Obstetrics and Pediatrics

The Second Article in a Series about the Significance of Genetic Science for Catholic Health Care

A MEDICAL VIEW

BY JUDITH PRATT ROSSITER, MD

Dr. Rossiter is director, The Perinatal Center, St. Joseph Medical Center, Towson, MD.

Historically, genetics was a discipline whose place in clinical medicine was limited almost entirely to the field of pediatrics, including the diagnosis and treatment of inherited syndromes and inborn errors of metabolism. Subsequently, applications of genetics were expanded into the realm of obstetrics, as prenatal diagnostic techniques and ultrasound offered windows through which one could view the developing fetus. Over the past two decades, with vast improvements in molecular genetics techniques and with the sequencing of the human genome, the incorporation of genetics into every field of medicine has become commonplace.

Early Pediatric Genetics

Pediatric genetics began as a descriptive field. Many syndromes were named by and for those physicians who first systematically described the syndromes' clinical features. For example, in a manuscript published in 1866 entitled "Observations on an Ethnic Classification of Idiots," J. L. H. Down, MD, characterized the features of Down syndrome.[1] Although descriptions of clinical syndromes were carefully recorded, beginning in the mid 1800s, understanding of their underlying mechanisms did not occur until many years later.

The first chromosome disorder identified was in 1959, when Jerome Lejeune, MD, reported that Down syndrome resulted from the presence of an extra copy of chromosome 21 (trisomy 21). In the 1940s, the accumulation of phenylketones was recognized as the cause of severe mental retardation in the metabolic condition phenylketonuria (PKU). Following this discovery, a screening test for PKU was developed by Robert Guthrie, MD, ultimately resulting in the birth of newborn screening in 1961. Currently, newborn screening is performed throughout the United States and accounts for the vast majority of genetic testing.

The Technologies Advance

The introduction of genetics into obstetric practice in the United States began with the availability of amniocentesis for prenatal diagnosis in the early 1960s. In this procedure, a small amount of amniotic fluid is obtained to test for fetal chromosome abnormalities or inherited conditions. Widespread application of genetic screening to obstetrics began in the mid-1980s with the introduction of maternal serum screening to identify pregnancies at risk for fetal neural tube defects or Down syndrome.

As technologies advance and as our understanding of inherited conditions increases, genetic testing and screening during pregnancy continue to grow. Carrier screening for recessive conditions is intended to identify couples at risk for having children with inherited diseases that are either debilitating or lethal. If both members of a couple carry a deleterious mutation in the same gene, each of their children has a 25 percent risk of inheriting the abnormal gene from both parents, thus being affected with the disease. The carrier parents usually have no clinical manifestations of the disorder.

In October 2001, the American College of Obstetricians and Gynecologists and the American College of Medical Genetics published a combined report outlining guidelines for pre-

conception and prenatal carrier screening for cystic fibrosis. The authors recommended that "cystic fibrosis carrier screening be offered to all couples in whom one or both partners are Caucasian and are planning a pregnancy or seeking prenatal care."[2] Outside of newborn screening, these recommendations represent the largest application of genetic screening in the United States to date.

Identifying Risk for Down Syndrome

With the movement of women into the workforce and the resultant delay in childbearing, the increasing risk of fetal chromosome abnormalities with advancing maternal age has become more apparent and—if the number of pages in medical journals devoted to a subject is any indication—a topic of great interest.

Screening for fetal chromosome abnormalities was introduced in the 1980s.

The majority of these articles focus on the question: How can we noninvasively identify those pregnancies at risk for Down syndrome (trisomy 21)? Initially, the only "screen" was a patient's age, with a gradual increase in risk for a fetus with an abnormal number of chromosomes with each subsequent year. For example, the risk of any chromosome abnormality in a live-born child of a 20-year-old is approximately 1:1,500; the risk to a 35-year-old is 1:180; and the risk to a 45-year-old is approximately 1:18.[3]

Over the years, maternal serum screening for fetal chromosome abnormalities has been expanded and refined. The screening was first introduced in the mid-1980s, following the retrospective observation of a low maternal serum concentration of alpha-fetoprotein (AFP, the primary fetal protein) in a pregnancy from which a baby with trisomy 18 was delivered. Further investigation revealed a consistent association between low maternal serum AFP concentration and fetal chromosome abnormalities, specifically trisomy 21 and trisomy 18.[4] This relationship proved to be significant, ultimately resulting in the incorporation of maternal serum screening for Down syndrome into routine obstetrics practice.

