Advances in molecular genetics and fetal imaging have enriched our ability to secure early prenatal diagnosis of a rapidly enlarging spectrum of genetic and developmental disorders. *Pari passu*, a newly added layer of diagnostic uncertainty has dawned created by an extant lack of knowledge about polymorphisms and developmental structural and functional variations. Cognizance of “normal” has always been important and is especially critical in the evolution of fetal health. Analyses via chromosomal microarrays and whole-genome sequencing make mandatory the need to first delineate normal variation, if erroneous decision making is to be avoided.

The widening scope of molecular diagnostics and fetal imaging has increased opportunities for predictive, preconception, preimplantation and prenatal diagnosis. Consequently, genetic counseling for prenatal diagnosis can be expected increasingly to involve newly recognized microdeletion and microduplication syndromes (see Chapter 10), early adult-onset malignancies, neurodegenerative, cardiovascular and other fatal genetic disorders, as well as those with significant morbidity.

Against this background, physicians in all specialties are expected to be cognizant of new developments in genetics that facilitate the prevention or avoidance of genetic or acquired defects. In context, women at risk for having progeny with defects expect to be informed about their odds and options, preferably during preconception counseling. Their concerns are serious, given the significant contribution of genetic disorders to morbidity and mortality in children and adults.

**The incidence, prevalence and burden of genetic disorders and congenital malformations**

Various measures reflect the population burden of genetic disease and congenital anomalies. Common assessments include the incidence or prevalence of the disorder/defect, the associated morbidity and mortality, the degree of disability and suffering, life expectancy and economic burden. Indeed, many factors influence efforts to accurately determine the incidence or prevalence of congenital anomalies or genetic disorders. Box 1.1 encompasses the majority of known etiologic categories, discussed below, which help explain sometimes striking differences among major studies. It is almost impossible to account for all these potentially confounding factors in a study and rarely has any one study come close.

**Incidence and prevalence**

Estimates of aneuploidy in oocytes and sperm reach 18–19 percent and 3–4 percent, respectively. Not surprisingly, then, about one in 13 conceptions results in a chromosomally abnormal
More than 12,000 monogenic disorders and traits have been catalogued. Estimates based on 1 million consecutive livebirths in Canada suggested a monogenic disease in 3.6 in 1,000, consisting of autosomal dominant (1.4 in 1,000), autosomal recessive (1.7 in 1,000) and X-linked recessive disorders (0.5 in 1,000). Polygenic disorders occurred at a rate of 46.4 in 1,000 (Table 1.1).

At least 3–4 percent of all births are associated with a major congenital defect, mental retardation or a genetic disorder, a rate that doubles by 7–8 years of age, given later-appearing and/or later-diagnosed genetic disorders. If all congenital defects are considered, Baird et al. estimated that 7.9 percent of liveborn individuals have some type of genetic disorder by about 25 years of age. These estimates are likely to be very low, given, for example, the frequency of undetected defects such as bicuspid aortic valves that occur in 1–2 percent of the population. The bicuspid aortic valve is the most common congenital cardiac malformation.
prenatal diagnosis over a 21-year period (1979–1999) in a well-defined population showed a drop of 80 percent in the birth prevalence of DS. A later report from the Paris Registry of Congenital Anomalies (2001–2005) noted a “fairly stable prevalence of DS (7.1 per 10,000 livebirths) over time.” A study from Newcastle, England, based on ascertainment of all cases of NTDs revealed a twofold reduction in the birth prevalence between 1984–1990 and 1991–1996. A Scottish study aimed at assessing the impact of prenatal diagnosis on the prevalence of DS from 1980 to 1996. Both births and pregnancy terminations were included. Pregnancy terminations for DS rose from 29 percent to about 60 percent. In contrast, the prevalence of DS noted by the Dutch Paediatric Surveillance Unit in 2003 was 16 per 10,000 livebirths, exceeding earlier reports and thought to reflect an older maternal age cohort. In the US, a DS prevalence rate of 13 per 10,000 was found in metropolitan Atlanta (1979–2003).

The effect of folic acid supplementation, via tablet or food fortification, on the prevalence of NTDs, now well known to reduce the frequency of NTDs by up to 70 percent, (see Chapter 23) has only recently been assessed in this context. A Canadian study focused on the effect of supplementation on the prevalence of open NTDs among 336,963 women. The authors reported that the prevalence of open NTDs declined from 1.13 in 1,000 pregnancies before fortification to 0.58 in 1,000 pregnancies thereafter (see Chapter 23).

In a population-based cohort study by the Metropolitan Atlanta Congenital Defects Program, the risk of congenital malformations was assessed among 264,392 infants with known gestational ages born between 1989 and 1995. Premature infants (<37 weeks of gestation) were found to be more than twice as likely to have been born with congenital malformations than infants at term. Twins have long been known to have an increased rate of congenital anomalies. A UK study of 2,329 twin pregnancies (4,658 twins) and 147,655 singletons revealed an anomaly rate of 405.8 per 10,000 twins versus 238.2 per 10,000 singletons (relative risk (RR) 1.7). The prevalence rate of anomalies among known monochorionic twins (633.6 per 10,000) was nearly twice that found in dichorionic twins (343.7 per 10,000) (RR 1.8).

and in the final analysis may cause higher mortality and morbidity rates than all other congenital cardiac defects. A metropolitan Atlanta study (1998–2005) showed an overall prevalence of 81.4 per 10,000 for congenital heart disease among 398,140 livebirths. These numbers lead to a significant genetic disease burden and have accounted for 28–40 percent of hospital admissions in North America, Canada and England. Notwithstanding their frequency, the causes of over 60 percent of congenital malformations remain obscure.

The availability of prenatal diagnosis and maternal serum screening for neural tube defects (NTDs) and Down syndrome (DS) has also affected the birth frequency of these two most common congenital defects. One French study of the impact of prenatal diagnosis over a 21-year period (1979–1999) in a well-defined population showed a drop of 80 percent in the birth prevalence of DS. A later report from the Paris Registry of Congenital Anomalies (2001–2005) noted a “fairly stable prevalence of DS (7.1 per 10,000 livebirths) over time.” A study from Newcastle, England, based on ascertainment of all cases of NTDs revealed a twofold reduction in the birth prevalence between 1984–1990 and 1991–1996. A Scottish study aimed at assessing the impact of prenatal diagnosis on the prevalence of DS from 1980 to 1996. Both births and pregnancy terminations were included. Pregnancy terminations for DS rose from 29 percent to about 60 percent. In contrast, the prevalence of DS noted by the Dutch Paediatric Surveillance Unit in 2003 was 16 per 10,000 livebirths, exceeding earlier reports and thought to reflect an older maternal age cohort. In the US, a DS prevalence rate of 13 per 10,000 was found in metropolitan Atlanta (1979–2003).

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Table 1.1 The frequencies of genetic disorders in 1,169,873 births, 1952–1983

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate per million livebirths</th>
<th>Percentage of total births</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Dominant</td>
<td>1,395.4</td>
<td>0.14</td>
</tr>
<tr>
<td>Recessive</td>
<td>1,665.3</td>
<td>0.17</td>
</tr>
<tr>
<td>X-linked</td>
<td>532.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Chromosomal</td>
<td>1,845.4</td>
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</tr>
<tr>
<td>Multifactorial</td>
<td>46,582.6</td>
<td>4.64</td>
</tr>
<tr>
<td>Genetic unknown</td>
<td>1,164.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Total</td>
<td>53,175.3</td>
<td>5.32</td>
</tr>
<tr>
<td>B All congenital anomalies 740–759b</td>
<td>52,808.2</td>
<td>5.28</td>
</tr>
<tr>
<td>Congenital anomalies with genetic etiology (included in section A)</td>
<td>26,584.2</td>
<td>2.66</td>
</tr>
<tr>
<td>C Disorders in section A plus those congenital anomalies not already included</td>
<td>79,399.3</td>
<td>7.94</td>
</tr>
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</table>

a Sum is not exact owing to rounding.
b International Classification of Disease numbers.
A key study of homozygosity in consanguineous patients with an autosomal recessive disease showed that on average, 11 percent of their genomes were homozygous. Each affected individual had 20 homozygous segments exceeding 3 cM.

Incidence/prevalence rates of congenital defects are directly influenced by when and how diagnoses are made. Highlighting the importance of how early a diagnosis is made after birth, the use of echocardiography and the stratification of severity of congenital heart defects, Hoffman and Kaplan clarified how different studies reported the incidence of congenital heart defects varying from 4 in 1,000 to 50 in 1,000 livebirths. They reported an incidence of moderate and severe forms of congenital heart disease in about 6 in 1,000 livebirths, a figure that would rise to at least 19 in 1,000 livebirths if the potentially serious bicuspid aortic valve is included. They noted that if all forms of congenital heart disease (including tiny muscular ventricular septal defects) are considered, the incidence increases to 75 in 1,000 livebirths.

The frequency of congenital defects is also influenced by the presence or absence of such defects in at least one parent. A Norwegian Medical Birth Registry population-based cohort study of 486,207 males recorded that 12,292 (2.53 percent) had been born with a congenital defect. Among the offspring of these affected males, 5.1 percent had a congenital defect, compared with 2.1 percent of offspring of males without such defects (RR 2.4).

Maternal obesity also has the potential for increasing the prevalence of congenital anomalies. In a population-based case–control study excluding women with pre-existing diabetes, Watkins et al. compared the risks of selected congenital defects among obese women with those of average-weight women. They noted significant odds ratios for spina bifida (3.5), omphalocele (3.3), heart defects (2.0) and multiple anomalies (2.0). Others found a 2.2-fold increased risk of spina bifida in the offspring of obese women. Our own studies have pointed in the direction of a prediabetic state or gestational diabetes as the biologic mechanism accounting for the increased rate of congenital anomalies in the offspring of obese women. In contrast, markedly underweight women reportedly have a 3.2-fold increased risk of having offspring with gastroschisis. Young nulliparous women have an increased risk of bearing a child with gastroschisis, those between 12 and 15 years of age having a more than fourfold increased risk.

The frequency of congenital hypothyroidism, now known to be associated with up to a fourfold increased risk of additional congenital malformations, represents yet another factor that may influence incidence/prevalence rates of congenital anomalies. A French study of 129 infants with congenital hypothyroidism noted that 15.5 percent had associated congenital anomalies. Nine of the 129 infants had congenital heart defects (6.9 percent).

Women with epilepsy who are taking anticonvulsant medications have an increased risk of having offspring with congenital malformations, noted in one study as 2.7-fold greater than those without epilepsy. The possible reduction of other congenital malformations as a result of folic acid supplementation remains to be proved.

### Congenital malformations and infant morbidity and mortality

The leading cause of infant death in the United States in 2005 was congenital malformations, deformations and chromosomal abnormalities, accounting for 19.5 percent of all infant deaths. Survival is clearly dependent on the severity or lethality of the congenital defect. The Centers for Disease Control and Prevention assessed mortality rates for infants born with trisomy 13 and trisomy 18. Using death certificates and other source data, the authors identified 5,515 infants born with trisomy 13 and 8,750 born with trisomy 18. The median age at death for both trisomy 13 and trisomy 18 was 10 days. Survival to at least 1 year occurred in 5.6 percent of those born with trisomy 13 or trisomy 18. A regional study in The Netherlands noted lethal congenital malformations in 51 percent of stillbirths and 70 percent among those who died during the neonatal period. A Scottish study focused on the survival of infants with congenital anomalies up to the age of 5 years. They used a population-based and systematically validated registry of congenital anomalies containing 6,153 anomalous livebirths. Survival rates for these infants to the age of 5 were: chromosomal anomalies (48 percent), neural tube defects (72 percent), respiratory system anomalies (74
percent), congenital heart disease (75 percent), nervous system anomalies (77 percent) and DS (84 percent). The survival rate among males with congenital defects was 84 percent, compared with 97 percent in those born unaffected. Liu et al. examined temporal changes in fetal and infant deaths caused by congenital malformations in Canada, England, Wales and the United States. They concluded that the major factor responsible for the accelerated decline in infant deaths was prenatal diagnosis and elective abortion of fetuses with abnormalities. Given the frequency of DS, a more detailed discussion follows. NTDs are discussed in Chapter 24.

