50 Genetic Counseling

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Classical genetic counseling is aimed to help families with emotional support by disclosing and discussing the causes of certain “genetic” problems, the risks of recurrence, and the possibilities for prevention or other options. In many situations, no reliable figures for recurrence risk were available. The classic options in many cases included contraception, sterilization, adoption, or AID (artificial heterologous insemination by donor) (1–7).

Subsequently, a number of diagnostic techniques, applicable in pregnancy, became available, together with a much better understanding of genetically determined disease at many levels. Now, in many disorders, one can suggest undertaking further pregnancies, with the offer of *prenatal genetic counseling*: the phenotype may be examined (ultrasound, for malformations or growth retardation; cell biochemistry, for metabolic disorders) or the fetal genotype be examined (cytogenetic analysis, for chromosome disorders; DNA, for direct identification of mutant genes). There remain disorders for which no diagnosis is available or for which one can offer no more than “classical genetics,” but it is likely that many disorders at present of unknown cause will soon be understood at the biochemical or gene level, and that many presently “unmapped” genes will be mapped within the next decades (8).

The increased availability of prenatal diagnosis (available in more centers, for more patients, for more disorders) has stimulated the development of screening for genetic disease. Subpopulations at particular risk may be easily identified (e.g., older mothers) or identified only after specific testing (e.g., for thalassemia, hemoglobinopathies, Tay–Sachs disease, and, possibly, cystic fibrosis). The screening process may take place before or during an actual pregnancy; some screening methods, for example, biochemical markers, ultrasound, can be applied only during pregnancy (8).

The goal of genetic counseling is to *prevent birth defects* in cooperation with the couples (9). Without prevention, at least 3% to 4% of all births are associated with major congenital defect, mental retardation, or a genetic disorder.

Clinically significant chromosomal defects occurred in 0.65% of all births before prenatal diagnosis was introduced; an additional 0.2% of infants were born with balanced structural chromosome rearrangements. Congenital malformations, disruptions, and deformations with obvious *structural defects* were found in about 2% to 3% of all births. More than 9000 monogenic disorders and traits have been catalogued (10). Prevalence of monogenic disorders has been estimated to be 3.6 in 1000 live births, consisting of autosomal dominant (1.4 in 1000), autosomal recessive (1.7 in 1000), and X-linked (0.5 in 1000) (8).

The indications for *preconception genetic counseling* should be determined at the first visit and can be considered in a few clear categories:

- advanced maternal age,
- a previous fetus or child with a genetic disorder,
- a parent with a genetic disorder,
 - genetic disorders that pregnancy may aggravate,
 - maternal genetic disorders that may threaten fetal health and survival,
- a history of infertility,
- parental carrier of a genetic trait,
- family history of a genetic disorder,
- consanguinity (11), and
- environmental exposures that threaten fetal health.

Preconception counseling identifies specific risks and attendant options, which include the following:

- decision not to have children (includes consideration of vasectomy or tubal ligation),
- adoption,
- in vitro fertilization (IVF) and other reproductive technologies,
- carrier detection tests,
- presymptomatic diagnosis and predictive genetic testing,
- preimplantation genetic diagnosis (PGD), and
- folic acid supplementation in periconceptual period.

The optimal time to initiate counseling is not during pregnancy. Counselees whose first antenatal visits occur after the second missed menstrual period miss the critical period of organogenesis, and patients referred well after conception have lost almost all their options except selective abortion.

The ideal genetic counseling is composed of (12)

- an appropriately trained professional,
- relevant and objective information,
- assurance of the counselee’s understanding,
- psychologic support,
- informed consent,
- assuring autonomous decision-making,
- confidentiality of genetic information,
- considering familial implications, and
- appropriate handling of potential discrimination of testing.

The option of further pregnancies includes the option of prenatal diagnosis, which, in turn, includes the option of pregnancy termination. Many couples, even in high-risk situations, will be lucky and have a healthy child; only a few will go through the trauma of one or several terminations. Couples identified by screening as “high risk” may be at very high risk (25%) in the cases of monogenic traits, at a lower risk (10% ±) if identified through positive

biochemical tests, or at relatively low risk ($1\% \pm$) if identified by maternal age (13).

Decisions on pregnancy testing and termination must be the couple's own; it is the duty of the counselor to support and to inform, but not to persuade. Some couples refuse the idea of interrupting pregnancy, for example, for religious reasons. Unlike some infectious diseases, which may be controlled by immunization, compulsory screening, and therapy, genetic diseases do not endanger society directly. It is families that are affected by them (14–16).

