Inheritance

Chapter 20

Many diseases have a genetic origin and are passed on in families. Most primary immunodeficiency diseases are inherited in one of three different ways: X-linked recessive, autosomal recessive or autosomal dominant. Family history and laboratory studies can be helpful in establishing the possible role of genes or chromosomes in a particular primary immunodeficiency disease and may be useful to identify a particular pattern of inheritance.

Inheritance of Primary Immunodeficiency Diseases

Most of our physical characteristics are passed along from parents to children. Examples of these include the color of our eyes and hair, and the proteins that determine our blood type. In the same manner, many primary immunodeficiency diseases are inherited, or passed on, in families. The DNA in our cells contains about 30,000 genes that are responsible for the characteristics that make an individual unique. These genes are packaged on long, string-like structures called chromosomes. Every cell in the body contains all the chromosomes and consequently, all of the genes necessary for life.

Each of our cells contains 23 pairs of chromosomes, hence, 23 sets of genes. One of each pair of chromosomes is inherited from our mother while the other is inherited from our father. Since genes are on these chromosomes, we also inherit one gene (or message) for a certain characteristic (such as eye color) from our biological mother and one gene for the same characteristic from our biological father.

During egg and sperm production, the total number of 46 parental chromosomes (23 pairs) is divided in half. One chromosome of each pair, and only one, is normally passed on in each egg or sperm. When fertilization of the egg occurs, the 23 chromosomes contained in the egg combine with the 23 chromosomes in the sperm to restore the total number to 46. In this way each parent contributes half of their genetic information to each offspring.

All of the chromosomes except the sex chromosomes are called autosomes and are numbered from 1-22 according to size. One additional pair of chromosomes determines the sex of the individual. These are called the sex chromosomes and are of two types, X and Y chromosomes. As shown in *Figure 1*, females have two X chromosomes, and males have an X and a Y chromosome. As a result of having two X chromosomes, females can only produce eggs that have an X chromosome. In contrast, since men have both an X and Y chromosome, half of the sperm produced will contain an X chromosome and half will carry a Y chromosome. The sex of the baby is determined by which type of sperm fertilizes the egg. If the sperm that fertilizes (or combines with) the egg carries an X chromosome, the child that results will be a female. If the sperm carries a Y chromosome, the child that results will be a male.

Types of Inheritance

Many diseases are genetic in origin and are passed on in families. Most of the primary immunodeficiency diseases are inherited in one of two different modes of inheritance: X-linked recessive or autosomal recessive; rarely, the inheritance is autosomal dominant. Laboratory studies can be helpful in establishing the possible role of genes or chromosomes in a particular primary immunodeficiency disease. In addition, family history information may help to identify a particular pattern of inheritance, as can comparisons to other families with similar problems.

Consult the appropriate handbook chapter or your physician to learn whether a particular primary immunodeficiency disease is genetic, and if so, what form of inheritance is involved.

X-linked Recessive Inheritance

Since women have two X chromosomes, they usually do not have problems when a gene on one X chromosome does not work properly. This is because the second

X chromosome usually carries a normal gene and compensates for the abnormal gene on the affected X chromosome. Men have only one X chromosome, which is paired with their male-determining Y chromosome. The Y chromosome does not carry much active genetic information. Therefore, if there is an abnormal gene on the X chromosome, the paired Y chromosome has no normal gene to compensate for the abnormal gene on the affected X chromosome, and the boy (man) has the disorder. This special type of inheritance is called X-linked recessive.

In this type of inheritance, a family history of several affected males may be found. The disease is passed on from females (mothers) to males (sons). While the males are affected with the disease, the carrier females are generally asymptomatic and healthy even though they carry the gene for the disease because they carry a normal gene on the other X chromosome. The diagram in *Figure 2* illustrates how this kind of inheritance operates in the usual situation.