**Down syndrome**
The special problems and associated defects in DS are well known, as is the increasing life expectancy. Studies from Japan, Denmark, England, Australia and Canada highlight the increased life expectancy with DS. Baird and Sadovnik reported a large study of 1,610 individuals with DS identified in more than 1,500,000 consecutive live-

![Survival curves for Down syndrome and for the general population of British Columbia.](image)

*Figure 1.1* Survival curves for Down syndrome and for the general population of British Columbia. (Reproduced with permission from Baird and Sadovnik, 1987.)
Table 1.2 Life expectancy with Down syndrome, to age 68 years\textsuperscript{51}

<table>
<thead>
<tr>
<th>Age</th>
<th>Total</th>
<th>Deaths</th>
<th>Withdrawals</th>
<th>Survival at start of age interval (%)</th>
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A study from the Centers for Disease Control and Prevention focused on the death certificates of 17,897 individuals with DS born between 1983 and 1997. These authors reported that the median age at death for those with DS increased from 25 years in 1983 to 49 years in 1997 (Figure 1.2). They also observed that the median age at death was significantly lower among blacks and people of other races when compared with whites with DS. The authors acknowledge the limitations of their study given the known problems with the epidemiologic use of death certificates.

An Australian cohort study of 1,332 people with DS who had registered for intellectual disability services between 1953 and 2000 calculated a life expectancy of 58.6 years, with 25 percent expected to live to 62.9 years. The oldest person with DS was alive at 73 years of age. Their calculations concluded that 75 percent of people with DS would survive to 50 years, 50 percent to 58.6 and 25 percent to 62.9. The authors cautioned that this study was not a birth cohort and also omitted some deaths that occurred in infancy or early childhood. Nevertheless, they found that life expectancy of those with DS is approaching that of the general population of Australia, now approximating 76 years for males and 81.7 years for females. Another more recent Australian study found an overall survival figure for DS of 90 percent to at least 5 years of age. The known co-morbidity of DS and earlier onset Alzheimer’s disease casts a longer shadow. Over 50 percent of DS patients over 50 years develop Alzheimer’s disease and up to 84 percent of those with dementia develop seizures.

Table 1.3 reflects the common associated defects that occur in DS and the more common complications that can be anticipated, monitored, prevented and treated.

**The goal and purpose of prenatal diagnosis**

The fundamental philosophy of prenatal genetic diagnosis is to provide reassurance to couples at risk so that they may selectively have unaffected children even if their procreative risk for having defective offspring is unacceptably high. Fetal defects serious enough to warrant parental election of abortion are generally found in less than 5 percent of all cases studied, based on current indi-
sible for such high-risk couples to have children that they would otherwise never have conceived. As a consequence, the number of children born because of prenatal diagnosis is much higher than the very small number of pregnancies terminated because of the detection of grave fetal defects. Pre-

Figure 1.2 Median age at death of people with Down syndrome by sex (upper), by racial group (middle) and with or without congenital heart defects (CHD) by racial group (lower). (Reproduced with permission from Yang et al., 2002.)
CHAPTER 1  Genetic Counseling: Preconception, Prenatal and Perinatal

multiple-specialty clinical, counseling and laboratory teams. For the more common indications for prenatal diagnosis (such as advanced maternal age), the well-informed obstetrician should be able to provide the necessary information. However, a salutary observation in one study revealed that 43.3 percent of patients referred for amniocentesis exclusively for advanced maternal age had additional genetic risks or significant concerns regarding one or more genetic or congenital disorders. Neither a questionnaire in the physician’s office nor limited consultation time is likely to reveal many of these disorders. This group required more extensive genetic counseling. In a Hungarian study 98 percent and 92 percent of counsellees expected detailed information and the possibility of control over decision making, respectively.

Prerequisites for genetic counseling

Genetic counseling is a communication process concerning the occurrence and the risk of recurrence of genetic disorders within a family. The aim of such counseling is to provide the counselee(s) with as complete an understanding of the disorder and/or problem as possible and of all the options and implications. The counseling process is also aimed at helping families cope with their problems and at assisting and supporting them in their decision-making.

The personal right to found a family is considered inviolable. Such reproductive autonomy is enhanced by genetic counseling, a process that both emphasizes freedom of choice and reviews the available options in order to enrich the decision-making process. All couples have a right to know whether they have increased risk of having children with genetic disease and to know which options pertain to their particular situation. The physician and genetic counselor has a clear duty and obligation to communicate this information, to offer specific tests or to refer couples for a second or more expert opinion. In the United States, at least, the full force of law supports the prospective parents’ right to know (see Chapter 33).

As Kessler stated so succinctly, “Because genetic counselors work with people filled with uncertainty, fear of the future, anguish and a sense
of personal failure,” they have unusual challenges and opportunities “to understand clients, give them a sense of being understood and help them feel more hopeful, more valued and more capable of dealing with their life problems.” The physician and genetic counselor providing genetic counseling should have a clear perception of the necessary prerequisites, guiding principles and potential problems.

Knowledge of disease
The need for a counselor to have extensive factual knowledge about disease in general, as well as about the disease for which counseling is being provided, hardly needs emphasis. Such knowledge should include how the diagnosis is made and confirmed, the test accuracy and limitations, the important co-morbidities, the recurrence risks, the mode of inheritance, the tests available to detect a carrier (and their detection rates), the heterogeneity and pleiotropic nature of the disease, the quality of life associated with survival, prognosis and the causes of death. When relevant, it is necessary to know about treatment and its efficacy.

The physician or genetic counselor who initiates genetic counseling for an apparently straightforward indication (e.g. advanced maternal age) may find one or more other familial conditions with which he or she has little or no familiarity. Such circumstances dictate referral for specialist consultation. A National Confidential Enquiry into counseling for genetic disorders by nongeneticists in the United Kingdom revealed that less than half of those with known high genetic risks were referred to medical geneticists. This study focused on a review of 12,093 “genetic events” involving potentially avoidable cases of DS, NTDs, cystic fibrosis, β-thalassemia and multiple endocrine neoplasia. Medical record reviews were frustrated by the poor quality of clinical notes, which lacked evidence of counseling. An urgent call was made for genetic management to be at least as well documented as surgical operations, drug records and informed consent. A Dutch study evaluated the levels of knowledge, practical skills and clinical genetic practices of 643 cardiologists. They noted low levels of self-reported knowledge and that only 38 percent had referred patients to clinical geneticists. Other physicians too have been found lacking in the necessary knowledge and communication skills.

After the prenatal diagnosis of a serious genetic disorder, the physician should be able to inform the family fully about the anticipated burden and to detail the effects of this burden on an affected child, the family, other siblings, the family economics and marital relations, along with any other pros and cons of continuing pregnancy. The reality of early Alzheimer disease in DS and the care requirements that may devolve on the siblings should not be omitted from the discussion. Exact details should also be known about the risks of elective abortion (see Chapter 28).

Expertise in genetic counseling
Genetic counseling is best provided by board-certified clinical geneticists and genetic counselors. In countries with this specialization, such service is provided by a team composed of clinical geneticists (physicians) and genetic counselors, working in concert with clinical cytogeneticists, biochemical and molecular geneticists. It is, however, impractical and not cost effective to provide such formal counseling for every woman before prenatal diagnosis for advanced maternal age. It is necessary for the obstetrician to be fully informed about the indications for amniocentesis and to explain the techniques and requirements for obtaining the fluid, the limitations of the studies, the risks of chromosomal abnormality in the offspring of the patient being counseled, the risks of the procedure and, when pertinent, all matters concerned with elective abortion of an abnormal fetus.

Gordis et al. concluded that the way in which an obstetrician managed patients at risk regarding referral for genetic screening was closely related to that obstetrician’s attitudes and education. Physicians in practice should be aware of the nuances and needs in the genetic counseling process, including the key psychologic aspects. Perhaps most important is the requirement that they recognize limitations in their knowledge of uncommon or rare genetic disorders and be alert to situations requiring referral. Obstetricians or family practitioners are not expected to have an extensive knowledge of all diseases but they should be able to recognize that a condition could be genetic. Concern about litigation should not act as
a constant reminder to physicians of the need to consult or refer75–77 (see Chapter 33).

**Ability to communicate**

Many physicians are not born communicators and most have not had formal teaching and training to hone their communication skills. Recognizing these deficiencies, the American Academy of Pediatrics has provided valuable guidance and made specific recommendations for the development and teaching of communication skills,79 as have others.79a,79b

Simple language, an adequate allocation of time, and care and sensitivity are keys to successful genetic counseling. Technical jargon, used with distressing frequency,80 is avoided only through conscious effort. How an issue requiring a decision is framed,81 and the nature of the language used,82 may influence the patient’s choice.83 Counseling is facilitated when three key questions are asked: “Why did you come?” “What exactly do you hope to learn?” and “Have I answered all your questions and concerns?”

Although the explanation of exact statistical risks is important, patients often pay more attention to the actual burden or severity of the disease in question. How risks are explained and expressed is a skill to be mastered. Key to the exposition is the patients’ educational level, cultural background and the requirement of an interpreter (who may even bedevil a superb counselor). The use of numeric probabilities, relative risk, risk reduction or simple numbers of chance (1 in 100) or words (almost never, sometimes, more often than not)84 are choices a counselor must make. Clearly, the simpler, the better and the more likely the information is understood. Patients’ perceptions of risk not infrequently differ markedly from those of the counselor, a realization that should elicit no comment. An essential ingredient of the counseling process is time. The busy practitioner can hardly expect to offer genetic counseling during a brief consultation. Distress and misunderstanding are invariable sequelae of such hastily delivered counseling.

**Knowledge of ancillary needs**

For the couple at high risk of having a child with a serious genetic disorder, prenatal diagnosis is not the sole option. Even in situations in which a particular disease is diagnosable prenatally, it is important to be certain that other avenues are explored. Prospective parents who are known, for example, to be carriers of an autosomal recessive disorder may be unaware of the possibility of sperm or ovum donation or may be unwilling to raise the question. This option may be viewed more favorably than prenatal diagnosis and elective abortion. Physicians should be certain that their patients are familiar with all the aforementioned important options, as well as with adoption, vasectomy, tubal ligation, treatments of the mother and/or fetus during pregnancy and other methods of assisted reproduction (e.g. intracytoplasmic sperm injection,85 epididymal sperm aspiration,86 and preimplantation genetic diagnosis) (see Chapters 7 and 29).

**Empathy**

Empathy embodies the ability to not only understand the perspectives and emotions of others but to communicate that understanding.87 Much more than the communication of risk figures for a particular disorder is required in the genetic counseling process. Warmth, care, sympathy, understanding and insight into the human condition are necessary for effective communication. The difficulty of assimilating information and making rational decisions in the face of anxiety88 should be recognized and vocalized. Empathy and sensitivity enable the counselor to anticipate and respond to unspoken fears and questions and are qualities that make the counseling experience most beneficial and valuable to the counsees.

For example, a couple may have been trying to conceive for 10 years and, having finally succeeded, may be confronted by a callous physician who is impatient about their concerns regarding amniocentesis and elective abortion. Another couple may have lost their only child to a metabolic genetic disease and may be seeking counseling to explore the possibilities for prenatal diagnosis in a subsequent pregnancy or even treatment following prenatal diagnosis, as in the case of galactosemia. They may have in mind past problems encountered in prenatal diagnosis or may be aware of the uncertain outcome of treatment.

Sensitivity and awareness of the plight of prospective parents are critical prerequisites and
include the need to recognize and address the usually unspoken fears and anxieties. They may have had a previous affected child with physical/mental deficits and experienced stigmatizing encounters, including intrusive inquiries, staring and pointing, devaluing remarks and social withdrawal.\textsuperscript{89}

Beyond the qualifications and factual knowledge of the counselor is the person, who is key to successful and effective counseling. Attitude, body language, warmth, manners, dress, tone of voice and personality are facets that seriously influence the credibility and acceptance of the counseling offered. Curiously, counselors rarely realize during their counseling session that they are simultaneously being assessed. Patients assess the apparent knowledge and credibility of the counselor, seek and are encouraged by evidence of experience and consider the information provided in light of the counselor’s attitude, body language and other non-verbal characteristics.

Quintessential prerequisites for the empathetic genetic counselor include the following.