Nevertheless, the indirect effect of genetic disease on society cannot be ignored. Unlike infectious diseases, genetic diseases do not threaten the health of other people, but they do burden society (e.g., the cost of institutional care for handicapped children). The question arises whether anybody has the right to insist on the birth of a child who will suffer from an undoubtedly incurable disease and also severely burden public finances. Some people do insist on continuing such pregnancies, and there is no doubt that the right to make individual decisions must be respected.

Often couples coming for genetic counseling are full of fears and anxiety, oppressed with the memory of one or more ill or dead children. Couples appreciate the opportunity for a counseling session and discussion, and the offer of prenatal diagnosis will be accepted by most of them (17,18).

Counseling sessions may often be strongly psychological in nature (19–24). It is essential to present a clear and full description of the relevant disorder and to answer all questions honestly and promptly. A good and harmonious relationship should develop or be developed between the counselor and the couple. The physician–patient relationship, always important in medicine, here is replaced by a physician/counselor–family relationship, which deepens in the course of counseling. This sort of relationship is necessary for the proper help and management of high-risk couples in this situation. A great deal depends on the character of the individual physician.

GENETIC TESTING

The completion of the Human Genome Project was a phenomenal accomplishment, providing researchers with the reference sequence of the human genome, which has subsequently led to the identification of many genes associated with human disease. Development of new technologies has made it possible to study these genes, search for disease-causing mutations, and develop genetic tests (25). Genetic testing has the potential to offer dramatic benefits, both clinically and psychologically, for patients and their families. The array of benefits begins with the clarification of diagnosis and prognosis, which assists in decision-making about clinical care. Testing for familial mutations makes available predictive, carrier, and prenatal testing, all of which provide risk assessment for family members of an affected patient to assist them in making complex personal, medical, and reproductive decisions. In addition, there are a multitude of genetic tests available to those with no family history of genetic disease that can provide information about potential reproductive or future health risks.

The process of ordering genetic testing can be a complex and often bewildering process for health-care professionals. There are challenges related to test selection, laboratory choice,

standards of practice, and ethical issues. Commonly, genetic counselors receive requests for genetic testing for disorders for which gene identification has only recently been reported in the scientific literature. Often these requests come from primary care providers, but increasingly they come from families who follow the research on a particular genetic disease that has been diagnosed in their family. The immediacy with which peer-reviewed research findings are available on publicly available Internet sites speeds up this process (26).

Historically, the broad categories of genetic tests were (i) cytogenetic tests (chromosome analysis), (ii) molecular tests (DNA analysis), and (iii) biochemical tests (enzyme assays, metabolites, protein analysis). Globally, cytogenetic tests detect changes in chromosome number, structure, and arrangement. Molecular tests look for changes in the DNA sequence, methylation, deletions, and duplications, and biochemical tests detect changes in the gene products, such as changes in levels of enzymes and proteins. Evolving technologies have led to considerable overlap between these categories of genetic tests as there are cytogenetic tests that actually use molecular/DNA methodologies, such as fluorescent in situ hybridization analysis and chromosomal microarray analysis. Genetic tests have different clinical applications, and these will influence the specific technology selected (26).

In genetic testing, it is often important to take into account both the genotype and the associated phenotype. The genotype is defined as the genetic makeup and the phenotype as the observable traits, characteristics, and symptoms. In an “ideal” genetic test, there is one-to-one relationship between the genotype and the phenotype. However, it is possible to have a genetic test that can accurately identify changes in genotype but can be quite limited in its ability to predict phenotype, particularly type and severity of symptoms, age of onset, and disease course. This limitation in predicting outcome can be particularly challenging and requires that genetic counselors use a wide variety of critical thinking, educational, and counseling skills in discussing these testing issues with patients.

Genetic testing is now widely available for diagnostic confirmation, predictive testing, and carrier and fetal risk assessment. Genetic counselors have a crucial role in evaluating the clinical usefulness of these tests as they work with patients and their families to assess the medical and personal benefits, as well as the risks, of undergoing testing. Critical thinking and assessment skills are needed to determine whether genetic testing is clinically indicated and in selecting the type of genetic test and the appropriate laboratory. Genetic counselors must be knowledgeable about test validation procedures and laboratory variability. Through consideration of the clinical utility of the genetic test and client-focused genetic counseling should precede the use of any genetic test. These considerations are particularly important before the utilization of new technologies, which may have a higher likelihood of inconclusive test results, or use of genetic tests whose outcomes directly influence medical interventions (27).

