier testing, the child’s dissent should be definitive. It is more complicated if there are health risks associated with the carrier status because there may be more pressure on parents to seek testing and to be able to do so even over the objections of the adolescent to make informed medical decisions.

What is Shari’s risk of being a BRCA carrier and of developing breast cancer?
Shari’s mother is known to have a BRCA mutation. BRCA is an autosomal dominant gene. If Shari’s mother is a BRCA carrier, Shari has a 50% chance of inheriting this gene. However, BRCA is not completely penetrant, meaning that even if Shari inherits the gene, her risk of developing breast cancer is between 30% and 85%. Given the high number of relatives with breast cancer, her risk is probably on the higher side. If she does not inherit the gene, her risk of developing breast cancer is similar to the general population (about 1 in 9 women).

**What are the risks and benefits of knowing one is a BRCA carrier?**

The most common reason for undergoing predictive genetic testing with a positive family history is to clarify one’s risk status. While all women are at risk for breast cancer (1 in 9), those who carry a BRCA mutation are at much higher risk of getting breast cancer and of getting breast cancer at a younger age. All of the professional statements, however, discourage predictive testing for adult-onset diseases in childhood. The arguments are the child’s right to privacy; the child’s right to make this decision as an adult; the unknown effect of identifying carriers when the information is not relevant for years or decades; concerns about self-identity and how others will treat the child; concerns that a child who tests negative may experience survivor guilt. Additional risks of knowing one is a carrier for BRCA include psychosocial stress and anxiety about one’s increased cancer risk. Other risks include concerns about discrimination, particularly for health insurance, although the Genetic Information Nondiscrimination Act of 2008 should reduce this problem. There may, however, be discrimination with life insurance. There is also the concern of social stigmatization.

The benefit of knowing if one is a carrier for BRCA is that there are actions a woman can take to reduce her risk of breast cancer, although none of these actions are needed until adulthood, which is one reason to discourage testing of minors. Recommendations for adult women with BRCA include more frequent mammography screening starting at a younger age. Some women will choose to undergo prophylactic surgery.

Again, the data to date do not necessarily confirm that the best time for predictive genetic testing is young adulthood. To the extent that the data do not show serious harm, it may be morally appropriate to give families greater deference. However, because the information is elective, the adolescent should be part of the decision-making process. If there are no health risks in childhood, the adolescent’s refusal should be respected.

**What role should Shari play in deciding about BRCA genetic testing?**

In general, the guidelines discourage predictive genetic testing during adolescence, even if Shari is eager for this information. Given that we know of no health benefits for BRCA testing of minors, the child’s dissent should be definitive. Thus, to the extent that the policies may be modified to permit greater family discretion, the adolescent should have a say in the decision-making given that the information is purely elective. Such a practice also acknowledges the adolescent’s emerging right to privacy about health information as well as her right not to know.

Whether the adolescent should be able to get testing alone is more controversial. Consider the case in which there is a positive family history but the parent has not yet undergone genetic testing. A minor’s request for genetic testing may challenge a parent’s right to privacy. To date adolescents have greatest autonomy in health care decisions regarding sexual and reproductive health, not for life planning. Given the complexity of genetic information and the frequency of
misunderstandings about genetic results, a policy of involving parents and children in predictive genetic testing for late-onset conditions is morally justifiable. This is not to deny that parents can obtain this information prenatally, only to argue that the elective nature of the information places some constraints on parental autonomy. Nor should this be understood as a testament in support of wide-scale predictive genetic testing of children. In general, the presumption should be against testing to allow the child to decide whether or not he or she wants this information as an adult. However, if the parent and adolescent want this information, the justification for the state to override family autonomy is weak at best.

**Conclusions and Suggestions**

Genetic policies developed in the early days of genetic testing treated genetic testing as exceptional. As genetic testing and screening becomes more mainstream, policies will need to be revised to become more consistent with other health care policies. In general, parents have wide discretion in health care decision-making for their children.

Currently, consent is not needed for newborn screening. Given the expansion of newborn screening to include conditions that do not meet the Wilson and Jungner public health screening criteria, this will need to be reconsidered.

Consent for newborn screening must also be reconsidered if we want to use residual blood spots for research purposes.

In general, carrier testing of minors should be discouraged. However, to the extent that carrier status is associated with health risks, carrier testing should be permitted, if not encouraged.

In general, predictive testing of minors for late-onset conditions should be discouraged. However, families and not physicians must decide whether the benefits outweigh the risks. The parents and the maturing adolescent should be involved in deciding whether to undergo predictive testing for adult-onset conditions when no treatment is necessary or feasible during childhood.

*This instructor’s guide was developed by Mary B. Adam, MD, MA, PhD, FAAP; Douglas S. Diekema, MD, MPH, FAAP; Mark R. Mercurio, MD, MA, FAAP; and the American Academy of Pediatrics Committee on Bioethics and Section on Bioethics.*

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