The Sex Chromosomes

CHAPTER 20; FIGURE 1
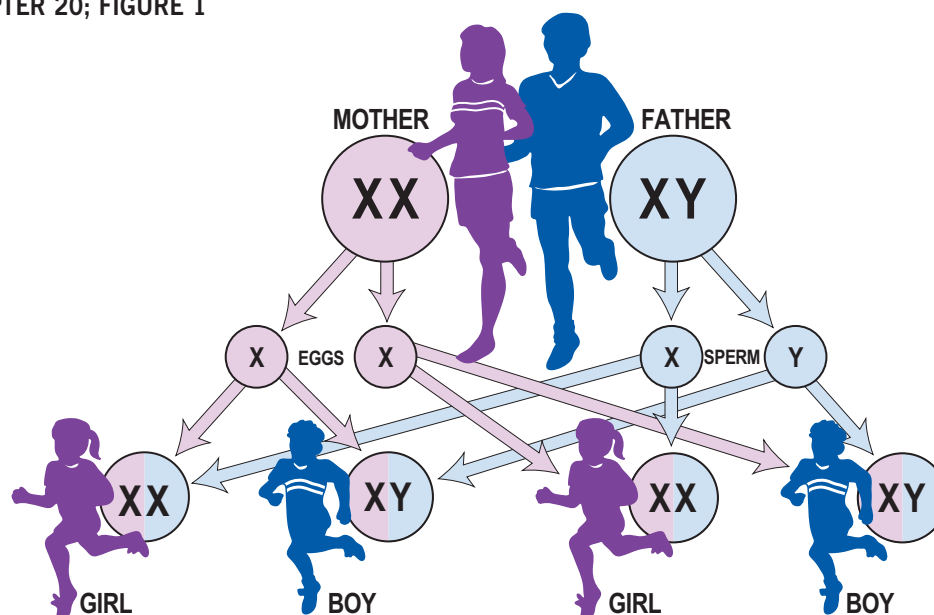
(Types of Inheritance continued)

X-Linked Agammaglobulinemia (XLA) is used as the specific example. Parents in the situation shown in *Figure 2* can have four different types of children with respect to XLA.

The X chromosome is diagrammed as an "X." An X chromosome that carries the gene for agammaglobulinemia is represented by an "AX." A normal X chromosome is represented by an "NX." A "Y" represents a Y chromosome.

The mother, who is a carrier, can produce two kinds of eggs—one containing an X chromosome carrying the agammaglobulinemia gene (AX) and one containing an X chromosome with a normal gene (NX). The father, who is unaffected, can produce two kinds of sperm— one containing a normal X chromosome (NX), and one containing a Y chromosome.

If the egg containing the agammaglobulinemia X chromosome (AX) combines with (or is fertilized by) the sperm containing the normal X chromosome, then a daughter who is a carrier (AX/NX) is produced. The gene for agammaglobulinemia is balanced out by the normal gene on the other X chromosome.

If the egg containing the agammaglobulinemia X chromosome (AX) combines with the sperm containing the Y chromosome (Y), then a male who is affected with agammaglobulinemia (AX/Y) is produced. In this case, there is no gene on the Y chromosome that corresponds to the gene that can cause agammaglobulinemia, and only the agammaglobulinemia gene is active in the child.

If the egg containing the normal X chromosome (NX) combines with the sperm containing the normal X chromosome (NX), then a normal female (NX/NX) is produced. In this case the child does not carry the agammaglobulinemia gene. Finally, if the egg containing the normal X chromosome (NX) combines with the sperm containing the Y chromosome (Y), then a normal male (NX/Y) results.

X-linked Recessive Inheritance - Carrier Mother

CHAPTER 20; FIGURE 2
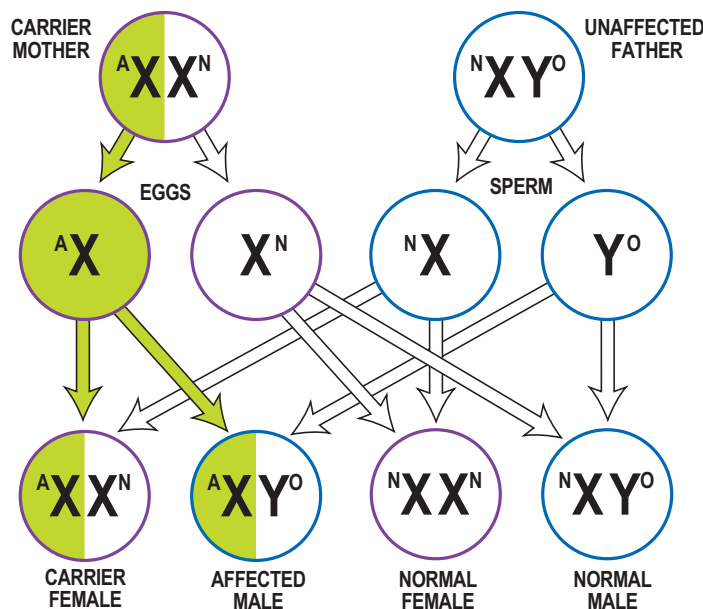
(Types of Inheritance continued)