To appropriately select a diagnostic laboratory for their clients, genetic counselors must be aware of the rapidly evolving standards by which clinical laboratories are certified and the increasing involvement and oversight of other

government agencies and interested entities from the private sector. When a genetic counselor is not familiar with a laboratory, the genetic counselor should inquire about the laboratory's accreditation, the additional voluntary professional guidelines the laboratory follows, and the laboratory's participation in proficiency testing, both external and internal. In addition, it is important to determine the laboratory's experience with the particular test being considered and the specific technology utilized, as well as the training and certification of the laboratory and medical directors and other staff. In general, laboratories that voluntarily participate in multiple certification programs and that adhere to guidelines provided by professional organizations provide testing at a higher standard and should be utilized whenever possible.

Genetic counselors play a critical role in ensuring that their patients receive the "ideal genetic test," one that has optimal parameters for them. Genetic counselors should continue to participate actively in research aimed at evaluating the impact of the genetic testing outcomes and work with other stakeholders in defining enhanced oversight of genetic testing and global practice guidelines for the appropriate use of genetic tests (28–34).

QUESTIONS TO BE ANSWERED

Four questions must be answered by the genetic counselor: (i) What is the disease in question (clinical and laboratory diagnosis)? (ii) How severe is it (prognosis and therapeutic possibilities)? What can be done to treat the affected child postnatally? (iii) How is it caused/inherited (risk of recurrence)? (iv) What can be done to avoid or prevent the disease (prenatal diagnosis)? (35).

Diagnosis

Knowledge of the disease in question is a prerequisite of genetic counseling. Confirmation of an exact diagnosis, which is of basic importance, may be difficult. Obtaining old or recent medical records, pedigree analysis, careful history-taking, clinical examination of relatives, special laboratory tests, and other investigations (may be involving referral to other specialist departments) can all be relevant or necessary procedures (36).

The family history and pedigree are the basis for providing clients referred for genetic evaluation and counseling with a diagnosis, risk assessment, education, and psychosocial support. Accuracy, detail, and relevance are paramount. The genetic counseling student must develop a mastery of this fundamental task and employ standardized pedigree symbols and nomenclature that enhance the utility of the information obtained. The family history and pedigree have come a long way since the era of Francis Galton. An accurate and complete family history and pedigree lay the foundation for the highest standards of patient care and genetic counseling. They are tools now clearly viewed as having an essential role in all aspects of health care (37–41).

Disease, whether genetic or nongenetic, may be due to a variety of factors. Genetic disease is particularly likely to be heterogeneous in this respect. For example, a muscular dystrophy may result from a number of mutant genes. Among the common types of muscular dystrophy, we have the facioscapulohumeral form, which is characteristically auto-

somal dominant, and myotonic dystrophy, also autosomal dominant. "Limb-girdle" muscular dystrophy, a diagnosis that probably comprises a number of disorders, is autosomal recessive. Duchenne, Becker, and Emery–Dreifuss muscular dystrophies are all X-linked recessive, with fairly distinct, but overlapping, phenotypes; under some conditions, they can manifest, usually in mild degree, in females also (e.g., symptomatic carriers). Sometimes investigation of a family with "muscular dystrophy" reveals that the primary disease was not in the muscles at all but, for example, a spinal muscular atrophy, originating in the anterior horn cells, or a more generalized disorder, for example, a glycogenosis (42).

A practically identical clinical picture is characteristic of some of the commoner types of mucopolysaccharidoses. However, Hurler, Scheie, and Sanfilippo diseases are of autosomal recessive inheritance, whereas the Hunter disease is X-linked recessive.

It should be noted that there are diseases that do not usually manifest until adulthood (e.g., Huntington disease, facioscapulohumeral muscular dystrophy), and that in connection with certain diseases of recessive (autosomal or X-linked) inheritance, heterozygotes may also show clinical symptoms, for example, axillary and pubic hair may be sparse in heterozygotes for testicular feminization, cutaneous symptoms may be seen by gene carriers for Fabry disease, and nephrolithiasis occurs in heterozygotes for cystinuria.

In some cases, medical documents may be incomplete, or unobtainable; certain tests, which are now considered essential for the diagnosis, may not have been carried out or available at that time. There may be no histologic information, no postmortem report, no roentgenograms, no photographs, no biochemical results. Genetic counseling cannot be based on a diagnosis like "mental retardation," "growth disorder," or "degenerative disease." Sometimes an exact diagnosis, like "achondroplasia," may be clearly misleading. To make a correct diagnosis, with a few exceptions, requires detailed and correct information (42).