1. Acknowledge the burden and empathize about the sadness or loss (e.g. a previous child; recurrent miscarriage; a deceased affected parent; a patient who has experienced mastectomy and chemotherapy for breast cancer with daughters at risk).
2. Vocalize the realization of the psychologic pain and distress the person or couple has experienced (e.g. recurrent pregnancy loss followed by multiple IVF efforts and subsequently a successful pregnancy with a fetal defect).
3. Compliment the coping that has been necessary, including the stress a couple might have to endure, despite sometimes conflicting feelings.
4. Recognize (and explain) psychologic difficulties in decision making when faced with a prenatal diagnosis of the same disorder affecting one parent (discussion of self-extinction, self-image and issues of guilt and survival).
5. Fulfill the patient’s need for hope and support and actively avoid any thoughtless comments\textsuperscript{66} that may erode these fundamental prerequisites. Well-intentioned statements are not infrequently perceived in a very different way.\textsuperscript{78}

It is self-evident that empathy would engender greater patient satisfaction and may well be correlated with clinical competence.\textsuperscript{90}

**Sensitivity to parental guilt**

Feelings of guilt invariably invade the genetic consultation; they should be anticipated, recognized and dealt with directly. Assurance frequently does not suffice; witness the implacable guilt of the obligate maternal carrier of a serious X-linked disease.\textsuperscript{90a} Explanations that we all carry harmful genes often helps. Mostly, however, encouragement to move anguish into action is important. This might also help in assuaging any blame by the husband in such cases.\textsuperscript{91}

Guilt is not only the preserve of the obligate carrier. Affected parents inevitably also experience guilt on transmitting their defective genes.\textsuperscript{92,93} Frequently, a parent expresses guilt about an occupation, medication or illegal drug that they feel has caused or contributed to their child’s problem. Kessler et al.\textsuperscript{93} advised that assuaging a parent’s guilt may diminish their power of effective prevention, in that guilt may serve as a defense from being powerless.

Guilt is often felt by healthy siblings of an affected child, who feel relatively neglected by their parents and who also feel anger toward their parents and affected sibling. What is termed “survivor guilt” is increasingly recognized, as the new DNA technologies are exploited. Experience with Huntington disease and adult polycystic kidney disease\textsuperscript{94–100} confirm not only survivor guilt with a new reality (a future) but also problems in relationships with close family members. Huggins et al.\textsuperscript{97} found that about 10 percent of individuals receiving low-risk results experienced psychologic difficulties.

**Principles in genetic counseling**

Eleven key principles are discussed that guide genetic counseling in the preconception, prenatal and perinatal periods. This section is in concert with consensus statements concerning ethical principles for genetics professionals\textsuperscript{91,102} and surveyed international guidelines.\textsuperscript{103}

**Accurate diagnosis**

Clinical geneticists, obstetricians or pediatricians are frequently confronted by patients seeking guidance because of certain genetic diseases in their families. A previous child or a deceased sibling or parent may have had the disease in question. The
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consecutive, spontaneously aborted fetuses, almost one-third had malformations, most associated with increased risks in subsequent pregnancies. Myotonic muscular dystrophy type 1 (DM), the most common adult muscular dystrophy, with an incidence of about 1 in 8,000, serves as the paradigm for preconception, prenatal and perinatal genetic counseling. Recognition of the pleiomorphism of this disorder will, for example, alert the physician hearing a family history of one individual with DM, another with sudden death (cardiac conduction defect) and yet another relative with cataracts. Awareness of the autosomal dominant nature of this disorder and its genetic basis due to a dynamic mutation reflected in the number of trinucleotide (CTG) repeat units raises issues beyond the 50 percent risk of recurrence in the offspring of an affected parent. As the first disorder characterized with expanding trinucleotide repeats, the observation linking the degree of disease severity to the number of triplet repeats was not long in coming. In addition, the differences in severity when the mutation was passed via a maternal rather than a paternal gene focused attention on the fact that congenital DM was almost always a sign of the greatest severity and originating through maternal transmission. However, at least one exception has been noted. There is about a 93–94 percent likelihood that the CTG repeat will expand on transmission. This process of genetic anticipation (increasing clinical severity over generations) is not inevitable. An estimated 6–7 percent of cases of DM are associated with a decrease in the number of triplet repeats or no change in number. Rare cases also exist in which complete reversal of the mutation occurs with spontaneous correction to a normal range of triplet repeats. There are also reports of patients born with a decreased number of triplet repeats who nevertheless show no decrease in the severity of their DM. Instead of simply accepting the patient’s description of the disease – for example, muscular dystrophy or a mucopolysaccharidosis – the counselor must obtain confirmatory data. The unreliability of the maternal history, in this context, is remarkable, a positive predictive value of 47 percent having been documented. Photographs of the deceased, autopsy reports, hospital records, results of carrier detection or other tests performed elsewhere and other information may provide the crucial confirmation or negation of the diagnosis made previously. Important data after miscarriage may also influence counseling. In a study of 91 consecutive, spontaneously aborted fetuses, almost one-third had malformations, most associated with increased risks in subsequent pregnancies.

Myotonic muscular dystrophy type 1 (DM), the most common adult muscular dystrophy, with an incidence of about 1 in 8,000, serves as the paradigm for preconception, prenatal and perinatal genetic counseling. Recognition of the pleiomorphism of this disorder will, for example, alert the physician hearing a family history of one individual with DM, another with sudden death (cardiac conduction defect) and yet another relative with cataracts. Awareness of the autosomal dominant nature of this disorder and its genetic basis due to a dynamic mutation reflected in the number of trinucleotide (CTG) repeat units raises issues beyond the 50 percent risk of recurrence in the offspring of an affected parent. As the first disorder characterized with expanding trinucleotide repeats, the observation linking the degree of disease severity to the number of triplet repeats was not long in coming. In addition, the differences in severity when the mutation was passed via a maternal rather than a paternal gene focused attention on the fact that congenital DM was almost always a sign of the greatest severity and originating through maternal transmission. However, at least one exception has been noted. There is about a 93–94 percent likelihood that the CTG repeat will expand on transmission. This process of genetic anticipation (increasing clinical severity over generations) is not inevitable. An estimated 6–7 percent of cases of DM are associated with a decrease in the number of triplet repeats or no change in number. Rare cases also exist in which complete reversal of the mutation occurs with spontaneous correction to a normal range of triplet repeats.

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potential complications of pregnancy (Box 1.2) in the prospective affected mother is crucial.\textsuperscript{127}

The lack of CAG triplet expansion among individuals presenting with Huntington disease-like symptoms and a family history of neurodegenerative disease has focused attention on phenocopies of Huntington disease.\textsuperscript{128} Estimates of such phenocopies range between 1 and 2.4 percent of patients manifesting Huntington disease-like signs with a family history of a neurodegenerative disorder.\textsuperscript{129} Among the reported phenocopies found thus far are a familial prion disease\textsuperscript{128} and a triplet expansion (CAG/CTG) in the junctophilin-3 gene on chromosome 16 in patients presenting with Huntington disease-like manifestations.\textsuperscript{130}

The guiding role to explain a clinical diagnosis as due to a single cause will not always apply. Careful attention to the clinical presentation, including the family history, will enable recognition of more than a single disorder. Two examples include a personal case of hypohidrotic ectodermal dysplasia and the Loeps–Dietz syndrome and a reported case of concomitant spinal muscular atrophy and Rett syndrome.\textsuperscript{131}

**Nondirective counseling**

Physicians are accustomed to issuing therapeutic directives and indeed, patients invariably depend on such instructions to improve their health status. Such directive approaches are not consonant with the overwhelming consensus of opinion that governs genetic counseling. Nondirective genetic counseling has been endorsed by medical geneticists\textsuperscript{108,132–135} as well as by the World Health Organization Expert Committee on Genetic Counseling\textsuperscript{136} and in a multinational study focused on the attitudes of genetic counselors.\textsuperscript{137,138} In an analysis of nondirective genetic counseling, Kessler\textsuperscript{139} preferred this definition: "Nondirectiveness describes procedures aimed at promoting the autonomy and self-directedness of the client.” The role of the physician and genetic counselor is to provide the most complete information available, remaining impartial and objective in this communication process while recognizing a tenet of medicine as being to prevent disease. This might not be an easy task. Hsia\textsuperscript{140} validly observed that optimistic counselors may tell anxious individuals not to worry, whereas pessimistic ones might unwittingly exaggerate the significance of even small risks. Not unexpectedly, significant differences in counseling techniques mirror the divergent views of counselors on the goals, content and process of genetic counseling.\textsuperscript{14}

On the other hand, Kessler\textsuperscript{139} believes that the difficulties counselors have with answering direct questions and being nondirective reveal a lack of skill and an incompetence, which he lays at the door of inadequate training. In calling for correction of the major inadequacies in counseling, training and skill, he emphasized that nondirectiveness is an “active strategy” aimed at “evoking the client’s competence and ability for self-direction.” The expansion of genetic counseling training and degree programs (at least in the USA) has ameliorated many of these issues.

Michie et al.\textsuperscript{142} studied nondirectiveness in genetic counseling. They defined directiveness as advice and expressed views about or selective reinforcement of counselee’s behavior, thoughts or emotions. Not unexpectedly, they concluded that genetic counseling as currently practiced was not characterized, either by counselors, counselee or a standardized rating scale they used, as uniformly nondirective.

Clarke\textsuperscript{143} remarkably argued that nondirective genetic counseling in the context of prenatal diagnosis is “inevitably a sham,” largely because of the...
“structure of the encounter between counselor and client.” He further contended “that an offer of prenatal diagnosis implies a recommendation to accept that offer, which in turn entails a tacit recommendation to terminate a pregnancy” if the fetus is abnormal. Forty years ago, it was emphasized that the offer of prenatal diagnosis was not associated with any explicit or implicit commitment to abort. Clarke further opined that “non-directive counseling was unattainable, despite the counselor’s motives, since the offer and acceptance of genetic counseling has already set up a likely chain of events in everyone’s mind.” Experienced clinical geneticists were taken aback by his views and rightly so. He regarded reproductive choice as part of the “1980s consumerism model of clinical genetics.” The personal values of geneticists/counselors may influence behavior in clinical practice and individual vigilance is necessary to abide by the nondirective principle. This may be less challenging than imagined given the reported highly valued benevolence, self-direction and pattern of concern for the welfare of others. Clarke ignored a fundamental tenet of genetic counseling founded in a free society, where choice is not a fad but a right. His ideas suggest contempt for the views (and hence choices) of the public, maintaining that respect for the handicapped is not achievable in a society that “makes judgements about what types of people are worthy of life.” Others have reported that people’s decision-making processes are more rational than they might appear to be. Simms noted that with hindsight, 80 percent of parents with handicapped children would have aborted their pregnancies. Later, in taking Clarke to task, she concluded that it was “his professional duty to advise parents to the best of his ability, not to make decisions for them. They will have to live with the consequences: he will not.”

The intrinsic danger of using a directive approach is the opportunity (even subconscious or inadvertent) for the physician/counselor to insinuate his or her own religious, racial, eugenic or other beliefs or dictates of conscience into the counseling that is offered. A breach of this principle, supported by some, invites the provider to visit upon the patient unwarranted conscious or subliminal prejudices. Some obstetricians, for example, are known to have specifically not offered or referred patients for prenatal genetic studies because of their antiabortion views and have unconscionably exaggerated the specific risks of amniocentesis in order to discourage prenatal genetic studies. A Mexican study showed that physicians in specialties other than clinical genetics tend to counsel directly.

The duty of the physician and genetic counselor is to communicate all the available information and then to assist a counselee to recognize his or her major priorities, beliefs, fears and other concerns in order to make possible the counselee’s rational decision making. To remain impartial is difficult and takes valuable time and conscious effort but it is largely attainable. Time-pressed nongeneticists providing genetic counseling may easily experience slippage between choice and coercion. The difficulty lies mainly in trying to remain impartial while aiming to prevent the occurrence of genetic disease. The insinuation of the physician’s prejudices into the decision-making process of the counselee constitutes a moral affront to individual privacy and reproductive autonomy.

In rare instances, family circumstances may challenge the need to adhere to personal autonomy and nondirective counseling. The right of one monozygous twin at 50 percent risk for Huntington disease not to know information after predictive testing should be respected. If there is possible harm to the co-twin, Chapman suggested that testing should “be denied in the absence of mutual consent.” She further argued that in the interest of beneficence, directive counseling is acceptable for individuals at 50 percent risk of Huntington disease, who suffer from depression, lack social support and have a history of attempted suicide. For these patients, psychiatric evaluation and counseling, rather than predictive testing, have been recommended. In a study of counseling following prenatal diagnosis of Klinefelter syndrome, Marteau et al. found that pregnancy was almost two and a half times more likely to continue when counseling was provided by a geneticist.

