Session 14. Genetic and Genomic Testing and Screening of Children

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Overview

Every year, approximately 4 million children in the United States undergo genetic testing as part of newborn screening (NBS). This is the most common form of genetic testing performed. Other children undergo genetic testing as part of a diagnostic workup for clinical problems (from progressive muscle weakness to developmental delays), to help determine proper dosing of medications (pharmacogenetics), or as part of research protocols. With the completion of the human genome project, there are hopes that genetic variation will be integrated into clinical medicine (personalized medicine). This will be simplified as sequencing of the entire genome (genomic sequencing) or at least the proteins (exome sequencing) becomes cheaper and quicker. The expansion of genetic and genomic testing and screening in pediatrics raises ethical issues regarding the limits of state authority, the limits of parental autonomy, and what rights to privacy, if any, do children have with respect to their parents.

This module will explore the ethical issues that arise regarding whether and when to perform genetic and genomic testing and screening of children. Participants will become aware of the history of NBS and why screening can be performed without parental permission. Participants will examine the benefits and risks of carrier genetic testing of minors and consider under what circumstances it should be encouraged, permitted, or discouraged. They will also evaluate the benefits and risks of predictive genetic testing of children for adult-onset disorders and consider under what circumstances it should be encouraged, permitted, or discouraged. Finally, the participants will examine the benefits and risks of disclosing secondary findings from whole genome/whole exome sequencing and consider under what circumstances it should be encouraged, permitted, or discouraged.

Instructor's Guide

- Case Summary
- Alternative Case
- Learning Objectives
- Suggested Reading for Instructor
- Further Reading
- Case Discussion
- Conclusions and Discussions

Case Summary

Shari, a 15-year-old, comes to your office with her mother. Her infant brother, Bob, had an abnormal newborn screen for cystic fibrosis (CF), but a sweat test was negative, indicating that he does *not* have cystic fibrosis. Bob was found to have one CF mutation (delta F507, the most common mutation). Shari's parents were initially angry because they were not aware that newborn screening was being performed. After doing some research, they agreed to carrier screening themselves, and both were found to carry the delta F 507 mutation. Shari is very healthy and tall, and her parents and physicians are not concerned that she has CF, but they want to know if Shari can be tested to determine her carrier status. Shari's mother as well as Shari's maternal grandmother and 2 maternal aunts all had breast cancer in their early 30s. They have been tested and found to have a 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 Shari's paternal family. Shari's father asks whether it would be cheaper in the long-run to just sequence Shari's entire exome (or genome) so that they will know all of Shari's health and reproductive risks. Shari is ambivalent about genetic or genomic testing.

- Why do parents not know that their child had newborn screening performed?
- How should pediatricians respond to a refusal of newborn screening?
- What is the likelihood that an individual is a carrier
- What are the pros and cons of knowing one's carrier status
- What are the pros and cons of knowing one's risk for adult-onset conditions that run in your family?
- What are the pros and cons of knowing one's risk for adult-onset conditions that do not run in your family?
- Is sequencing ready for use in the general pediatric population?
- What are the pros and cons of screening for the ACMG 56 whenever sequencing is performed?

Alternative Case

Mr and Mrs Jones are expecting their first child. During their prenatal visit, you explain that their child will have a heel prick for newborn screening. Mrs. Jones would like to refuse the test to avoid a blood draw because they have no family history of childhood-onset metabolic or genetic conditions. When they realize how many conditions are being evaluated, Mr. Jones asks whether it would make more sense to just do whole genome or whole exome sequencing to know about all possible health risks.

Learning Objectives

1. Become aware of the history of US newborn screening.
2. Understand when carrier identification of minors occurs and the risks and benefits of this identification.