Examples of Primary Immunodeficiency Diseases with X-Linked Recessive Inheritance:

- X-Linked Agammaglobulinemia (XLA)
- Wiskott-Aldrich Syndrome
- Severe Combined Immune Deficiency (SCID), caused by mutations in the common gamma chain
- Hyper IgM Syndrome, due to mutations in CD40 ligand
- X-Linked Lymphoproliferative Disease, two forms
- Chronic Granulomatous Disease (CGD), the most common form

The chances for a given egg combining with a given sperm are completely random. According to the laws of probability, the chance for any given pregnancy of a carrier female to result in each of these outcomes is as follows:

- Carrier female: 1 in 4 chance or 25%
- Agammaglobulinemia male: 1 in 4 chance or 25%
- Normal female: 1 in 4 chance or 25%
- Normal male: 1 in 4 chance or 25%

It should be noted that the outcome of one pregnancy is not influenced by the outcome of a previous pregnancy. Just as in coin flipping, the fact that you get a "heads" on your first toss does not mean you will get a "tails" on the next. Similarly, if you have a son with agammaglobulinemia with your first pregnancy, you are not guaranteed to have an unaffected child with your second pregnancy; your chances of having a son with agammaglobulinemia are still 1 in 4 (25%) with each pregnancy.

In several of the X-linked primary immunodeficiency diseases, carrier females can be identified by laboratory tests. If the gene mutation in a given family has been determined, genetic testing can identify carriers for any disease. Consult with your physician or genetic counselor to learn if carrier detection is available in your specific situation.

With earlier diagnosis and improved therapy, many young men with X-linked disorders, such as agammaglobulinemia, are reaching adulthood and having children of their own. *Figure 3* illustrates the

X-linked Recessive Inheritance - Affected Father

CHAPTER 20; FIGURE 3
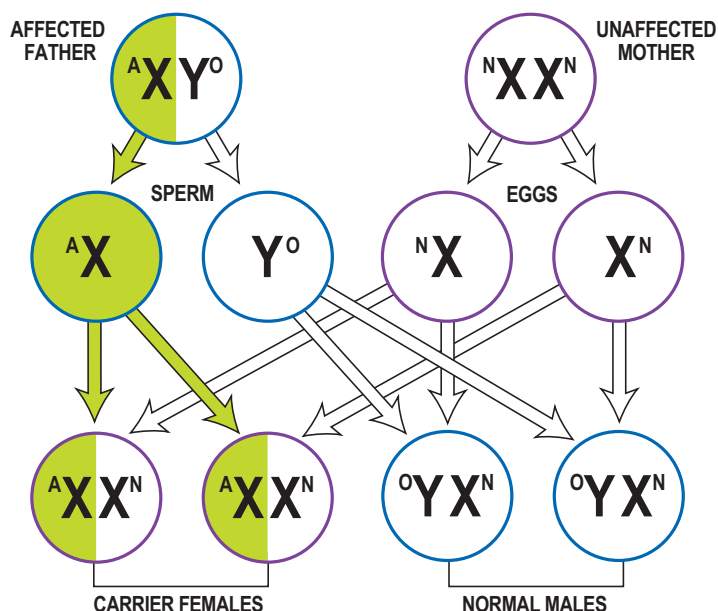
(Types of Inheritance continued)

kind of children that a man with XLA would have if he married a woman who did not carry the gene for agammaglobulinemia. As can be seen in *Figure 3*, all of the daughters of an affected male would be carrier females and none of the sons would be affected.

Autosomal Recessive Inheritance

If a primary immunodeficiency disease can only occur if two abnormal genes (one from each parent) are present in the offspring, then the disorder is inherited as an autosomal recessive disorder. If an individual inherits only one gene for the disorder, then he or she carries the gene for the disorder but does not have the disorder itself.

In this form of inheritance, males and females are affected with equal frequency. Both parents carry the gene for the disease although they themselves are healthy. *Figure 4* illustrates how this kind of inheritance operates in the usual situation. ADA-SCID is used as the specific example.