Prognosis and Therapy

Without a correct diagnosis, the genetic counselor cannot tell the parents whether there is a high or low risk of recurrence within the family, whether tests can be carried out to detect those persons/couples at high risk of having an affected child, whether prenatal diagnosis is possible (and if so, how, where, and when), whether the disease is in any way treatable, whether the severity is highly variable within a family, whether there are other (as yet undiscussed) serious implications, or whether other "reproductive options" are available.

Although much genetic disease remains untreatable, the counselor must know the possibilities for the disease in question. He/she must be up-to-date and informed about surgical procedures and appliances (e.g., neonatal or prenatal surgery, transplantation, artificial limbs), about medical treatment (e.g., physiotherapy and antibiotic therapy for cystic fibrosis, use of restricted/special diets—for phenylketonuria/galactosemia, use of specific vitamins—pyridoxine for certain epilepsies, hydroxocobalamin for B₁₂ transport disorders), and about what is available within the community (e.g., help from social services, financial help for parents with handicapped children, institutional care). He/she must be able to discuss

Table 1 General Population Risks	
Condition	Risk
Fetal loss	
in the first trimester	1/6
in the second and third trimesters	1/30–1/100
Neonatal death	1/100
Malformation detectable at birth	1/33
Mental retardation	1/50
Chronic disease in adulthood	1/5

more remote possibilities, such as “gene therapy,” within a realistic perspective. He/she must be able to talk to the parents in a way, and at a level, that is appropriate to their preexisting knowledge and education, and their degree of anxiety or depth of grief. He/she must be prepared to educate them further. He/she must be understood and supportive (42).

Genetic Risk

This term covers two concepts: the *general population risk* of a disorder/disease and the risk, or recurrence risk, of a disorder/disease in a specific family situation.

Many couples have no idea at all of general population risks. They may imagine that it is extremely unusual to abort spontaneously, bear a baby with a malformation, or have a child with mental retardation. They cannot understand how such things can happen, if they are not in the family already. They do not understand why a particular disaster happened to them, as they had done nothing to deserve or provoke it.

The general population risks for a few commonplace situations are given in Table 1. All genetic counseling has to be given, and understood, against this general “background” risk. For example, a couple may be horrified to be told there is a 1% recurrence risk for a certain malformation; they may perceive that as a very high-risk situation (although 100 to 1 odds in a gambling situation are usually perceived as far from certainty!). It may help couples realize that an additional risk of 1% for a malformation is not so enormous when compared with the starting risk of 3% to 5%; they have only a 33% increase above the general risk level.

In some counseling situations, couples may be at increased risk for one or a number of problems, as compared with general population risks, yet one is not talking of “recurrence risk,” the condition provoking anxiety, and the request for counseling has not yet happened. In these situations, *actual risk* may not be very high, though much above the general population level. For example, a woman of 40 has a risk of bearing a live-born with Down syndrome that is 20-fold the risk she ran when she was only 20. Yet the actual risk is only 1/100. Similar low levels of risk (yet high, compared with general population risks) may be associated for example with exposure to teratogens or radiation; slightly higher levels of risk will be run in cousin marriages.

Very high levels of risk, for a problem that has not yet appeared within the family, will seldom be met with except in connection with specific screening programs, for example, detection of Tay–Sachs heterozygotes in Ashkenazi Jews, of thalassemia carriers in Mediterranean populations; in these situations, when both (prospective) parents are heterozygotes, the risk of an affected child is 25%. In, virtually, all of these

very high-risk situations identified by screening, a prenatal test can be offered: but this would *not* be acceptable to *all* couples.

When a disorder has already appeared within a family, recurrence risks may be *high* (>1/10), *intermediate* (1/10–1/100), or *low* (<1/100): use of these words, high, intermediate, low, is extremely arbitrary. The counselor’s use of such words may be at variance with the use, or perceptions, of the counseled couple. To the counselor a risk estimate may appear intermediate or low, yet to the counseled couple it is high. Risk figures can be “rewritten” by turning statements around; 1/100 recurrence risk, for a serious malformation may appear formidable to the threatened parents; it is more reassuring to be told there is 99% chance that the baby will be unaffected. Risk figures should be compared with general population risks. The nature of the disorder/problem itself, and the impossibility/possibility of prenatal diagnosis, will affect the way it is perceived (8).

In some situations, recurrence risk is very low. If problems with a previous pregnancy were due to teratogen exposure, and the teratogen can be avoided in further pregnancies, risks may not be much above the general population risk.

Most malformations are multifactorially determined. After a child with an isolated exomphalos, or tracheo-esophageal malformation, recurrence risk may be 1% to 2% only; although this represents a 20- to 40-fold increase over the general population level, it is still not a very daunting risk. After having a child with congenital heart disease, the recurrence risks are usually 2% to 5% (depending on the malformation type); the background rate, for congenital heart disease, is nearly 1% (8/1000).