Over time, additional markers have been added, to the extent that patients are now offered a "quadruple screen," including AFP, human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and dimeric inhibin-A (inhibin). With this screen, which is performed between 15 and 20 weeks of gestation (three-and-a-half to four-and-a-half months), the detection rate of pregnancies at risk for Down syndrome is 75 percent, with 5 percent (1 in 20) of all pregnancies being identified as "screen positive," that is, having a risk equal to or greater than that of a 35-year-old, 1:270.[5]

In the past decade, tremendous energy has been invested into moving screening for chromosome abnormalities into the first trimester (first 14 weeks or three months) of pregnancy. This can be accomplished by combining sonographic measurement of the space below the skin at the back of the fetal neck (nuchal translucency) with measurement of two maternal serum markers, pregnancy-associated plasma protein A (PAPP-A) and free beta hCG. This screening, performed between eleven-and-a-half and thirteen-and-six-sevenths weeks, can detect up to 85 percent of Down syndrome pregnancies.[6] Screening this early in pregnancy does, in fact, allow patients the greatest variety of reproductive options; the screening (some of which is contrary to Catholic moral teaching) has been enthusiastically accepted into clinical practice throughout the United Kingdom and in some parts of the United States.

Speaking personally, since we incorporated first-trimester screening into our center's practice, I have noted that patients increasingly opt for screening in an effort to avoid diagnostic testing and the attendant risk of pregnancy loss.

Current Diagnostic Procedures

When, through any screening method, a patient is identified as having an increased risk for a fetal chromosome abnormality, she is offered a diagnostic procedure that will provide a definitive answer. The current available techniques include placental biopsy or chorionic villus sampling (CVS); amniocentesis; and fetal blood sampling.

CVS is usually performed between 10 and 13 weeks (two to three months), preferably by a highly trained physician (usually a maternal-fetal medicine specialist or an obstetrician geneticist) and has a risk of miscarriage of 1:200, even when done by an experienced practitioner. Amniocentesis involves withdrawal of a small aliquot of fluid from the amniotic cavity, is most frequently done between 15 and 20 weeks (three and a half to four and a half months), but can be performed through term, and carries a 1:300 risk of miscarriage. Fetal blood sampling is limited to high-risk

circumstances, particularly when there is urgency in the timing of results. This technique, usually performed after 18 weeks (four months), entails obtaining blood from the umbilical cord under ultrasound guidance, and thus requires extensive training. The technique has a 1:100 (one percent) risk of pregnancy loss, even when performed by experienced hands. Patients who are appropriately counseled before a diagnostic procedure understand the technique, the alternatives, the information that may be gained, and the risks of the procedure.

Counseling Is Essential

Information obtained from prenatal diagnosis is often assumed to be solely for the purpose of determining whether to continue a pregnancy. My experience, based on directing prenatal diagnostic services at a Catholic hospital for eight years, is quite the contrary. Many patients are not interested in termination. Rather, they desire information that can help them either alleviate anxiety or to help prepare for the birth of a child with special needs.

Prenatal diagnosis allows for selection of an appropriate site for delivery, particularly should the baby require intervention in the newborn period, such as cardiac surgery. During the pregnancy, parents can meet with health care providers likely to be involved with their newborn's care, at a time when the immediate needs of the infant are not yet a concern. Often, the parents become educated about the baby's diagnosis, network with families of children with similar conditions, and select a pediatrician with familiarity with (or a willingness to learn about) the disease the baby is known to have. Counseling of patients who receive an abnormal result from prenatal diagnosis is essential so that they understand all of their options, are aware of the available resources, and feel supported, regardless of the decision they ultimately make.

Molecular Genetics and the Future of Prenatal Diagnosis

Recent advances in molecular genetics techniques allow information to be drawn from minuscule amounts of genetic material—as little as one cell. Two methods that have made this possible are polymerase chain reaction (PCR) and florescence in situ hybridization (FISH).

With PCR, specific segments of DNA can be copied from one or a few cells to make hundreds or thousands of copies of the gene segment(s) of interest. The copies can then be used to determine the genetic makeup of the original cell(s) with reference to a particular gene of interest, such as the cystic fibrosis gene for a family that has a 25 percent risk for having an affected child.