As illustrated in *Figure 4*, these parents, each of whom is a carrier, can have three different types of children with respect to SCID. The chromosome carrying the gene for SCID is diagrammed as a vertical line with the initials SCID next to it. The normal chromosome is diagrammed as a vertical line with the initial "N" next to it. The mother can produce two kinds of eggs—one containing the chromosome carrying the SCID gene and one containing a chromosome carrying the normal gene. Similarly, the father can produce two kinds of sperm— one kind containing the chromosome carrying the SCID gene and the other containing the chromosome carrying the normal gene. If an egg containing the SCID chromosome combines with a sperm containing the SCID chromosome, then a child with SCID is produced; in this case the child has two genes for SCID and no normal genes to counteract the SCID genes. If an egg containing the chromosome carrying the SCID gene combines with a sperm containing a normal chromosome then a carrier child results; in this case the

Autosomal Recessive Inheritance - SCID Example

CHAPTER 20; FIGURE 4
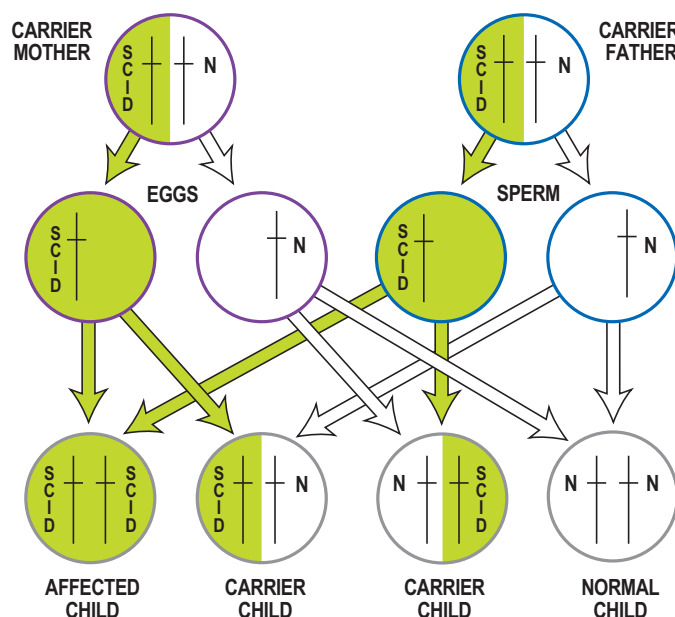
(Types of Inheritance continued)

gene for SCID is balanced by a normal gene and the child is well, but still carries the gene for SCID. Similarly, if an egg containing the normal chromosome combines with a sperm containing the chromosome carrying the SCID gene, a carrier child is produced.

Finally, if an egg containing the normal chromosome combines with a sperm containing the normal chromosome, a normal child who is not a carrier is produced.

The chances for a given egg to combine with a given sperm are completely random. According to the laws of probability, the chance for any pregnancy of carrier parents to result in each of the following outcomes is as follows:

- Affected child: 1 in 4 chance or 25%
- Carrier child: 2 in 4 chance or 50%
- Normal child: 1 in 4 chance or 25%

Again, it should be noted that the outcome of one pregnancy is not influenced by the outcome of a previous pregnancy. Just as in coin flipping, the fact that you get a "heads" on your first toss does not mean you will get a "tails" on your next. Similarly, if you have a child with SCID with your first pregnancy you are not guaranteed an unaffected child or a carrier child with your second pregnancy; your chances of having a child with SCID are still 25% or 1 in 4 with each pregnancy.

Examples of Autosomal Recessive Inheritance:

- Severe Combined Immune Deficiency, several forms
- Chronic Granulomatous Disease, several forms
- Ataxia-Telangiectasia

Autosomal Dominant Inheritance

In rare situations, a normal gene in the presence of a mutated gene cannot compensate for the defective gene; in this situation, the abnormal gene is said to exert a "dominant negative effect."

Examples of Autosomal Dominant Inheritance:

- Hyper IgE Syndrome, due to mutations in STAT3 (Jobs syndrome)
- Warts, Hypogammaglobulinemia, Infections and "Myelokathexis" (a form of neutropenia – low neutrophil counts) (WHIM syndrome)
- DiGeorge Syndrome
- Some rare forms of defects in the IFN- /IL-12 pathway

As illustrated in *Figure 5*, if one parent is affected with autosomal dominant Hyper IgE Syndrome, or Job's syndrome, due to a mutation in only one of the two genes for STAT3 (causing Job's syndrome), and the other parent has two normal STAT3 genes, only two types of children are possible.