When dealing with a malformation problem, the counselor must be sure that it is really isolated and not part of a syndrome (that may be monogenic); for example, an occipital encephalocele alone might suggest a recurrence risk, for all types of neural tube defects, of about 2%; if the encephalocele was accompanied by cystic kidneys or polydactyly, the Meckel syndrome would probably be diagnosed, with a recurrence risk of 25%.

In families with monogenic disorders, many relatives will run risks that are intermediate or low. For example, with a heterozygote frequency of 1/25 for cystic fibrosis, risk to the child of a woman whose brother was affected is 1/150, and risk to a child of a man whose brother’s child was affected is 1/200. In families with X-linked recessive disease, some females, with no closely affected relatives (but with many unaffected brothers or maternal uncles), will be at very low risk for being carriers or having affected sons.

The background general population risk is not identical with the risk within a given family (*specific risk*), nor with the risk calculated for a given pregnancy (*actual risk*). For example, the background risk for a healthy person of being heterozygous for cystic fibrosis is 1/25, and the risk of his/her child being affected by the disease is 1/2500. However, the situation will change completely if it is revealed that the couples already have a child suffering from cystic fibrosis. In this case, the specific risk that both members of the couples are heterozygotes is 1/1, and the risk for a further child being affected is 1/4. If the couples undertake a pregnancy, and the pregnancy tests give normal results, the actual risk for an affected child will fall to about nearly zero.

To talk about 100% reliability of a biochemical or molecular prenatal diagnosis is, in practice, nonsense. The counselor

should not use words like “never” or “always.” Instead, expressions like “probably not,” “a very high chance,” and “almost certainly” are preferable and might also avoid legal complications! (42).

To explain the concept of risk, we may use analogies, for example, one coin (heads/tails) may be useful in explaining autosomal dominant inheritance and two coins may explain recessive inheritance.

Discussion of risk situations demands tact. In particular, one should avoid laying “blame” to one member of the couple: this might be difficult in the case of autosomal dominant or X-linked recessive disorders or inherited chromosome rearrangements. It is better, if possible, to spread the “responsibility” to both members of the couple: for example, with an X-linked disorder and an affected male child, the mother gave the mutant gene, but without the paternal Y chromosome all would have been well.

In cases of multifactorial determination, it is important not to accuse anybody, e.g., the physician who prescribed a drug or the factory in which the counselee was exposed to chemicals (and which guaranteed the safety of her work). An unfortunate combination of environmental factors and predisposing genes may be stressed. The counselor should intervene to prevent any further, possibly dangerous, exposure (43,44).

In many cases, the client’s concerns center not on the diagnosis of an affected individual but on assessing future reproductive or personal health risk. The counselor can sometimes make such an assessment by analyzing the pedigree, taking into account the pattern of inheritance and the client’s relationship to individuals with the condition. Mathematical calculations may be needed to incorporate additional information (e.g., carrier frequencies, test sensitivity and specificity, numbers of affected and unaffected individuals, the client’s age) to modify the risk. Questions about carrier status may be resolved with appropriate laboratory tests. When a condition has a multifactorial basis or is genetically heterogeneous, the best risk estimates may come from epidemiologic data on other families with affected individuals. Answering concerns about potentially mutagenic or teratogenic exposures also usually relies on empirical data about the agent in question and on evaluating the timing, duration, and dose of the exposure. In some areas of genetic counseling, such as cancer risk assessment, factors such as reproductive history, hormone use, and lifestyle issues such as smoking, obesity, or alcohol use are also important variables in risk assessment.

Prenatal Diagnosis

In very many counseling situations, the specific recurrence risk is so low that apart from a general screening for malformations, further tests are superfluous. A simple reassurance may disappoint certain couples if they feel that their problem has been oversimplified.

For most couples running a higher than average risk/recurrence risk, one can offer prenatal diagnosis. Cases require individual assessment. The reliability and the safety of the diagnostic procedures should be discussed with the parents. These should be carefully weighed, bearing in mind the nature and severity of the disease/disorder prompting the desire for diagnosis/termination. It should be explained that the test(s) will be for one problem only or a limited range of

disorders, and normal results will not guarantee a child normal in *every* way.

The final decision, to accept or reject the offer of prenatal diagnosis, is for the couple to make. Their decision will reflect their attitude to the disorder in question, and also their feelings regarding termination of pregnancy, should the test show an “affected” fetus. They should *not* be required to give any consent in advance, regarding abortion in this latter eventuality.