3. Be able to discuss under what circumstances carrier identification of minors is/ought to be encouraged, permitted and discouraged.
4. Understand the risks and benefits of predictive genetic testing for adolescents.
    - Be able to discuss under what circumstances predictive genetic testing of minors is/ought to be encouraged, permitted and discouraged.
    - Develop some familiarity with the debate regarding the disclosure of secondary findings that are identified in pediatric exome or genomic sequencing.

Suggested Readings for Instructor

American Academy of Pediatrics, Committee on Bioethics, Committee on Genetics; American College of Medical Genetics and Genomics, Social, Ethical and Legal Issues Committee. Policy statement: Ethical and policy issues in genetic testing and screening of children. *Pediatrics.* 2013;131(3):620-622

Ross LF, Saal HM, David KL, Anderson RR; American Academy of Pediatrics; American College of Medical Genetics and Genomics. Technical report: ethical and policy issues in genetic testing and screening of children. *Genet Med.* 2013;15(3):234-245

Further Readings

American College of Medical Genetics and Genomics. Incidental findings in clinical genomics: a clarification. *Genet Med.* 2013;15(8):664–666

Botkin JR, Belmont JW, Berg JS, et al. ASHG Position statement: Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet.* 2015;97(1):6-21

Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565-574

Mardis ER. The $1,000 genome, the $100,000 analysis? Geno*me Med.* 2010;2(11):84

Ross LF, Rothstein MA, Clayton EW. Premature guidance about whole genome sequencing. *Per Med*. 2013;10(6):523-526

Wilfond B, Ross LF. From genetics to genomics: ethics, policy, and parental decision-making. *J Pediatr Psychol.* 2009;34(6):639-647

Case Discussion

Why were Shari's parents not aware that newborn screening was performed on their son Bob?
In the early 1960s, Dr Robert Guthrie developed a simple bacterial inhibition assay to measure phenylalanine in blood collected on filter paper to screen for phenylketonuria (PKU). PKU is an autosomal recessive metabolic condition which, if left untreated, can lead to intellectual disabilities. 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 F. Kennedy had a special interest in intellectual disabilities, in part because his sister Rose Marie was affected. A second key factor was the growing strength of the National Association for Retarded Citizens (NARC), now known as the ARC, a parent advocacy group that was keen on preventing disabilities. The third key factor was Robert MacCready, the state laboratory director for Massachusetts. MacCready, as chair of NARC's Public Health Service Committee, lobbied for mandatory legislation in Massachusetts because he thought uptake was not fast enough, and he was instrumental in encouraging Guthrie and NARC to support and advocate for mandatory legislation nationally. Guthrie and his supporters were successful, and today, in the United States, newborn screening is mandatory, meaning that it can be performed without parental permission, even without parental notification. However, in all states except Nebraska and South Dakota, parents have the right to refuse newborn screening.

What conditions are included in newborn screening?
Initially, expansion was slow because each condition required a separate screening test. However, the development of tandem mass spectrometry (MS/MS) in the 1990s, a platform technology that allows for screening for many conditions simultaneously with one sample, led to a rapid expansion in the early 2000s. Virtually all of the conditions included in NBS are autosomal recessive, meaning that both parents must be carriers to have an affected child. One exception is hypothyroidism, which is often not genetic. Severe combined immunodeficiency syndrome (SCID) is the first X-linked recessive condition to be added, and some states have also started to screen for X-linked adrenoleukodystrophy.

There is also newborn screening beyond the blood spot. Hearing screening is now universal in the United States, as is pulse oximetry screening to detect some cardiovascular and pulmonary conditions.

How should a pediatrician respond to a parental refusal of newborn screening?
The first step is to understand why parents 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 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 1/3000), the refusal does not qualify as neglectful.

What is Shari's risk of being a CF carrier?

The risk of being a carrier for many disorders varies depending on one's ancestry or ethnicity. In the Caucasian population, approximately 1 in 30 individuals are CF carriers. It is much less common in other ethnic groups. Because both of Shari's parents are carriers, it 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 2/3.