Concern for the individual
Many issues should be raised by the physician or genetic counselor during counseling. Communica-
tion should not depend on questions posed by the patient, who may not be cognizant of the subject’s dimensions or the available options. For example, in the case of a couple who are at risk of having a profoundly retarded child, the physician should explore the consequences for the inter-relationships of the couple, the effects on their other children, the suffering of the affected child, the possible social stigma and the economic and other societal implications, as well as the need for contraception. Many feel that the economic burden of a defective offspring on society should at least be mentioned as part of a comprehensive view of all issues being considered. Although this may not be unreasonable, the major emphasis should focus on the concern for the individual, whose priorities, needs and choices remain paramount. In the physician/counselor–patient relationship, concern for the individual should always over-ride consideration of the needs of society. Many avenues exist for society to influence the actions of its citizens. In genetic counseling, the role of the physician/counselor is not that of an advocate for society.

A couple may elect to have an amniocentesis that is indeed indicated without making a commitment to pregnancy termination if the fetus is found to be abnormal. Some may deny such couples the opportunity for prenatal genetic studies. All couples have a right to have information about their fetus and prenatal diagnosis is a fundamentally reassuring technique. More than 95 percent of such couples do not need to consider elective abortion. The few who are initially ambivalent almost invariably move to terminate the pregnancy after the detection of a serious fetal defect. Nevertheless, abortion may be declined after the prenatal diagnosis of disorders such as trisomy 21, anencephaly or trisomy 13. Concern for the individual includes providing ambivalent couples with the opportunity for reassurance or the choice to decline abortion with preparation for the consequences. Moreover, opportunities to save their offspring’s life, or at least to improve the outcome, now exist in specific circumstances (e.g. for omphalocoele). The availability of adoption should be emphasized.

Quite often, a patient declines an otherwise clearly indicated amniocentesis. Today, the standard of care dictates the need for an explanatory note in the patient’s record. A brief letter to the patient noting the indication for prenatal study and that such study was declined is also helpful. Litigation has ensued in which patients have maintained that no amniocentesis had been offered, while obstetricians (without notes in the records) have taken an opposite view.

**Truth in counseling**

Since the time of Hippocrates, physicians have often withheld the truth from their patients and, as Katz emphasized in *The silent world of doctor and patient*, defended the morality of this position. Sparing the patient emotional distress, removing hope and/or diminishing the physician’s personal esteem may have been some of the quintessential reasons for the lack of truth telling. While recognizing the modern change in moral sentiment, Lantos acknowledged that truth telling has become “morally obligatory.” Notwithstanding his preference that he “would not want a doctor judging the morality of my decision,” he remained uncertain about the value of the “comforting lie.”

In a number of situations in genetic counseling, it is possible that the facts may be deliberately distorted, de-emphasized or even hidden. Obstetricians opposed to prenatal genetic studies and abortion of an abnormal fetus have been known to deny the genetic origin of a disorder, to describe it as a fluke occurrence or to provide incorrect (much lower) recurrence figures.

The physician may be unable to establish an exact diagnosis, to be certain of the carrier status of an individual or to predict accurately the outcome of pregnancy when faced with a very unusual fetal karyotype. Painful as it may be to both parties, the physician must ensure that patients understand the limitations completely. The unexpected finding, for example, of an XYY fetus should not be withheld from the parents, despite the inability to predict with certainty the ultimate development of an individual so affected (see Chapter 7).

In the course of a prenatal diagnostic study, blood samples from both parents may be called for to elucidate a potential diagnostic dilemma. On occasion, such studies unexpectedly reveal non-paternity. Not sharing this information with the patient’s husband may subsequently have legal
impressions. The management and resolution of such a problem will most often rest on the nature of the dilemma (for example, translocation, deletion) to be solved. Advising the mother of these findings, as well as the paternity issue, is necessary, as is documentation in the physician’s notes.

The expanding indications for prenatal diagnosis and the use of molecular techniques for carrier detection and prenatal diagnosis are likely to increase the frequency of detected nonpaternity. The warning that the rate of infidelity is higher than the rate of inborn errors of metabolism should not be reserved for medical students only. Management is invariably tricky and medical, ethical and legal issues abound. An important guiding principle is that the noncarrier male partner should not be misled.

Confidentiality and trust

Action by the physician after the diagnosis of the carrier state for an X-linked disease demands more than simply offering prenatal studies in all subsequent pregnancies. There is an obligation to convey this information to the sisters of any such carrier female. The patient may, however, expressly forbid the physician to communicate this information, even to her sisters at risk, despite the international consensus that individuals have a moral obligation to communicate genetic information to their family members. Certain legal pitfalls involving the transmission of privileged communications and breach of medical ethics need to be considered by the conscientious physician faced with this rare but not unheard of situation. A view reinforced by the courts posits that there is a duty to warn the relative at risk as a standard of expected care despite the absence of a physician/counselor relationship, regardless of privacy laws! Prior consent to contact relatives (given frequent disaffection in families) is another option. The need for caution is clear when one realizes that in some states in the United States, the physician may lose his or her license to practice medicine after a breach of confidentiality.

Disclosure to third parties, other than relatives, also includes employers, insurance companies and schools. It is hoped that the confidentiality of the physician–patient relationship and the patients’ right to privacy and personal autonomy remain sacrosanct. The American Medical Association has affirmed the importance of keeping genetic information confidential. Established precedent for breaking this confidentiality relates to recognition by the physician of danger to a third party. Threats to kill a former girlfriend shared with a psychiatrist were recognized by the courts as knowledge that should have been communicated. Certainly, the clinical notes and letters should reflect the geneticist’s recommendation that the patient promptly contact the indicated close relatives who are at risk for a specific genetic disorder.

However, faced with an intractable patient, some guidance about disclosure is reflected in a statement issued by the American Society of Human Genetics in 1998. When serious and foreseeable harm to at-risk relatives can be anticipated, when the disorder is preventable or treatable or when reduction of risk through monitoring is achievable, disclosure is seen to be permissible. “The harm that may result from failure to disclose should outweigh the harm that may result from disclosure.” In practice, few geneticists appear to have warned at-risk relatives without patient consent. The vast majority of medical geneticists who decided not to warn such relatives were concerned by patient confidentiality issues and legal liability.

Timing of genetic counseling

Today, more than ever before, counseling before conception or marriage may provide opportunities for carrier detection, prenatal diagnosis or the presentation of other important options noted earlier. Therefore, 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 for selective abortion. Given the 70 percent protection afforded by periconceptional folate acid supplementation against the occurrence of an NTD (see Chapter 23), there is a need to advise women about the importance of preconception care.

Confronted by a fatally malformed newborn, the physician may attempt to counsel a couple on the very day of the birth of such a child or before the mother’s discharge from the hospital. Although
communication and support are both vital during those fateful days, the physician needs to recognize the great difficulty that anguished patients would have in assimilating or comprehending even the essence of any counseling. The physician/counselor should share with the couple his or her awareness that it is difficult to remember all the important information in the face of emotional upset and that it would be normal and expected for them to raise all the same questions some weeks later, when the entire subject could be fully covered. Support for the parents should continue to be available for many months.

**Parental counseling**

Physicians/counselors have a duty to convey information about the known options, risks, benefits and foreseeable consequences to couples with increased risks of having children with genetic defects. Such a duty may be difficult, if not impossible, to fulfill if only one member of the couple attends genetic counseling. The issues are usually complex and are frequently compounded by feelings of guilt and by ignorance, family prejudices, religious obstacles, fear and serious differences of opinion between partners. Hence, when possible (at the time the appointment is made would seem to be best), the necessity that the couple attend together should be emphasized. Physicians/counselors have often seen an extremely anxious parent attend counseling alone and then have learned later of the counselee’s incorrect interpretation to the partner, lack of appreciation of the true risk figures and unnecessary emotional chaos. Not even letters written to couples after the counseling session (a recommended procedure, to summarize the essence of the counseling provided) can safely substitute for face-to-face discussions with both, allowing for questions and interchange about the issues and an opportunity to examine the partner.

Genetic counselors should be cognizant of the complex interactive factors involved in parental reproductive decision making. Frets confirmed the importance of the burden of the disease in question and found that the interpretation of risk (high or low) and the wish to have children were paramount factors. The absence of personal experience of the disease was also found to be a significant influence. Frets identified a number of factors that were independently and significantly associated with problems experienced by 43 percent of counseled couples. These included no postcounseling support, recognition of high risk, disapproval by relatives, the presence of an affected child and decisions not to have a (or another) child. Due diligence is necessary for the partners of genetic disease carriers who clearly experience significant psychologic distress.

**Counselee education**

Hsia et al. emphasized that genetic counseling is an educational process in which the counselee acquires a set of facts and options. Fraser’s essential message was that genetic counseling does not involve telling families what they should do but rather what they can do. We maintain that members of the health professions should adopt as a guiding principle the critical imperative that the concept of genetic counseling be introduced in high school and in continuing public education about genetic disease. Children sensitized in school about the importance of the family history, elements of heredity, concepts of individual susceptibility and risk and opportunities for anticipatory prevention of unnecessary catastrophes are likely to better comprehend pregnancy risks and options.

Genetic counseling and prenatal diagnostic services are of little avail if many women attend for their first antenatal visit after 16 weeks of gestation. Currently, this is the case in many urban hospitals in the Western world, where between 20 and 40 percent of obstetric patients arrive at this late stage. Education beginning in high school and continued by public health authorities working in the public sector could effectively communicate the critical importance of preconception and prenatal care.

**Duty to recontact**

The remarkable and rapid advances in medical genetics have introduced a “new” responsibility related to the well-established requirement to disclose risk information that materially bears on a patient’s decision making. Pelias focused attention on the geneticist’s continuing obligation to recontact patients when new information develops that would prove material to them, so far as personal health and child bearing are concerned (see Chapter 33). The implications raise serious
CHAPTER 1 Genetic Counseling: Preconception, Prenatal and Perinatal

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escalating number of neurodegenerative disorders (e.g. Huntington disease; some of the spinocerebellar ataxias) and certain serious disorders including multiple endocrine neoplasia type 2B and breast, colon and other malignancies. Published recommendations and guidelines urge rigorous pretest and post-test genetic counseling and recommendations that testing of children younger than 18 years of age be proscribed, except in life-threatening disorders (e.g. multiple endocrine neoplasia type 2B). The inherent harm that could potentially be done by presymptomatic testing is the potential for demoralization and depression with possible suicidal consequences. Extreme caution is recommended in considering predictive testing for a disorder without curative, let alone meaningful, palliative treatment. Although for certain dominant disorders some 50 percent of individuals at risk may receive good news, the other 50 percent face, effectively, a death sentence. Given the remarkable pace of advances in human genetics, it may well be possible in the foreseeable future to develop a therapy that enhances the extant biologic mechanism already in place that delays the manifestations of later-onset disease for decades after birth. No life should be ruined by severe depression or suicide only to discover later that a critical palliative remedy has emerged.

Clearly, there are extraordinarily difficult circumstances related to planned child bearing in the face of 50 percent risks for a neurodegenerative disorder coupled with a wish not to know. In these special circumstances, predictive testing can be regarded as acceptable only if performed with extreme care, concern and professionalism.

Preconception care should begin during visits to the family physician after menarche. Reiterated and expanding discussions on personal health habits that will affect both the adolescent herself and a future child provide a basis for promoting good health behavior, while a solid grounding in knowledge about the hazards of smoking, drugs, alcohol, sexually transmitted diseases and nutrition is provided. Early adolescence is also a vital period during which to inculcate the importance of genes and the wisdom of assimilating and updating information on family history. Linkage of family history to the common experience of physical and mental handicap, outlined in the context

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ethical, legal and policy issues. Certainly, following genetic research and new meaningful results, an ethical duty to inform the patient has become apparent. Medical genetics consultations frequently involve only one encounter and the requirement to contact that patient years later may be regarded as both irrational and unreasonable. Pelias pointed to a 1971 case in which the University of Chicago failed to notify women who had been given diethylstilbestrol. The University had apparently become aware of the dangers of this drug but had delayed notification for 4–5 years. In yet another case, after a single visit to her gynecologist for insertion of an intrauterine device (a Dalkon Shield), a woman sued this physician for failing to notify her of the subsequently recognized risks of this device. In that case, as Pelias noted, the court allowed the case to proceed because of the continuing status of the physician–patient relationship and because the physician had a “separate duty to act.”

In cases in which reasonable expectations for significant advances exist (e.g. tests for carrier detection or prenatal diagnosis), the authors recommend that the patient be in contact annually and/or before planned child bearing. Pelias opined that this recommendation should be recorded in clinical notes and echoed in letters to referring physicians and patients alike. Ultimately, the responsibility to return for further counseling in the light of new advances must be vested with the patient’s primary care physician and shared with the patient. To a variable extent, the patient’s physician can be expected to remain cognizant of genetic risks family members may have and refer them for specific genetic counseling or testing when appropriate. However, given that tens of millions change their addresses annually and frequently seek other medical care, the patients themselves, once informed of potential advances and the need to remain in contact with a clinical geneticist, take on personal responsibility.