FISH technology involves attaching a fluorescent tag to a piece of DNA that is unique to a particular chromosome or chromosome segment. This "probe" (tagged DNA) is then used to identify that region, and by counting fluorescent signals in a cell, the number of copies of that chromosome or chromosome segment can be determined. For example, with a chromosome 21 probe, a normal cell would have two signals, whereas a cell from an individual with Down syndrome would have three.

The future may bring dramatic changes in prenatal diagnosis.

In combination with in vitro fertilization, PCR and FISH can be used for preimplantation genetic diagnosis. One or two cells are removed from each early embryo after in vitro fertilization. Depending on the condition for which the pregnancy is at risk, either PCR (for an inherited disease) or FISH (for chromosome abnormalities) is done. Only those embryos determined to be without the disorder are then "transferred," or placed into the uterus. And, though I am not proposing this, it is the case that some couples find this process to be preferable to prenatal diagnosis during pregnancy, particularly if they would like to avoid both pregnancy termination and a child with an inherited disease.

The future may bring dramatic changes in prenatal diagnosis. During pregnancy, a small number of intact fetal cells cross into the maternal circulation. Significant efforts have been focused on methods to identify and isolate these cells to allow for prenatal diagnosis without requiring an invasive procedure (CVS or amniocentesis). Though great strides have been made, this technology is far from ready for general practice. In contrast, many companies are actively developing microchips. These are tiny (e.g., two millimeters by two millimeters by one-tenth of a millimeter) chips coated with numerous small DNA segments (oligonucleotides) that can be used to test for dozens of different gene mutations at once, with an assay that can be run in a matter of min-

utes. This technology may soon be applied to carrier screening of pregnant women for a multitude of conditions, and perhaps even to fetal genome screening following CVS or amniocentesis.

Toward a National Agenda

Newborn screening is mandated by law throughout the United States, although each state legislature determines the extent of testing to be done in that state. As a result, the number of conditions for which screening is performed ranges from three to 36. All states screen for three conditions: phenylketonuria (PKU), hypothyroidism, and galactosemia. The rationale for newborn screening is to identify potentially treatable diseases prior to accumulation of metabolites (toxic substances) or intercurrent illness, which result in irreversible damage with most of the inborn errors of metabolism identified by newborn screening.

Newborn screening is mandated by law throughout the United States.

After a baby has been identified as having a disease, physicians immediately begin therapy and parental education in an effort to alter the long-term course of the disease. For some diseases, such as PKU, the impact of newborn screening and therapy has been dramatic. Untreated individuals with PKU develop severe mental deficiency, whereas those treated with dietary intervention can have normal IQs, hold regular jobs, and have families of their own. Although the promise of early intervention has not been universally realized, newborn screening is intended to improve the lives of children with inherited diseases.

Currently, the National Institutes of Health is working with a number of concerned parties, including the American Academy of Pediatrics, the Centers for Disease Control, the March of Dimes, and the Genetic Alliance to develop a national agenda for uniform newborn screening throughout the United States.

This agenda would involve nondiscriminatory screening, regardless of geographic location; centralized data collection; high-quality management; and resources for patient and family education. The participating organizations favor screening that uses tandem mass spectrometry (MS), a technique that allows identification of more than 20 inborn errors of metabolism. MS is somewhat controversial because many of the disorders it can identify have at present no available treatment of proven benefit.

Hope for the future of pediatric genetics extends beyond expanded newborn screening. Gene therapy has been successfully used to treat several inherited conditions, including severe combined immune deficiency and some lysosomal storage disorders.

Among the mechanisms by which gene therapy cures disease are:

- Introducing a functional gene
- Decreasing expression of an abnormal gene
- Enhancing expression of a normal gene

Over the years, numerous problems with gene therapy have been encountered. One involves targeting the gene to the specific cells or tissue in which gene expression must be altered. Another is identifying a suitable "vector," or vehicle, for introducing the genetic material into cells without compromising the patient as a whole. This has been a particular problem, as modified viruses have been used as vectors with varying success. Nevertheless, with continued investigation, gene therapy is likely to play a major role in treating some of the most devastating inherited conditions.

Difficult Decisions Ahead

As our understanding of the human genome increases, decisions will have to be made regarding testing and screening children for predisposition to adult-onset disease (such as diabetes and heart disease) and carrier status for recessive conditions. Currently, the American Academy of Pediatrics (AAP) recommends that such testing be deferred until adulthood, or at least adolescence, when the patient will have developed mature decision-making capability.