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. The statements give a variety of reasons for deferring carrier testing until adulthood, including (1) the minor's right to privacy; (2) the fact that many adults choose not to be tested; and (3) the unknown risks and benefits of screening for genetic information that will not be needed for a long period of time. Concern has been expressed that carrier identification of minors may lead to labelling 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 already do learn their carrier status in childhood. Sometimes this is known because it was identified as part of NBS. In many states, newborn infants who are carriers of sickle cell (known as sickle cell trait [SCT]) have been identified through NBS programs for almost 25 years, and the data do not show that this knowledge has been harmful. NBS programs are also identifying newborn infants who are carriers of CF, even though there are methodologies for CF screening that would not identify carriers. Other children know their carrier status because parents had prenatal testing performed, or because they were tested when a sibling was found to be affected. The psychological data about getting this information in childhood is 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 do 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 reproductive risk themselves.

Although being a carrier usually has no health implications, this is not always the case. For example, those with SCT are at increased risk of exertional heat illness (and the National Collegiate Athletic Association [NCAA] now requires screening of all college athletes for SCT). In general, though, carrier status is only identified for reproductive purposes, and the data are not clear about when it is the best time to learn this information. In some studies, some adults have stated that they wished they had known at a younger age. 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 regarding the voluntary nature 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 in a high school carrier screening program. One could argue that carrier information is about reproduction and should be covered by specialized consent statutes, which would allow adolescents to consent for themselves. On the other hand, one could argue that genetic information is complex and has familial implications, such that parental involvement should be required.

What role should Shari play in deciding about CF carrier testing?

In 2013, the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG) published a joint policy statement and technical report on genetic testing of children. In those publications, the AAP/ACMG position was to discourage carrier testing of adolescents unless it was clinically relevant. The American Society of Human Genetics (ASHG) came to the same conclusion in 2015.

What is Shari's risk of being a BRCA carrier and of developing breast cancer?

The risk of being a carrier for many disorders varies depending on one's ancestry or ethnicity. But in Shari's case, her mother is known to have a BRCA mutation. Because BRCA is an autosomal dominant gene, 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 not 100%, but rather falls between 30% and 85%. Given the high number of relatives with breast cancer, her risk of breast cancer if she were to have the mutation is 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. Although 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 genetic testing for adult-onset diseases in childhood. The arguments are (1) the child's right to privacy; (2) the child's right to make this decision as an adult; (3) the unknown impact of identifying carriers when the information is not relevant for years or decades; (4) concerns about self-identity and how others will treat the child; and (5) 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 Non-Discrimination Act (GINA) of 2008 should reduce this problem. There may, however, be discrimination regarding life insurance. There is also the concern of social stigmatization.

The benefit of knowing whether one is a carrier for BRCA is that there are actions a woman can take to reduce her risk of breast cancer. But there are no treatments or preventions that are recommended to begin in childhood, which is why testing minors is discouraged. Recommendations for adult women with BRCA include more frequent mammography screening starting at a younger age. Women may also choose to undergo prophylactic surgery.

What role should Shari play in deciding about BRCA genetic testing?
Again, both the joint statements by the AAP/ACMG and the recommendations of the ASHG are to discourage predictive genetic testing during adolescence even if Shari is eager for this information. Given that there are no clinical preventive measures or treatments that should change if one knows a person's BRCA status during childhood, the child's dissent should be definitive. This acknowledges the adolescent's emerging right to privacy about health information as well as her right not to know.

The data, however, do not necessarily confirm that the best time for predictive genetic testing is young adulthood. Rather, there may be circumstances in which predictive testing of adolescents is appropriate. If the family provides strong arguments why waiting would be harmful and both the parent(s) and adolescent want this information, they should receive appropriate genetic counseling. If the adolescent is assessed as being mature, is able to give rational reasons for wanting to be tested now, is able to give convincing arguments why waiting would be harmful, and has the support of his or her parent(s), then the justification for the state to override family autonomy is weak. This is not an endorsement of routine testing of adolescents for adult-onset conditions. 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. But if one is contemplating testing a minor for an adult-onset condition, the decision should be done during later adolescence when the minor can meaningfully participate and make his or her own benefit: risk evaluation. If there are no health risks in childhood, the adolescent's refusal should be respected. Ambivalence should be interpreted as a refusal.