The chromosome carrying the gene for Job's is diagrammed as a vertical line with the initials "JOBS" next to it. The normal chromosome is indicated as a vertical line with the initial "N".

In this situation, the father is affected, but since both his parents are normal, a "de novo" mutation had to have happened during the development of either the sperm or egg that formed the father. De novo refers to a "new" mutation causing an altered gene that was not present in either parent. De novo mutations occur regularly in the human genome, but since such a small fraction of the inherited DNA actually codes for functional genes, most de novo mutations go unnoticed. Only when such a mutation occurs in a critical gene does its presence become apparent in later generations. It has been estimated that for some rare X-linked diseases, as many as a third of newly diagnosed affected boys resulted from a de novo mutation that was not present in the genomic DNA of the mother.

The affected father produces two kinds of sperm, those containing the chromosome carrying the HIES (Job's) gene with the STAT3 mutation and those containing the chromosome carrying the normal gene. The unaffected

(Types of Inheritance continued)

mother, however, produces only eggs containing the chromosome with the normal gene. If such an egg combines with a sperm containing the chromosome with the HIES gene, the offspring (male or female) is affected. If the egg is fertilized by sperm containing the chromosome with the normal STAT3 gene, the offspring is unaffected.

Because the chances that a given egg combines with a given sperm (normal or with the HIES gene mutation) are completely random, the chance to have an affected child in this situation is 50% (2 in 4 possible outcomes). Again, the "coin flipping rule" applies: each pregnancy has a 50% chance of resulting in an affected child.

Autosomal Dominant Inheritance – Jobs Syndrome Example

CHAPTER 20; FIGURE 5
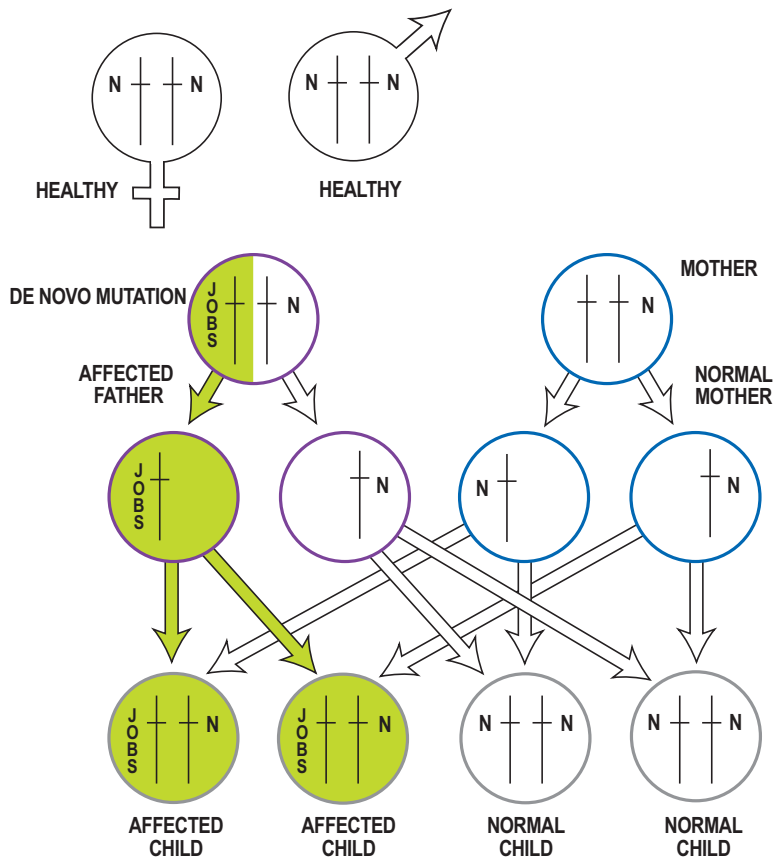
Carrier Testing

In many primary immunodeficiency diseases, carrier parents can be identified by laboratory tests. Consult with your physician or genetic counselor to learn if carrier detection is available in your specific situation.