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of personal risk in child bearing, provides a compelling and cogent framework on which physicians, teachers and parents can build.

This preparatory background may help educate all women about the importance of planning pregnancy. Over 50 percent of pregnancies in the United States are not planned and are often unintended.181 Physicians also need to reorient their practices so that women of child-bearing age understand that to optimize the chance of having a healthy child,171 prenatal care is best initiated before conception and not after the second missed menstrual period, as is still anachronistically practiced so widely.

The discovery or realization of nonpaternity at the time of prenatal diagnosis is fraught with potentially serious personal, medical, social and legal problems. The counseling provider has to be extremely adept in managing these cases. Warning about the potential discovery of nonpaternity as part of informed consent prior to testing182,183 may lead a pregnant woman to decline an indicated chorionic villus sample (CVS) or amniocentesis. Nondisclosure is ill advised when nonpaternity is discovered. In the effort to do no harm, we have requested a counseling session with the prospective mother alone. Her decision, taken in confidence, would govern further action. If, however, testing of the misattributed partner has genetic implications, nondisclosure becomes legally untenable.

Duty to warn
Physicians and counselors traditionally owe no duty to individuals with whom they have never met or entered into any treatment relationship. However, following the decision of the California Supreme Court (in Tarasoff v. Regents of the University of California),129 it has become clear that when a serious risk to the health or life of a third party is recognized, a duty of reasonable care evolves that demands protective action. Examples include contact with blood relatives at risk in situations of threatened violence, exposure to infection (HIV-AIDS) and now harmful genes (e.g. in familial adenomatous polyposis). A salutary lesson is provided in the study of 43 families with at least one sudden unexplained death.184 Identification of the genetic cardiac disorder (e.g. long QT syndrome) was made in 40 percent of the families who harbored 151 presymptomatic carriers! The loss of chance doctrine makes it incumbent upon geneticists/counselors to impress on their patients the need to warn blood relatives, if a serious genetic threat is determined. This counsel should be in writing and documented in the medical record. Litigated examples include failure to warn of the risk of medullary thyroid cancer, familial adenomatous polyposis with colon cancer and the fragile X syndrome (see Chapter 33).

Preconception genetic counseling
It is an anachronism that preconception care in the 21st century, despite being recognized as important, is not widely practiced.185,186 Expectations at the first preconception visit include routine documentation of the medical, obstetric and family history, the latter regarded arguably as the most important “genetic test”.187 This activity includes a review of medical records, photographs (e.g. previous stillbirths) and pertinent autopsy reports, radiographs, brain scans and chromosome or other special laboratory reports. Physical examination and necessary special tests also focus on acquired and genetic disorders that could, during pregnancy, threaten maternal and/or fetal welfare. Previously undiagnosed/undetected disorders may be determined for the first time at this visit and may be important for planned child bearing and the selection of future prenatal diagnostic tests. There is a need to insist that the male partner attend the preconception visit (or absolutely the first prenatal visit), providing an opportunity to detect at least obvious genetic disorders and solidify information possibly provided earlier about his family history. The senior author recalls, over many years during prenatal diagnosis counseling for other issues, diagnosing various disorders in male partners who were wholly unaware of their conditions, including osteogenesis imperfecta, Treacher–Collins syndrome, tuberous sclerosis, neurofibromatosis, Charcot–Marie–Tooth (type 1A) disease, limb girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, blepharophimosis, mitral valve prolapse, the XYY male and spinocerebellar ataxia.

The first preconception visit also serves to instruct about the need for folic acid supplemen-
tation for the avoidance of NTDs (see Chapter 23) and about diabetic control, management of obesity, cessation of illicit drugs, medications and alcohol. Referral to other specialists (e.g. neurologists), for tailoring medication requirements to safer and possibly less teratogenic agents, is also recommended. This is also the time for specialists caring for the same patient to confer about the planned care of their patient through pregnancy and for documentation of that exchange to be made.

**Indications for preconception genetic counseling**

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**

An arbitrary age of 35 years has functioned in the United States as an expected standard of care, which requires that a prospective mother be informed of her risks of having a child with a chromosome defect, informed of the recommendation for prenatal diagnosis and given an explanation of the risks of CVS or amniocentesis, with the associated details related to any problems, pitfalls or reservations. In some countries, largely for economic reasons, older ages have been used as an indication for prenatal study. Amniocentesis risks lower than 0.5 percent for fetal loss in some US centers prompt the offer of such studies earlier than 35 years of age (see Chapter 2).

While maternal age risk counseling is still necessary, risks derived from multianalyte maternal serum screening for DS (see Chapter 24) largely dominate decisions about amniocentesis.

Excluding infants with chromosome abnormalities, a prospective analysis of 102,728 pregnancies (including abortions, stillbirths and livebirths) in Texas found that the incidence of congenital malformations increased significantly and progressively in women after 25 years of age. The authors found that an additional age-related risk of non-chromosome malformations was approximately 1 percent in women 35 years of age or older. The odds ratio for cardiac defects was 3.95 in infants of women 40 years of age or older when compared with women aged 20–24 years.

**A previous fetus or child with a genetic disorder**

A genetic evaluation and counseling are usually indicated when a previous fetus or child has or had a genetic disorder, unless the matter is straightforward (e.g. previous trisomy 21) and the obstetrician is well informed. Careful inquiry should be made about the health status of a previous child. Failure or delay in the diagnosis of a monogenic disorder leaves the parents without the option of prenatal diagnosis in a subsequent pregnancy. Failure to make an early diagnosis of a genetic disorder during the first 5 years of life is not unusual. For example, the Rotterdam Clinical Genetics Group reported that 50 percent of children affected by neurofibromatosis had been treated for related symptoms before a specific diagnosis had been made. Such delay has become problematic given that the NF-1 gene and genes for many other monogenic disorders are routinely sequenced for a precise diagnosis.

Not infrequently, distressed parents will select a different physician for a subsequent pregnancy and a new or more recent insight may shed light on the cause of the previous defect. For example, confined placental mosaicism (see Chapter 6) may now serve to explain the discrepancy between reported chromosomal findings at the time of CVS and fetal tissues obtained at elective abortion. Confined placental mosaicism may also be associated with intrauterine growth restriction requiring serial ultrasounds during the pregnancy.

Given the heterogeneous nature of genetic disease, being alert to alternative mechanisms of causation will on occasion be rewarding. For example, during a consultation with a patient who had previously delivered a child with cystic fibrosis (CF), preparatory discussions about establishing the specific mutation from each parent could reveal that the father is not a carrier of the mutated CF gene. Although nonpaternity is more likely, a judicious approach would also include consideration of uniparental disomy. This mode of inheritance, in which an offspring can inherit two copies, part or all of a chromosome from one parent and no copy from the other parent, has been seen in a number of disorders, including Prader–Willi syndrome and Angelman syndrome. About 30 percent of cases of Prader–Willi syndrome are
caused by maternal uniparental disomy. These disorders, then, represent situations in which one parent is the source of both gene mutations for a recessively inherited condition. Disorders involving chromosomes 11, 14 and 15 have been notable. Uniparental disomy is caused primarily by meiotic nondisjunction events and followed by trisomy or monosomy “rescue.” Most cases described have been associated with advanced maternal age and have been detected primarily in the process of prenatal genetic studies.

Recognition of the molecular basis of a disorder from which a previous child died may provide a couple with an opportunity for prenatal diagnosis in a subsequent planned pregnancy. A caveat would be the availability of analyzable tissue from the deceased child. In the recent past this was mostly not done but with the escalation of new discoveries in genetics, tissues are now being frozen for potential future DNA analysis. The establishment of the molecular basis of recognized syndromes, previously undetectable prenatally, now provides new opportunities for couples seeking prenatal diagnosis. Examples abound (see Chapter 10) and include some of the craniosynostosis syndromes, certain skeletal dysplasias and many other disorders.

In one of our cases, a father with metaphyseal dysplasia of Schmid, troubled by the indignities and hurts of growing up with severe short stature, elected prenatal diagnosis at a preconception visit. Subsequent mutation analysis of conceived twins yielded a normal prenatal diagnosis result confirmed postnatally.

Heterogeneity and pleiotropism also require consideration in the context of a previous child’s disorder and anticipation of future prenatal diagnosis. For example, a previous child with tuberous sclerosis or a fetus with cardiac rhabdomyomas would prompt molecular analysis of the TSC1 and 2 genes for more precise future prenatal diagnosis.

A parent with a genetic disorder
Given the pace of advances in human genetics, physicians are advised to determine whether prenatal diagnosis has become available for the specific genetic disorder under discussion. Increasingly, these discussions may focus on a dominant genetic disorder affecting one parent, and the concern vis-à-vis prenatal diagnosis and pregnancy termination is about personal existence and self-extinction. This dilemma was exemplified by a young father with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) who, faced with our prenatal diagnosis of this disorder, by mutation analysis of the Notch3 gene, with his wife, elected termination. Mutation analysis in a subsequent pregnancy assured an unaffected fetus.

These consultations may invoke deep personal emotional conflict, especially when pleiomorphic genes are concerned. For example, a parent with tuberous sclerosis and normal intelligence could not be certain that an affected child would not be mentally retarded. This was especially evident in our series of 50 couples having prenatal diagnosis for tuberous sclerosis. Discovery of fetal cardiac rhabdomyoma led to sequencing of both the TSC1 and TSC2 genes in the fetus and diagnosis in one of the asymptomatic parents. Parental decisions are neither simple nor predictable. In a UK study of 644 deaf individuals and 143 with hearing impairment, 2 percent opined that they would prefer to have deaf children and would consider an elective abortion if the fetus was found to be hearing.

Certain genetic disorders may (1) threaten maternal health in pregnancy, (2) threaten fetal health and survival or (3) be aggravated by pregnancy.

Genetic disorders that threaten maternal health
Dramatic advances in medical care have resulted in more women affected by genetic disorders surviving to child-bearing age and becoming pregnant. There are several genetic disorders affecting the mother that can be aggravated and worsened during pregnancy. Awareness of these disorders facilitates better preconception anticipatory guidance and expectant management during pregnancy. Metabolic disorders that may worsen include ornithine transcarbamylase deficiency, homocystinuria, acute intermittent porphyria and lysinuric protein intolerance. Hyperammonemia during pregnancy/delivery or postpartum coma may be the presenting signs of a female heterozygote with ornithine transcarbamylase deficiency.
Thrombophlebitis and other thromboembolic events have been reported during pregnancy and operative delivery in women with homocystinuria.

Ehlers–Danlos syndrome IV, Marfan syndrome and Loeys–Dietz syndrome may have associated aortic/vascular rupture and uterine rupture during pregnancy and delivery. Diagnostic gene sequencing for all three disorders is available. In a study of 12 women with Loeys–Dietz syndrome with 21 pregnancies, six had one of these major complications.

Sophisticated care and counseling are necessary for women with Marfan syndrome who are considering pregnancy. A Dutch study of 63 affected women who had 142 pregnancies revealed that in 40 percent of completed pregnancies, there was an obstetric and/or neonatal complication. Prematurity, preterm premature rupture of membranes, cervical incompetence and increased (7.1 percent) fetal and neonatal mortality were reported.

Among the guidelines for Marfan syndrome recommended by Lipscomb et al. are the following.

1. Women with Marfan syndrome who are planning to have children should be encouraged to do so in their early 20s, given that the mean age for aortic dissection is 32 years.

2. Women should be counseled that there is a significant likelihood of aortic dissection if the aortic root dimension exceeds 4.0 cm or if there has been a steady increase in this dimension over preceding visits.

3. Monthly echocardiography during pregnancy should begin as early as 6 weeks of gestation. Lipscomb et al. emphasize that aortic catastrophes are not confined to late pregnancy, labor and the postnatal period.

4. Vaginal deliveries with epidural anesthesia are recommended for women with stable aortic measurements <4 cm during pregnancy.

5. Elective cesarean section with epidural anesthesia is recommended for women with changes in aortic root dimensions during pregnancy and for those with measurements exceeding 4 cm.