The couples decide whether or not to undertake pregnancy and they decide whether or not to accept an offer of prenatal diagnosis. However, prenatal testing is time-consuming, laborious, and expensive; it uses human resources and materials that are, as a result, not available to others; it involves certain risks for the mother and fetus. If a couple are convinced that they would not terminate pregnancy in any event (an “affected” fetus), they will probably also be convinced that the risks, to mother and pregnancy, are not worth taking.

In some autosomal or X-linked recessive situations, prenatal diagnosis is, at present, impossible, even though the genetic risk is high. In this difficult situation, some counseled couples will decide the 25% recurrence risk is too high and will choose termination of an existing pregnancy, sterilization, conception by AID, or divorce and remarriage. Other couples regard the 75% chance of a healthy child a sufficient encouragement to make at least one more attempt to have a healthy child.

Decision-Making of the Couple: Nondirective Counseling

The physician/counselor gives information and the parents, in light of their own individual circumstances and attitudes, make the decision (45–48).

The parental decision will depend on a number of factors: of importance may be their optimistic or pessimistic attitude of mind, their ethical and religious principles, their level of education, and/or their social circumstances. Their previous experiences with the disease in question may also be of decisive importance. Many couples declare that they do not want to undergo another tragedy. This is a most convincing argument.

The personality of the counselor, too, is of great importance: the way in which information is imparted, the content and clarity of such information, the manner in which the couples’ own questions, fears, and problems are discussed and dealt with. Decision-making is extremely difficult and painful for some couples, and decisions will often have lifelong consequences. The counselor should help the couple to the best of his/her ability.

All over the world, genetic counseling is primarily done by biologists, geneticists, and various medical specialists, mainly pediatricians and obstetricians (49). Pregnant women and their partners facing various genetic problems can base their decision on information and advice made available by these professionals’ knowledge and expertise. Counseling can follow two principles: the more widely used nondirective genetic counseling and the so-called directive genetic counseling (50–53). Because the current era is dominated by legal claims against physicians, the nondirective method is more acceptable and more easily defensible, even though in *Ethical Considerations in Prenatal Diagnosis*, in many cases, patients expect and demand a decision-shaping process closely guided

by the physicians. When applying the nondirective method, the genetic counselor is ready to share information in a nondirective manner without committing to any potential alternative. It is very important that having thoroughly described the disease in question, the consultant should also inform the patient about the risk of occurrence and/or recurrence. After that, diagnostic alternatives should be described and offered—if there are any. This has to be done in a fashion so that the patients seeking counseling can understand the basic facts, and it may vary with the given circumstances. The patient's fear and anxiety must not be worsened by giving an opinion expressed in mystical complicated sentences that are incomprehensible to ordinary people. By this point, the couples have already started the decision-making process. The physician leaves it to the patients to use the intensive interactive process to arrive at their final decision (50,53–55).

PREDICTIVE TESTING AND PRESYMPTOMATIC DIAGNOSIS

Predictive (susceptibility) testing (sometimes called “predisposition testing” in the case of mutations with less than 100% penetrancy) identifies healthy individuals who may have inherited a genetic predisposition that puts them at increased risk of developing a multifactorial disease (e.g., Alzheimer disease or cancer), but who may never develop the disease in question (56). *Presymptomatic diagnosis* refers the identification of healthy individuals who may have inherited a gene for a late-onset monogenically inherited disease and, if so, will develop the disorder if they live long enough (e.g., Huntington disease) (57,58). DNA arrays could potentially include mutation probes for a large panel of late-onset disorders and an extended spectrum of mutations and polymorphisms for each one, dramatically complicating an already thorny genetic and social counseling problem (59). Do we have the right to inform the patient about the existence of untreatable disease before symptoms appear? Is it necessary to do so? Are we obliged to do that? Is this individual ill at all? Can or need populations be screened for certain diseases? Indeed, the development of some diseases might be slowed down if changes in lifestyle were implemented. The knowledge, however, that the development of serious disease is inevitable in a later stage of one's life could put a heavy burden on his everyday existence and might even change an individual's personality. Surviving in the knowledge that one is to expect to develop a malignant tumor by the age of 30 to 40 years is difficult (60–62). By the same token, possessing the relevant information might result in more careful diagnostic examinations, which should have a substantial effect on the life expectancy (8).