In addition, the AAP does not support carrier screening except in relation to a pregnancy. However, practitioners may soon be confronted by anxious parents who want genetic testing of their children for a variety of conditions, hoping that early identification may improve outcome, despite an absence of supportive data. The risks in running the test include possible inaccurate interpretation of the results, an absence of proven beneficial intervention, and stigmatization. Genetic testing of children should be approached with great caution. ■

NOTES

1. J. L. H. Down, "Observations on an Ethnic Classification of Idiots," *Clinical Lecture Reports, London Hospital,* 1866. The text can be found at http://home.vicnet.net.au/~dealcc/Downs.htm.
2. American College of Obstetricians and Gynecologists and American College of Medical Genetics, *Preconception and Prenatal Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines,* American College of Obstetricians and Gynecologists, Washington, DC, 2001.
3. E. B. Hook, "Rates of Chromosome Abnormalities at Different Maternal Ages," *Obstetrics and Gynecology,* vol. 58, no. 3, 1981, pp. 282-285.
4. I. R. Merkatz, et al., "An Association between Low Maternal Serum Alpha-Fetoprotein and Fetal Chromosome Abnormalities," *American Journal of Obstetrical Gynecology,* vol.148, no. 7, 1984, pp. 886-894.
5. N. J. Wald, W. J. Huttly, and A. K. Hackshaw, "Antenatal Screening for Down's Syndrome with the Quadruple Test," *Lancet,* vol. 361, no. 9,360, 2003, pp. 794-795.
6. N. J. Wald, H. C. Watt, and A. K. Hackshaw, "Integrated Screening for Down's Syndrome Based on Tests Performed during the First and Second Trimesters, " *New England Journal of Medicine,* vol. 341, no. 7, 1999, pp. 461-467.

AN ETHICAL VIEW

BY CAROL A. TAUER, PhD

Dr. Tauer is professor emeritus, College of St. Catherine, St. Paul, MN, and currently visiting faculty, Center for Bioethics, University of Minnesota, Minneapolis.

Genomic advances promise to revolutionize the provision of health care in the coming decades. With these advances come new challenges. How can the benefits of genomic progress be provided in a way that is ethically sound and consistent with the values of the Catholic health ministry? Because much genetic testing and counseling is related to reproductive decisions and reproductive medicine, Catholic institutions may have a tendency to avoid offering genetic services. Yet experience shows that genetic services can be provided in ways that are consistent with Catholic values. Indeed, given the increasing importance of genomics, "the critical question for Catholic health care is not so much *whether* we should pursue genomic advances, but, rather, *how* we should pursue them."[1]

The Catholic Health Association has prepared a Catholic vision statement to guide our consideration of genomics. This statement, *Harnessing the Promise of Genomics: A Catholic Vision toward Genomic Advances,* focuses on three foundational principles:

- The *principle of human dignity* requires that we respect every human life, its value and its potential, and that we work to eliminate practices that discriminate among humans on the basis of perceived or actual limitations.
- The *principle of relationality* requires a balance between the needs and desires of an individual, on one hand, and, on the other, the responsibilities and relationships of that individual within the family, the community, and the larger society.
- The *principle of solidarity* reminds us of our obligation to care for those who are most needy, economically, physically, or psychologically, and our responsibility, as we pursue medical and genomic advances, to ensure basic health care for all.Although abstract, these three principles have direct application in concrete situations encountered in genomic medicine. In this article, I will examine their application in two broad areas: (1) genetic testing and screening in relation to reproductive decisions; and (2) screening and testing of children, including newborn screening and presymptomatic genetic testing.

Preventing the Transmission of Genetic Diseases

Prospective parents as well as their obstetric providers hope for the birth of a healthy child. The healing mission supported by the Catholic Church recognizes that preventing a disease or disabling condition is generally preferable to trying to deal with its effects later on. The goal is not perfectionism but the basic health status that is the foundation for normal human flourishing.

The church has long recognized this goal, even in its *Code of Canon Law,* where one of the impediments to valid marriage—blood relationship—was originally based on the belief that the offspring of two closely related individuals were "subject to grave physical and mental weakness."[2] Blood relationship was used to identify couples who were likely to transmit a hereditary defect,

JOURNAL OF THE CATHOLIC HEALTH ASSOCIATION OF THE UNITED STATES www.chausa.org

HEALTH PROGRESS®

Reprinted from *Health Progress*, July-August 2005