6. Hypertension must be treated aggressively and ideally with β-blockers.

7. Routine β-blocker treatment slows the rate of aortic dilation and should be used at least after the first trimester.

8. Prophylactic antibiotics should be used because of the likely associated presence of mitral valve prolapse.

Additional advice would be to avoid contact sports, physical exhaustion and isometric exercises (push-ups, pull-ups) or weight lifting. Encouraged by promising therapeutic response to an angiotensin II receptor blocker in a mouse model of Marfan syndrome and a limited clinical study, a randomized trial comparing β-blocker therapy is in progress.

First-trimester spontaneous abortion and gastrointestinal bleeding during pregnancy have been described in women with pseudoxanthoma elasticum. Worsening of the mother’s pulmonary status is seen with cystic fibrosis. An increase in the size and number of neurofibromata during pregnancy in women affected with neurofibromatosis type 1 may occur (in 60 percent of 105 cases in one study) and has resulted in both cosmetic changes as well as significant morbidity (paraplegia with rapid growth of intraspinal tumors). Hyper tension may be a problem for the pregnant patient with either neurofibromatosis type 1 or autosomal dominant polycystic kidney disease. As well as causing potentially life-threatening events for both the fetus and mother affected by myotonic muscular dystrophy, the condition itself may worsen during a pregnancy. Hematologic disorders may complicate pregnancy by altering normal physiology.

Carriers of hemophilia A are best cared for by a high-risk perinatal obstetric group. Prenatal sex determination (whether or not prenatal diagnosis by mutation analysis is chosen) is important for the management of labor and delivery, with special reference to the possible need for cesarean section. In addition, vacuum-assisted delivery with an affected male could result in a massive cephalohematoma requiring blood transfusion. Moreover, a high incidence of primary and secondary post-partum hemorrhage in carriers of hemophilia A (22 percent) and hemophilia B (11 percent) should further inform anticipatory care.

Maternal genetic disorders that may threaten fetal health and survival

Among the more common examples in this category are diabetes, sickle cell disease, epilepsy, and...
lupus erythematosus. Fetal loss, stillbirth and malformations are the primary concerns. Lupus is associated with a significant frequency of congenital heart block in seropositive mothers and electronic fetal monitoring in the third trimester and during labor is important. However, caution should attend plans for immunosuppressive treatment. In a Brazilian study, 32 (78 percent) of 41 fetuses with normal cardiac anatomy and seropositive mothers received no treatment, with livebirth and 1-year survival rates of 97 percent and 93 percent respectively. As many as 60 percent of mothers of offspring with congenital heart block have lupus or other connective tissue disorders. Maternal myotonic muscular dystrophy, which may be presymptomatic, is a key example in which both the life and health of the mother and fetus/child may be threatened. In addition to the earlier discussion, serious-to-fatal fetal/neonatal complications can be anticipated. One study showed that 12 percent of the offspring of affected women are stillborn or die as neonates, 9 percent survive although severely affected and 29 percent are affected later. Awareness of the obstetric-related risks facilitates optimal pregnancy care but does require in-depth preconception discussion.

Untreated maternal phenylketonuria (PKU) represents a potentially unmitigated disaster for the fetus and child. Besides pregnancy loss, there is a 90 percent likelihood of mental retardation, cardiac or other defects in the offspring of mothers who undertake pregnancy without being on strict preconception dietary therapy. Caution needs to be exercised in counseling women with PKU, especially if adherence to diet has been an issue. Comprehension and decision making may be less than adequate given the increased realization of residual behavioral and intellectual deficits. Similar cautions are obvious for other disorders (e.g. fragile X syndrome; see Chapter 9) where similar limitations may be evident and complicate informed consent and decision making generally.

**Genetic disorders that pregnancy may aggravate**

Women who are severely affected by CF may jeopardize their survival by becoming pregnant and should be advised accordingly. Those with mild-to-moderate disease are likely to have a successful pregnancy. A French study in which the outcome was known for 75 patients noted a prematurity rate of 18 percent and one maternal death during pregnancy. Later, some 12 deaths were recorded after pregnancy, with three in the year following the pregnancy. Four affected children were diagnosed after birth. Clearly, partners should be tested for their CF carrier status before the initiation of pregnancy in a woman with CF (see Chapter 17). A Norwegian study of pregnancy with CF noted preterm delivery in 24 percent of cases and the development of gestational diabetes in four of 23 patients. Similar observations were made in a Swedish study, except that these authors noted an overall mortality rate of 19 percent among 48 patients. If pregnancy is pursued regardless of counseling, special care and attention will be necessary and hospitalization is commonly needed at some time during the third trimester (see Chapter 17). Women with severe sickle cell disease may also become sicker during pregnancy and should be counseled accordingly. In some women, epilepsy is aggravated by pregnancy and could threaten the life of both mother and fetus. Given the potential teratogenic risks of anticonvulsants (in the 7–10 percent range), change to the least teratogenic medication should be achieved in the preconception period and should be done under the direct guidance of a neurologist.

Prospective mothers with insulin-dependent diabetes mellitus (IDDM) could find their disorder harder to control during pregnancy. Diabetes should be well controlled before pregnancy. The better the control, the lower the risk of having a child with congenital defects. An Australian study noted that with good preconception care of type 1 IDDM, the major congenital malformation rate decreased from a high of 14 percent to 2.2 percent. Notwithstanding extant knowledge about IDDM and pregnancy, a report of 273 women noted rates of stillbirth (1.85 percent), perinatal mortality (2.78 percent) and congenital anomalies (6 percent). In our study maternal obesity clearly posed an increased risk of congenital malformations (as noted earlier), probably through a metabolic route involving prediabetes. In women with congenital myopathies,
including central core disease and cytoplasmic body myopathy, cesarean sections may be needed more frequently and some deterioration in pregnancy and weakness after delivery may be experienced. Anesthetic risks may be increased in women with central core disease in whom malignant hyperthermia may be a complication.

A history of infertility

About 10 percent of couples have infertility problems. A World Health Organization multicenter study concluded that the problem appeared predominantly in males in 20 percent of cases, predominantly in females in 38 percent and in both partners in 27 percent. In the remaining 15 percent of cases, no definitive cause for the infertility was identified. Care should be exercised in the preconception counseling of a couple with a history of infertility. In the absence of a recognizable cause, karyotyping of both is recommended. Unrecognized spontaneous abortions may have occurred without the patient’s awareness, caused by overt structural chromosome rearrangements or microdeletions or duplications (see Chapter 10). Recognized habitual abortion due to the same causes would also require cytogenetic analysis. Such studies may reveal a parent (rarely both) with a chromosomal rearrangement with significant risks for bearing a child with mental retardation and/or malformations who could benefit from prenatal diagnosis.

Other disorders characteristically associated with recurrent pregnancy loss include the X-linked disorders, steroid sulfatase deficiency, and incontinentia pigmenti. Acceptance of thrombophilia as a cause awaits the results of randomized controlled trials. A recently recognized cause in about 8 percent of women experiencing recurrent abortion is mutations occurring in the SYCP3 gene, which encodes an essential component of the synaptonemal complex, key to the interaction between homologous chromosomes.

Although the investigation to determine the cause of male or female infertility can be extensive, three observations are pertinent here. First, we recognized that congenital bilateral absence of the vas deferens (CBAVD), which occurs in 1–2 percent of infertile males, is primarily a genital form of CF. Men with CBAVD should have CF gene mutation analysis. After analysis of 100 of the most common mutations, we found that only 35.9 percent of men with CBAVD had two identifiable mutations, 31.5 percent had only one mutation recognized and no CF mutation was found in the remainder. Sequencing of the CFTR gene should follow, especially if the partner is a CF gene mutation carrier. The mutation detection rate is likely to exceed 92 percent including large gene rearrangements. Of interest is the observation of Traystman et al. that CF carriers may be at higher risk for infertility than the population at large.

Some patients with CBAVD (21 percent in one study) also have renal malformations. These patients may have a normal sweat test and thus far no recognizable mutations in the CF gene. Renal ultrasound studies are recommended in all patients with CBAVD who have normal results on a sweat chloride test and no identified mutations.

The partner of a male with CBAVD should routinely be tested for the common CF mutations and optimally by gene sequencing. Such couples frequently consider epididymal sperm aspiration, with pregnancy induced by in vitro fertilization. Precise prenatal diagnosis can be achieved only if specific mutations have been recognized.

Second, Y chromosome microdeletions occur in 10–20 percent of men with “idiopathic” azoospermia or severe oligospermia. Genes, including DAZ (“deleted in azoospermia”), YRRM (Y chromosome RNA recognition motif) and others may be deleted singly or together in the region of Yq11.23. Couples must be informed that male offspring of men with these interstitial deletions in the Y chromosome will have the same structural chromosome defect. The female partner of the male undergoing intracytoplasmic sperm injection (ICSI) needs explanations about procedures and medications for her that are not risk free. Patients should realize that ICSI followed by in vitro fertilization is likely to achieve pregnancy rates between 20 and 24 percent, a success rate not very different from the approximately 30 percent rate in a single cycle after natural intercourse at the time of ovulation. Pregnancy follow-up data from cases culled from 35 different programs reported in a European survey and a major American study of 578 newborns showed no increased occurrence of congenital malformations. However, a statisti-
Genetic Disorders and the Fetus

A previously affected offspring. In virtually all ethnic groups, particular recessive disorders occur more frequently than in the population at large\(^{256}\) (Table 1.4). Increasingly, carrier tests will become available for these various ethnic groups. Carrier testing for cystic fibrosis (Caucasians), Tay–Sachs and Canavan diseases (Ashkenazi Jews), sickle cell disease (blacks), α-thalassemia (Asians) and β-thalassemia (peoples of Mediterranean descent) is regarded as standard and indicated simply on the basis of ethnicity.

Individuals of French-Canadian ancestry living in New England were reported to have a maximum frequency of heterozygosity for Tay–Sachs disease or Sandhoff disease of 1 in 42.\(^{257}\) Enzymatic analysis of hexosaminidase was confirmed by mutation analysis with exclusion of benign pseudodeficiency mutations. In contrast to these findings, which could reflect ascertainment bias, are the prior salutary observations of Palomaki et al.\(^{258}\) These authors recorded no cases of Tay–Sachs disease in 41,000 births to couples who were both of French-Canadian ancestry. Further studies are necessary before formal recommendations can be made for carrier testing in this ethnic group.

Notwithstanding the screening guidelines for CF in Caucasians, a family history of CF is a direct indication for mutation analysis.\(^{259}\) Moreover, given the ability to detect over 90 percent of CF carriers by routine testing of the most common mutations (see Chapter 17), all Caucasian couples should be offered these analyses at the preconception visit.\(^{260}\) Unfortunately, even after DNA mutation analysis, couples may not be aware of the

### Parental carrier of a genetic disorder

The first preconception visit should be the time to establish the carrier state for a chromosomal rearrangement or a gene mutation in prospective parents.

Physicians should be alerted to the possibility of chromosomal rearrangements or gene mutations that one or the other partner might carry relative to a history of previous recurrent spontaneous abortions, infertility or previous offspring with a chromosomal or single gene defect or a positive family history. Referral for genetic counseling in these circumstances is appropriate given complex questions relative to risk, prognosis in a future pregnancy and potential pitfalls/reservations concerning prenatal diagnosis (see Chapter 6).

Determination of single gene mutations in carriers may be prompted by the patient’s ethnic group, a family history of a specific genetic disorder or a previously affected offspring. In virtually all ethnic groups, particular recessive disorders occur more frequently than in the population at large\(^{256}\) (Table 1.4). Increasingly, carrier tests will become available for these various ethnic groups. Carrier testing for cystic fibrosis (Caucasians), Tay–Sachs and Canavan diseases (Ashkenazi Jews), sickle cell disease (blacks), α-thalassemia (Asians) and β-thalassemia (peoples of Mediterranean descent) is regarded as standard and indicated simply on the basis of ethnicity.