At the same time, it raises the question of who is entitled to know the information, that is, confidentiality, the individual affected or his relatives. One might think that only the individual affected should, but with the disease in question being a genetic one, are the relatives not affected too? Do they not have the right to know their risk? Is the parent obliged to tell his or her child? Can the child request the performance of a predictive test? (63) Can the parent make a decision on whether the examination should be performed for her minor child? (64). Susceptibility testing and presymptomatic

diagnostics in the absence of therapeutic options should be available if certain conditions are met. It is important that the individual be provided thorough information about the limits of testing, and the information contribute to enhancing the pathography and informing the family because, in many cases, it is impossible to predict the onset and seriousness of a particular disease and its symptoms. Awareness of susceptibility could induce a change in the lifestyle that could prevent or prolong the development of a disease. If a disease is inevitable, the individual will have the chance of planning for his or her short life, as in the case of Huntington disease. Such genetic information can influence plans for marriage and having children (8). The problem is further complicated by the shortcomings of available predictive genetic tests that still carry a factor of serious uncertainty about whether a disease will develop and, if it does, when exactly and to what extent. Given the onus of this information, if there is no medical advantage concerning prevention or treatment, these examinations can best be postponed until adulthood, when the individual is able to make decisions on crucial aspects of his own life. Considering the likely rapid dissemination of predictive tests, there is an urgent need to develop a well-thought-out, detailed legal framework. Prohibition cannot be allowed because it would deprive the individual of rather important information. The proper regulation would eliminate the situation of diametrically opposed interests among the parties and would make them interested in wide-ranging examinations.

TERMINATION OF PREGNANCY BECAUSE OF GENETIC INDICATIONS

Recent advances in technology have enabled the development of a wide range of methods for prenatal diagnosis (65). The demands of modern society are for a healthy “perfect baby” (66). The new techniques are aimed at early diagnosis of the abnormal fetus at a point where parents who wish to do so may terminate the pregnancy. The emphasis is not on the removal of the defective child, but rather on the provision of life for new healthy children, who may otherwise never have been born.

The most challenging moments of genetic counseling arise when a decision has to be made on the disposition of a pregnancy (67). From the consultant's point of view, those situations are the most difficult when the problem is so severe and the diagnosis is so bad that termination on a genetic basis may be proffered. Even in this case, the goal of nondirective counseling is to inform the patient about this option. The woman is about to resolve one of the most difficult situations of her life. The problems of fetal life have often been put in the center of debates, not only in professional circles, but also as a political issue. The rigid attitude of the Roman Catholic Church is well known and stirs a lot of debates even within that faith community. The church turns a deaf ear to the issue of termination and does not accept contraception as a legitimate option (with a few exceptions). Thus, it is difficult to provide the opportunities offered by the achievements of prenatal diagnosis to Catholics. In some liberal circles' view, parents must be assured of having the widest possible sphere of authority. This cannot be readily accepted by a physician or an obstetrician-geneticist.

The weight of the decision depends on the gestational age of the pregnancy and other factors. Decisions on serious conditions detected in the first trimester are made easier (40). Given that most diagnoses are made in the second trimester, a very close relationship has sometimes developed between the fetus and the expectant mother by decision time. She may have seen its face during an ultrasound examination, and she may even know her offspring's sex. Realizing her widening waistline, the people around her may learn about the pregnancy, and this knowledge and having to wait make it even more difficult for her to cope. The necessity to make a decision presents a major state of crisis, the extent of which depends, among other things, on the obstetrical anamnesis. In such a case, the task is to give the relevant facts, help the patient to consider them thoughtfully and calmly, and encourage her to develop positive prospects for the future. It is important to outline the possible short-term and long-term consequences of the decisions, the risk of the defect being recurrent, and the details of its heredity.

If the woman opts to continue her pregnancy, she needs to be briefed on what sort of aid she can rely on from the fields of medicine and social services, as well as family care. Those deciding to terminate the pregnancy must be informed about the procedure to relieve tension and distress. In any case, this should ease the anxiety regarding the operation itself. It must be stressed that if the couple opts to terminate the pregnancy, the procedure must be initiated as early as possible. The methods used for midterm abortions vary from country to country. Third-trimester abortion also has a place in obstetrical practice. It is justified if the fetus will be unable to survive after birth, and the couple requests termination of pregnancy. Parents have a right to make this decision if the continuation of the pregnancy may increase the risk of maternal complications with no effect on fetal outcome (68,69).