Reproductive Options

After the birth of a child with a special problem, many families face complicated decisions about future pregnancies. The risk of recurrence and the burden of the disorder are two important factors in those decisions. For instance, if a problem is unlikely to occur again, the couple may proceed with another pregnancy even if the first child's problem is serious. Or if the risk of recurrence is high, but good treatment is available, the couple may be willing to try again. On the other hand, when both the risk and the burden are high, the circumstances may seem unfavorable to some families. It should be emphasized that these decisions are personal. Although important information can be gained from speaking to a pediatrician, immunologist, obstetrician and/or genetic counselor, ultimately the parents must decide which option to choose.

There are options available regarding family planning for families with members who have genetically determined (inherited) primary immunodeficiency diseases. In some situations, prenatal testing of a fetus in the uterus can determine whether the infant will be affected.

Chorionic villus sampling (CVS) or amniocentesis can be performed to obtain a fetal sample for chromosome, gene or biochemical testing. CVS is usually scheduled at 10-13 weeks of pregnancy and involves the retrieval of a tiny sample of the developing placenta from the womb. Amniocentesis is typically performed at 16-17 weeks of pregnancy and involves the withdrawal of fluid containing fetal cells that surrounds the fetus. Both procedures have a small risk of miscarriage that should be balanced against the benefits of the testing.

Chromosome studies can be performed on cells from CVS or amniocentesis. In addition to determining the chromosome number and structure, this study will identify the sex of the fetus. For conditions that are X-linked, identification of the sex will help determine whether the fetus could be affected by the disease (if male) or could be a possible carrier (if female). The fetal sample can also be used to provide DNA (deoxyribonucleic acid) for gene testing. There are two main types of DNA studies: direct and indirect. For some of the primary immunodeficiency diseases, specific gene changes, or mutations, can be identified in affected individuals. If the specific change, or mutation, is known in the affected family member who has the disorder, the mutation can then be tested for in the DNA from a fetal sample obtained during a subsequent pregnancy. This direct testing of the DNA for a specific mutation is the most accurate form of DNA testing. If a specific mutation has not been identified, or cannot be identified, a family linkage study may be possible to follow the mutated gene's transmission through the family. Normal DNA variations near the gene in question, called polymorphisms or markers, can be identified in some families. The inheritance of these markers near the gene of concern can be used to determine whether the gene has been passed on to the fetus.

In certain situations, other prenatal testing techniques may provide information about the risk of an affected fetus. For some conditions, biochemical measurement of a particular enzyme or protein in the fetal cells may provide an alternative method of testing for the disorder. Absence or severe deficiency of the enzyme produced by the gene mutation would indicate the presence of the disorder. A detailed sonogram at 16-18 weeks of pregnancy can often identify the sex of the fetus. This

(Reproductive Options continued)

information can be helpful to families deciding whether to undergo amniocentesis for an X-linked disorder. For some families, testing chorionic villus or amniotic fluid cells will not provide the proper information about the fetus's status, but testing of the fetus's blood will provide the proper information. This procedure can be performed after 18 weeks of pregnancy and involves the insertion of a needle into the fetus's umbilical cord or liver vein to withdraw a small amount of blood for testing.

If an affected fetus is identified through prenatal testing, the couple can then decide whether they wish to continue the pregnancy. Some couples at risk for autosomal recessive disorders elect to use donor sperm through a process called artificial insemination. Alternatively, in both autosomal recessive and X-linked recessive disorders, donor eggs can be used. The risk for an affected child is reduced substantially by using an unrelated donor, as the donor would be unlikely to be a carrier of the same condition. Finally, for certain conditions, testing of the early embryo may be possible after in vitro fertilization (conception outside the womb).

This process, called pre-implantation diagnosis, allows for those embryos unaffected with the genetic condition to be transferred to the woman's uterus. Afterwards the child is carried like any other until birth. Although this type of procedure is not yet readily available for the majority of the primary immunodeficiency diseases, it may be more accessible in the future.

Finally, the option of maintaining the current family size may seem best to some couples. This may be because the possibility of having an affected child is unacceptable or because the demands of the current family are high. Expansion of the family just may not be desired. Careful consideration of these options is important before decisions can be reached. In addition, periodic consultation with the medical staff can be helpful in keeping current with recent medical advances that could potentially provide more information for your family. Once again, it should be emphasized that these decisions are personal. Although important information can be gained from speaking to your pediatrician, immunologist, obstetrician and/or genetic counselor, the parents ultimately decide which option they choose.