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<th>Ethnic group</th>
<th>Genetic disorder</th>
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<td>Africans (blacks)</td>
<td>Sickle cell disease and other disorders of hemoglobin</td>
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<td>α- and β-thalassemia</td>
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<td>Glucose-6-phosphate dehydrogenase deficiency</td>
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<td>Benign familial leukopenia</td>
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<td>High blood pressure (in females)</td>
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<td>Afrikaaners (white South Africans)</td>
<td>Variegate porphyria</td>
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<td>Fanconi anemia</td>
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<td>American Indians (of British Columbia)</td>
<td>Cleft lip or palate (or both)</td>
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<td>Armenians</td>
<td>Familial Mediterranean fever</td>
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<tr>
<td>Ashkenazi Jews</td>
<td>A-β-lipoproteinemia&lt;br&gt;Bloom syndrome&lt;br&gt;Breast cancer&lt;br&gt;Canavan disease&lt;br&gt;Colon cancer&lt;br&gt;Congenital adrenal hyperplasia&lt;br&gt;Dysferlinopathy (limb girdle muscular dystrophy 2B)&lt;br&gt;Dystonia musculorum deformans&lt;br&gt;Factor XI (PTA) deficiency&lt;br&gt;Familial dysautonomia&lt;br&gt;Fanconi anemia (type C)&lt;br&gt;Gaucher disease (adult form)&lt;br&gt;Glycogen storage disease (type 1a)&lt;br&gt;Iminoglycinuria&lt;br&gt;Maple syrup urine disease&lt;br&gt;Meckel syndrome&lt;br&gt;Niemann–Pick disease&lt;br&gt;Pentosuria&lt;br&gt;Spongy degeneration of the brain&lt;br&gt;Stub thumbs&lt;br&gt;Tay–Sachs disease</td>
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<td>Chinese</td>
<td>Thalassemia (α)&lt;br&gt;Glucose-6-phosphate dehydrogenase deficiency (Chinese type)&lt;br&gt;Adult lactase deficiency</td>
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<td>Eskimos</td>
<td>E1 pseudocholinesterase deficiency&lt;br&gt;Congenital adrenal hyperplasia</td>
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<td>Aspartylglucosaminuria&lt;br&gt;Congenital nephrosis</td>
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<td>French-Canadians</td>
<td>Neural tube defects&lt;br&gt;Tay–Sachs disease</td>
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<td>Irish</td>
<td>Neural tube defects&lt;br&gt;Phenylketonuria&lt;br&gt;Schizophrenia</td>
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<td>Italians (northern)</td>
<td>Fucosidosis</td>
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<td>Japanese and Koreans</td>
<td>Acatalasia&lt;br&gt;Dyschromatosis universalis hereditaria&lt;br&gt;Oguchi disease</td>
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<td>Maori (Polynesians)</td>
<td>Clubfoot</td>
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<td>Mediterranean peoples (Italians, Greeks, Sephardic Jews, Armenians, Turks, Spaniards, Cypriots)</td>
<td>Familial Mediterranean fever&lt;br&gt;Glucose-6-phosphate dehydrogenase deficiency (Mediterranean type)&lt;br&gt;Glycogen storage disease (type III)&lt;br&gt;Thalassemia (mainly β)</td>
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<td>Norwegians</td>
<td>Cholestasis-lymphedema&lt;br&gt;Phenylketonuria</td>
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<td>Yugoslavs (of the Istrian Peninsula)</td>
<td>Schizophrenia</td>
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</tbody>
</table>

limitations of these results. In one study, over half of those having CF carrier tests were unaware of their residual risk after having received a negative test result, while in another report only 62 percent correctly understood their results 6 months after testing.

Among the many items to be considered during the preconception visit are the potential physical features indicative of sex-linked disorders that may manifest in female carriers (Table 1.5). With or without a family history of the disorder in question, referral to a clinical geneticist would be appropriate for final evaluation of possible implications. Failure to recognize obvious features in a manifesting female may well result in a missed opportunity for prenatal genetic studies and an outcome characterized by a seriously affected male (or occasionally female) offspring. Of crucial additional importance in considering manifesting female carriers of sex-linked disorders is the realization that carrier females for Duchenne and Becker muscular dystrophy have preclinical or clinically evident myocardial involvement in 45–84 percent of cases. A study of 197 females aged 5–60 years who were carriers of either Duchenne or Becker muscular dystrophy revealed progressive dilated cardiomyopathy, myocardial hypertrophy and/or dysrhythmias. The American Academy of Pediatrics recommended that female carriers be informed of their risks, have a full cardiac evaluation in late adolescence or early adulthood and be re-evaluated at least every 5 years. Unfortunately, a majority of carriers have not been informed of their risks or had cardiac evaluations.

Dilemmas may also occasionally arise in counseling, for example, for a mildly retarded female with fragile X syndrome, compounded in one report in which the partner was also retarded. The involvement of close relatives is key to the counseling needs in this type of situation.

### Table 1.5 Signs in females who are carriers of X-linked recessive disease

<table>
<thead>
<tr>
<th>Selected disorders</th>
<th>Key feature(s) that may occur</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achromatopsia</td>
<td>Decreased visual acuity and myopia</td>
<td>263</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>Neurologic and adrenal dysfunction</td>
<td>264, 265</td>
</tr>
<tr>
<td>α-thalassemia/mental retardation</td>
<td>Rare hemoglobin H inclusions in red blood cells</td>
<td>266</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>Microscopic hematuria and hearing impairment</td>
<td>267</td>
</tr>
<tr>
<td>Amelogenesis imperfecta, hypomaturation type</td>
<td>Mottled enamel vertically arranged</td>
<td>268</td>
</tr>
<tr>
<td>Arthrogryposis multiplex congenita</td>
<td>Club foot, contractures, hyperkyphosis</td>
<td>269</td>
</tr>
<tr>
<td>Borjeson syndrome</td>
<td>Tapered fingers, short, widely spaced, flexed toes, mild mental retardation</td>
<td>270</td>
</tr>
<tr>
<td>Choroideremia*</td>
<td>Choreoretinal dystrophy</td>
<td>271</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>Cutaneous and mucocutaneous lesions</td>
<td>272, 273</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>Bifid uvula</td>
<td>274</td>
</tr>
<tr>
<td>Conductive deafness with stapes fixation</td>
<td>Mild hearing loss</td>
<td>275</td>
</tr>
<tr>
<td>Congenital cataracts*</td>
<td>Posterior suture cataracts</td>
<td>276</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>Pseudohypertrophy, weakness, cardiomyopathy/conduction defects</td>
<td>277–279</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>Retinal pigmentation</td>
<td>280</td>
</tr>
<tr>
<td>Emery–Dreifuss muscular dystrophy</td>
<td>Cardiomyopathy/conduction defects</td>
<td>281</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>Angiokeratomas, corneal dystrophy, “burning” hands and feet</td>
<td>282</td>
</tr>
<tr>
<td>FG syndrome</td>
<td>Anterior displaced anus, facial dysmorphism</td>
<td>283</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>Mild-to-moderate mental retardation, behavioral aberrations, schizoaffective disorder, premature ovarian failure</td>
<td>284–286</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Hemolytic crises, neonatal hyperbilirubinemia</td>
<td>287</td>
</tr>
<tr>
<td>Hemophilia A and B</td>
<td>Bleeding tendency</td>
<td>288</td>
</tr>
</tbody>
</table>
A family history of a genetic disorder
The explicit naming of a specific genetic disorder when the family history is being discussed facilitates evaluation and any possible testing. Difficulties are introduced when neither family nor previous physicians have recognized a genetic disorder within the family. Such a disorder may not be uncommon (e.g., factor V Leiden deficiency) but nevertheless unrecognized. Clinical clues would include individuals in the family with deep vein thrombosis, sudden death possibly due to a pulmonary embolus and yet other individuals with recurrent pregnancy loss. For some families, individuals with quite different apparent clinical features may in fact have the same disorder. For example, there may be two or more deceased family members who died from “kidney failure” and another one or two who died from a cerebral aneurysm or a sudden brain hemorrhage. Adult polycystic kidney disease (APKD) may be the diagnosis, which will require further investigation by both ultrasound and DNA analysis. Moreover, two different genes for APKD have been cloned (about 85 percent of cases due to APKD1 and close to 15 percent due to APKD2) and a rare third locus is known. In yet other families, a history of hearing impairment/deafness in some members and sudden death in others may translate to the autosomal recessive Jervell and Lange–Nielsen syndrome. This disorder is characterized by severe congenital deafness, a long QT interval and large T waves, together with a tendency for syncope and sudden death due to ventricular fibrillation. Given that a number of genetic cardiac conduction defects have been recognized, a history of an unexplained sudden death in a family should lead to a routine electrocardiogram at the first preconception visit and possibly mutation analysis of at least five long
Consanguinity

Consanguineous couples face increased risks of having children with autosomal recessive disorders; the closer the relationship, the higher the risks. A study in the United Arab Emirates of 2,200 women ≥15 years of age (with a consanguinity rate of 25–70 percent) concluded that the occurrence of malignancies, congenital abnormalities, mental retardation and physical handicap was significantly higher in the offspring of consanguineous couples. The pooled incidence of all genetic defects regardless of the degree of consanguinity was 5.8 percent, in contrast with a nonconsanguineous rate of 1.2 percent, similar to an earlier study. A Jordanian study also noted significantly higher rates of infant mortality, stillbirths and congenital malformations among the offspring of consanguineous couples. A Norwegian study of first-cousin Pakistani parents yielded a relative risk for birth defects of about twofold. In that study, 28 percent of all birth defects were attributed to consanguinity. An observational study of 5,776 Indian newborns noted a prevalence of 11.4 per 1,000 births with a consanguinity rate of 44.74 percent.

The occurrence of rare, unusual or unique syndromes invariably raises questions about potential consanguinity and common ancestral origins. Clinical geneticists will frequently be cautious in these situations, providing potential recurrence risks of 25 percent. Consanguineous couples may opt for the entire gamut of prenatal tests to diminish even their background risks, with special focus on their ethnic-specific risks.

Environmental exposures that threaten fetal health

Concerns about normal fetal development after exposure to medications, illicit drugs, chemical, infectious or physical agents and/or maternal illness are among the most common reasons for genetic counseling during pregnancy. Many of these anxieties and frequently real risks could be avoided through preconception care. Public health authorities, vested with the care of the underprivileged in particular, need to focus their scarce resources on preconception and prenatal care and on the necessary public education regarding infectious diseases, immunization, nutrition and genetic disorders.

In preconception planning, careful attention to broadly interpreted fetal “toxins” is necessary and avoidance should be emphasized. Alcohol, smoking, illegal drug use, certain medications and X-ray exposure require discussion. Estimates of the prevalence of the fetal alcohol spectrum disorder approximate 1 percent in the USA but in certain regions and countries rates reach as high as 10 percent. There is a limited list of known and proven human drug teratogens. Maternal use of specific teratogenic medications, such as isotretinoin, may be missed, unless the physician expressly inquires about them.

Preconception advice to avoid heat exposure in early pregnancy is now appropriate. Our observations (see Chapter 23) showed a 2.9 relative risk for having a child with a NTD in mothers who used a hot tub during the first 6 weeks of pregnancy. A report from the Spanish Collaborative Study of Congenital Malformations noted a 2.8-fold
increased risk of DS in the offspring of women ≥35 years of age and who were taking oral contraceptives when they became pregnant.333

**Identification of preconception options**
The time to deal with unwanted risks is not during the second trimester of pregnancy, as is so often the case in practice. Preconception counseling will identify specific risks and attendant options, which include the following.

1. Decision not to have children (includes consideration of vasectomy or tubal ligation)
2. Adoption
3. *In vitro* fertilization
4. Gamete intrafallopian tube transfer or allied techniques
5. Artificial insemination by donor
6. Ovum donation (includes surrogacy)
7. Intracytoplasmic sperm injection
8. Carrier detection tests
9. Prenatal diagnosis (CVS, amniocentesis, cordocentesis, ultrasound, MRI)
10. Preimplantation genetic diagnosis
11. Fetal treatment for selected disorders
12. Folic acid supplementation in periconceptual period (see Chapter 23)
13. Selective abortion

**Genetic counseling as a prelude to prenatal diagnosis**
Prospective parents should understand their specific indication for prenatal tests and the limitations of such studies. Frequently, one or both members of a couple fail to appreciate how focused the prenatal diagnostic study will be. Either or both may have the idea that all causes of mental retardation or congenital defects will be detected or excluded. It is judicious for the physician to urge that both members of a couple come for the consultation before CVS or amniocentesis. Major advantages that flow from this arrangement include a clearer perception by the partner regarding risks and limitations, a more accurate insight into his family history and an opportunity to detect an obvious (although unreported or undiagnosed) genetic disorder of importance (e.g. Treacher–Collins syndrome, facioscapulohumeral dystrophy or one of the orofacial–digital syndromes). Women making an appointment for genetic counseling should be informed about the importance of having their partner with them for the consultation, avoiding subsequent misunderstanding about risks, options and limitations.

Before prenatal genetic studies are performed, a couple should understand the inherent limitations both of the laboratory studies and, when relevant, of ultrasound. For detection of chromosomal disorders, they should be aware of potential maternal cell admixture and mosaicism (see Chapter 6). When faced with potential X-linked hydrocephalus, microcephaly or other serious X-linked disorders and the realization of less than 100 percent certainty of diagnosis, couples may elect fetal sex determination as the basis for their decision to keep or terminate a pregnancy at risk. For some biochemical assays and invariably for DNA linkage analyses, results may be less than 100 percent certain.