Fetal disease or disorder diagnosed in a twin pregnancy may be concordant or discordant. In the former situation both fetuses are affected, and termination may be carried out as for a single pregnancy. In a discordant twin pregnancy, when only one of the fetuses is affected, three outcomes are possible: (i) the couple may decide against any form of termination; (ii) the parents may decide to lose both fetuses, the affected and the healthy one; (iii) partial selective termination, bringing about death of the affected twin while preserving the normal one, may be attempted. The dead fetus develops into a fetus papyraceus, while the other fetus should develop normally (70). Multifetal pregnancy reduction also has become a well-established and integral part of infertility therapy and the attempts to deal with sequel of aggressive infertility management. Now we have very clear and precise data on the risks and benefits as well as an understanding that the risks increase substantially with the starting and finishing number of fetuses in multifetal pregnancies (71). Regardless of the method, the objective is to get the procedure over within the shortest possible time and in the least intrusive way. The patient ought to get back to her home as soon as possible to be able to deal with the tragedy with her loved ones. Access must be made available to post-termination counseling (50,55).

POST-TERMINATION FETOPATHOLOGY AND COUNSELING

Fetopathology is a postmortem specialty concerned with causes and mechanisms of reproductive loss. In late first and early second trimesters, prenatal diagnosis of fetal anatomy by ultrasound became a major factor leading to termination. Even in centers with high rate of accurate prenatal ultrasound, a high percentage of fetuses with correctly diagnosed anomalies have additional defects that are not recognized by ultrasound. At the post-termination autopsy, the fetopathologist must concentrate on small, even minute anatomic details to find these additional defects to refine the pretermination diagnosis. It cannot be emphasized enough that with all terminations and pregnancy losses, the placenta should be submitted to the pathologist and the pathologist has to evaluate it in context with the clinical history and the postmortem findings of the fetus. The precise description of a clinically suspected anomaly and fine details of dysmorphic features and a solid final diagnosis are essential to the correct estimation of the recurrence risk so that the appropriate plan for surveillance in subsequent pregnancies can be instituted. Discussion of postmortem findings at regular fetal pathology/dysmorphology meetings is also recommended for education as part of a multidisciplinary approach. In these ways, fetopathology serves to promote the quality of the care of the individual and public health (72,73).

PREIMPLANTATION DIAGNOSIS

PGD is a technique devised within the last 20 years used primarily to identify genetic disorders or defects in human pre-embryos created by IVF prior to their implantation for gestation (74). PGD is intended to result in the selective destruction of extracorporeal human pre-embryos following genetic diagnosis. PGD is an attractive means of preventing genetic diseases, which, as an alternative to traditional prenatal genetic diagnosis, can avoid the need for termination of the affected fetuses. PGD is also used to detect aneuploidy and to select chromosomally normal pre-embryos for implantation, mostly in women of advanced maternal age undergoing IVF. The purpose of PGD is not simply to inform couples about the genetic nature of their pre-embryos, but the explicit purpose is also to transfer healthy pre-embryos (75). As a matter of general principle, prevention of the birth of a genetically or otherwise diseased or disabled child is plainly a morally legitimate goal. Nevertheless, strong moral objections have been made to the use of PGD to determine conditions that cannot plausibly be called "diseases," such as sex and the absence of desirable physical, mental, or social characteristics. The selection of an embryo's sex via PGD is done for two basic reasons: (i) preventing the transmission of sex-linked genetic disorders and (ii) choosing sex to achieve gender balance in a family with more than one child, to achieve a preferred order in the birth of children by sex, or to provide a parent with a child of the sex he/she prefers to raise. While little extended ethical debate exists regarding the former, sex selection for the purpose of preventing the transmission of sex-linked genetic disease, the latter is the subject of heated ethical disagreement (76). If some services become embroiled in the sex selection and in the detection of conditions having little or nothing to do with health and

disease and some traits unrelated to health in order to satisfy patient demand or be a profitable business, its practitioners will get, and deserve, serious ethical criticism (77).

SUMMARY

Over the last four decades, the portion of the patient population that needs genetic counseling services has steadily expanded. In the early years, genetic counselors met mostly with parents of children with genetic diseases or adults who had relatively uncommon disorders. Now we are counseling patients and families who are at relative risk for cardiovascular, oncologic, neurologic, and other common diseases (8,78).

The principles of genetic counseling are universal, even though the practice of genetic counseling varies nationally and internationally.

Genetic counseling is a dynamic profession, which undergoes rapid change with the discovery of new genetic information and the development of new genetic tests and treatment options.

The role of the genetic counselor is to provide the most complete information available. His/her role is *not* that of an *advocate* for society. The geneticist has continuing obligation to *recontact* patients when new information develops.

The 20th century witnessed revolutionary progress in the science of genetics that coincided with increasing societal demands, and therefore genetic counseling became an integral part of modern medicine and health care (79,80).

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