Whether the adolescent should be able to get predictive testing for adult-onset conditions without involving his or her parent(s) 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 and outside of the reproductive context, it is not clear that there are compelling arguments to justify this.

Is the use of sequencing technologies ready for routine use?
Sequencing technologies have been under development since the early days of the Human Genome Project. Current screening usually focuses on whole exome sequencing, which targets the protein coding regions (< 2% of the genome) to reduce time and cost. Whole genome sequencing is more comprehensive and allows one to interrogate single-nucleotide variants (SNVs) and copy number variants (CNVs)—either of which may be clinically relevant in diagnostic dilemmas. Next generation sequencing uses a variety of sequencing methodologies that sequence DNA and RNA much more quickly and cheaply than the previously used Sanger sequencing. Although some sequencing has been quoted at costing less than $1000 per sample, Mardis argues that this ignores many of the other costs associated with interpretation of the results and counselling. Currently, sequencing is not a first-line diagnostic methodology.

Should adult-onset conditions identified secondarily with sequencing be disclosed to parents and children?
Although sequencing is not being used as a first-line diagnostic tool, it is being used in some settings for diagnosis with increasing success. In March 2013, the ACMG independently

published a statement in which it argued in favor of intentionally seeking out 56 genetic mutations known to be highly penetrant (at least in high-risk populations) whenever sequencing was performed, regardless of whether the patient or physician requested it, and even if they asked not to be informed. Although the ACMG refers to this as opportunistic screening, critics have labeled it a mandatory hunt. After significant professional and public debate, the ACMG continues to recommend interrogating all samples for these 56 genetic mutations, but they do acknowledge the right of patients and surrogates to refuse such information.

Whether returning secondary findings that identify mutations for adult-onset conditions should even be offered when the sample comes from a child remains controversial. The benefits of learning this information when sequencing is performed on a child is that it may warn a family about a health risk previously not seen or at least not recognized within a family. That is, it may benefit either the child, the parent, or both. Proponents support the additional screening because the sample is already being analyzed, although laboratorians object on the grounds that screening for the ACMG 56 requires additional interrogation, and it is not clear who will pay for this. The AAP/ACMG joint statements as well as the more recent ASHG statement all argue against identifying adult-onset conditions in childhood. Although the statements permit exceptions because family anxiety, for example, this is not relevant in unsuspecting (low-risk) families. Rather, such identification and disclosure ignores the child's right not to know and the child's right to privacy of health information from his or her own parents.

Identifying and disclosing risks of adult-onset conditions that are secondarily identified from sequencing is different than testing Shari for BRCA when she is known to come from a high-risk family in which the gene is highly penetrant (which may not be the case when BRCA is found in the low-risk population). Second, Shari has some lived experience with breast cancer and genetic screening, which can help inform her decision. Third, Shari may be experiencing anxiety from the uncertainty with which she lives, which is not the case for adolescents in the low-risk population who may be unaware of such risks.

Conclusions and Suggestions

In general, parents have wide discretion in health care decision making for their children. But there are limits, particularly when the health implications are not relevant to the child during childhood.

In general, carrier testing of minors should be discouraged.

In general, predictive testing of minors for late-onset conditions should be discouraged. However, in extenuating circumstances, when the family believes that not testing is causing serious psychological harm, testing may be permissible.

Sequencing is not ready for use in healthy children. It is increasingly being used as a second- or third-tier test for children with diagnostic dilemmas. When performed on pediatric samples, there should be limited return of secondary findings for conditions that do not present in childhood or are only relevant for reproductive purposes.

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