The time taken to determine the fetal karyotype or other biochemical parameters should be understood before amniocentesis. The known anxiety of this period can be appreciably aggravated by a long, unexpected wait for a result. The need for a second amniocentesis is rarer nowadays but in some circumstances, fetal blood sampling remains an additional option that may need discussion. Despite the very unlikely eventuality that no result may be obtained because of failed cell culture or contamination, this issue must be mentioned.

The potential possibility for false-positive or false-negative results should be carefully discussed when applicable. Any quandary stemming from the results of prenatal studies is best shared immediately with the couple. The role of the physician in these situations is not to cushion unexpected blows or to protect couples from information that may be difficult to interpret. All information available should be communicated, including the inability to accurately interpret the observations made. This is especially so with the advent of the chromosomal microarray (see Chapter 10). DNA analysis of cultured amniocytes may yield an uninterpretable microdeletion/duplication which then requires parental studies in an effort to determine significance. The frequency with which no clear answer can be provided is still to be determined.
Other key issues to be considered by the genetic counselor and discussed when appropriate with the consultand follow.

**Informed consent**

Patients should be told that prenatal diagnosis is not error free. Although the accuracy rate for prenatal diagnostic studies exceeds 99 percent, it is not 100 percent. Errors have occurred in all of the following ways and most, at least in the United States, have been followed by frequently successful lawsuits. (see Chapter 33).

1. Failure to offer prenatal diagnosis.
2. Failure to provide accurate information regarding risks of occurrence or recurrence.
3. Failure to explain significantly abnormal results, with catastrophic consequences.
4. Failure to provide timely results of prenatal diagnosis, resulting in the birth of a child with a chromosome abnormality.
5. Failure to communicate the recommendation from the laboratory to perform a second amniocentesis in view of failed cell culture, resulting in the birth of a child with a detectable genetic defect.
6. Failure to determine the correct fetal sex or genetic disorder, due to maternal cell contamination.
7. Failure to diagnose a defect because of a sample or slide mix-up.
8. Failure to order indicated tests (e.g. karyotype of prospective mother when her sister or sibling’s child had DS, chromosome type unknown and which in fact was due to an unbalanced translocation).
9. Failure to analyze the fetal karyotype correctly.
10. Failure to recognize significant chromosomal mosaicism.
11. Incorrect interpretation (or erroneous reinterpretation) of a biochemical or DNA assay.
12. Failure to run appropriate controls for a biochemical assay.
13. Failure to order the correct test.
14. Failure to send or direct a sample for specific testing to a known laboratory.
15. Failure to communicate critical laboratory results to the physician and depending upon a fax or voicemail transmission.
16. Incubator failure or infection of cell cultures, resulting in failure of cell growth, no time for a repeat study and subsequent birth with a chromosomal (or detectable) anomaly.
17. Failure to offer maternal serum screening or to correctly interpret and act on results.
18. Failure to understand a laboratory report coupled with failure to clarify the results by contacting the laboratory.
19. Failure to detect obvious fetal defects on ultrasound.
20. Failure to recommend periconception folic acid supplementation (see Chapter 21) with subsequent birth of a child with a neural tube defect.
21. Failure to offer indicated carrier detection tests (ethnicity; family history).
22. Failure to deliver a blood sample to the laboratory in a timely manner, with the subsequent birth of a child with spina bifida and hydrocephalus.
23. Failure to advise change or discontinuance of a teratogenic medication (e.g. valproic acid), resulting in the birth of a child with spina bifida.
24. Delay/failure in making a timely diagnosis of a serious genetic disorder in a previous child, thereby depriving parents of risk data and of the options for prenatal diagnosis (among others) in a subsequent pregnancy, resulting in the birth of another affected child.

From a previous worldwide survey of prenatal diagnosis and two formal amniocentesis studies, an error rate between 0.1 and 0.6 percent seems likely. After communication of all the necessary information concerning amniocentesis and prenatal genetic studies pertinent to the couple and especially tailored to their particular situation, an informed consent form should be signed and witnessed. Consent forms used for minor surgery should suffice for CVS and amniocentesis. However, each physician should have a specific form covering all key eventualities.

It is crucial to ensure not only that the language in the consent form is nontechnical and easily understandable but also that the form is available in the language best understood by the couple. Although the medicolegal validity of such forms may still be questioned, the exercise ensures at least a basic discourse between doctor (or the doctor’s staff) and patient. For patients who decline prenatal studies, maternal serum screening or specific genetic tests, physicians are advised to document their discussion and the patient’s refusal in the medical record. In successful litigation, some
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plaintiffs have claimed that prenatal diagnostic studies or maternal serum screening were neither discussed nor offered by their physicians.

**Carrier detection**
Before any effort to make a prenatal diagnosis of an autosomal recessive or sex-linked biochemical disorder, the carrier state should be documented (see above). For autosomal recessive disorders, particular attention should be paid to the parents’ ethnic origin (see Table 1.4). A previous birth of an affected child with an autosomal recessive disorder might alert the physician to consanguinity. DNA mutation analysis facilitates carrier detection for a host of disorders not previously detectable prenatally (see Chapter 11). Recognition of compound heterozygosity in a couple will influence discussions about prognosis and should also initiate tracking of carriers through the respective families.

**Presymptomatic or predictive testing**
Presymptomatic or predictive testing is available for a rapidly increasing number of disorders, especially neuromuscular and neurodegenerative (see Chapter 11). Huntington disease is the prototype and predictive testing using guidelines promulgated by the World Federation of Neurology and the International Huntington Association is well established. Various programs report that a majority of patients are able to cope when it is found that they are affected, and at least after a 1-year follow-up, potential benefit has been shown even in those found to be at increased risk. A European collaborative study evaluated 180 known carriers of the Huntington disease gene mutation and 271 noncarriers, all of whom received a predictive test result. Although the follow-up was only 3 years for about half the group, pregnancies followed in 28 percent of noncarriers and only 14 percent of carriers. Prenatal diagnosis was elected by about two-thirds of those who were carriers.

As others earlier, we remain very concerned about the use of a test that can generate a “no hope” result. Even in sophisticated programs offering Huntington disease tests, fewer than expected at-risk individuals requested testing. A multicenter Canadian collaborative study evaluated the uptake, utilization and outcome of 1,061 predictive tests, 15 prenatal tests and 626 diagnostic tests from 1987 to 2000. The uptake for predictive testing was about 18 percent (range, 12.5–20.7 percent). Of the 15 who had prenatal tests, 12 had an increased risk which led to pregnancy termination in all but one.

The motivations leading to the very difficult decision to have or not to have a predictive test are being recognized as extremely complex. In a Danish study before DNA tests were available, one in 20 individuals at risk for Huntington disease committed suicide, more than double the population rate, highlighting earlier reports of high suicide rates and emphasizing the erosive effects of uncertainty. However, a worldwide assessment of suicide rates, suicide attempts or psychiatric hospitalizations after predictive testing did not confirm a high rate of suicide. In their worldwide questionnaire study sent to predictive testing centers, the authors noted that 44 individuals (0.97 percent) among 4,527 tested had five suicides, 21 suicide attempts and 18 hospitalizations for psychiatric reasons. All those who committed suicide had signs of Huntington disease, while 11 (52.4 percent) of the 21 individuals who attempted suicide were symptomatic. Others have written about the psychologic burden created by knowledge of a disabling fatal disease decades before its onset.

Hayden warned that it is inappropriate to introduce a predictive test that “has the potential for catastrophic reactions,” without a support program, including pretest and post-test counseling and specified standards for laboratory analyses. In one study, 40 percent of individuals tested for Huntington disease and who received DNA results required psychotherapy. A 5-year longitudinal study of psychologic distress after predictive testing for Huntington disease focused on 24 carriers and 33 tested noncarriers. Mean distress scores for both carriers and noncarriers were not significantly different but carriers had less positive feelings. A subgroup of tested persons were found to have long-lasting psychologic distress.

On the other hand, an increasing number of examples already exist (see Chapter 11) in which presymptomatic testing is possible and important to either the patient or future offspring or both. Uptake has been high by individuals at risk, espe-
cially for various cancer syndromes. Use of DNA linkage or mutation analysis for ADPKD may lead to the diagnosis of an unsuspected associated intracranial aneurism in 8 percent of cases (or 16 percent in those with a family history of intracranial aneurism or subarachnoid hemorrhage) and pre-emptive surgery, with avoidance of a life-threatening sudden cerebral hemorrhage. In a study of 141 affected individuals, 11 percent decided against bearing children on the basis of the risk. These authors noted that only 4 percent of at-risk individuals between 18 and 40 years of age would seek elective abortion for an affected fetus. The importance of accurate presymptomatic tests for potential at-risk kidney donors has been emphasized. Organ donation by a sibling of an individual with ADPKD, later found to be affected, has occurred more than once.

Individuals at 50 percent risk for familial polyposis coli (with inevitable malignancy for those with this mutated gene) who undergo at least annual colonoscopy could benefit from a massive reduction in risk (from 50 percent to <1 percent) after DNA analysis. Individuals in whom this mutation was found with greater than 99 percent certainty may choose more frequent colonoscopies and eventually elective colonic resections, thereby saving the lives of the vast majority. The need for involvement of clinical geneticists is especially evident in this and other disorders in which complex results may emerge. Giardiello et al. showed that physicians misinterpreted molecular test results in almost one-third of cases.

Families with specific cancer syndromes, such as multiple endocrine neoplasia, Li–Fraumeni syndrome or von Hippel–Lindau disease, may also benefit by the institution of appropriate surveillance for those shown to be affected by molecular analysis when they are still completely asymptomatic, once again, in all likelihood, saving their lives. For example, elective thyroidectomy is recommended for multiple endocrine neoplasia type 2B by 5 years of age in the child with this mutation, given the virtual 100 percent penetrance of this gene and the possible early appearance of cancer. Predictive testing even of children at high genetic risk poses a host of complex issues. Where life-threatening early-onset genetic disorders are concerned, testing in early childhood still requires the exercise of parental prerogatives. However, failure to test because of parental refusal may invite the reporting of child neglect.

No longer hypothetical is the prenatal diagnosis request by a pregnant mother for fetal Huntington disease without the knowledge of her at-risk partner who does not wish to know his genetic status. In preserving the partner’s autonomy and recognizing maternal rights, we have in the past honored such requests. Mothers have in these circumstances, faced with an affected fetus, elected to terminate the pregnancy, invoking miscarriage as the reason to her unknowing partner. Distressing as it is to contemplate such a marital relationship, textured on the one hand by extreme care and on the other hand by deceit born of sensitivity, consider our report of symptomatic Huntington disease at 18 months of age and diagnosed at the age of 3 years. These cases pose difficult ethical, moral and legal questions but at least in the United States, United Kingdom and Australia, a woman’s request for prenatal diagnosis would be honored. Homozygotes for Huntington disease are rare and reported in one out of 1,007 patients (0.1 percent). Counseling a patient homozygous for Huntington disease about the 100 percent probability of transmitting the disorder to each child is equivalent to providing a nonrequested predictive test, while failing to inform the patient of the risks would be regarded as the withholding of critical information. Pretest counseling in such cases would take into consideration a family history on both sides and therefore be able to anticipate the rare homozygous eventuality.

Identification of specific mutations in the breast/ovarian cancer susceptibility genes (BRCA1 and BRCA2) has opened up difficult personal decision making as well as consideration concerning future prenatal diagnosis. DudokdeWit et al. laid out a detailed and systematic approach to counseling and testing in these families. In their model approach, important themes and messages emerge.

1. Each person may have a different method of coping with threatening information and treatment options.
2. Predictive testing should not harm the family unit.
3. Special care and attention are necessary to obtain informed consent, protect privacy and con-
fidelity and safeguard “divergent and conflicting intrafamilial and intergenerational interests.” A French study noted that 87.7 percent of women who were first-degree relatives of patients with breast cancer were in favor of predictive testing. Two specific groups of women are especially involved. The first are those who, at a young age, have already had breast cancer, with or without a family history and in whom a specific mutation has been identified. Recognizing their high risk for breast and/or ovarian cancer, these women have grappled with decisions about elective bilateral mastectomy and oophorectomy and mastectomy of a contralateral breast. Current estimates of penetrance are 36–85 percent lifetime risk for breast cancer and 16–60 percent lifetime risk for ovarian cancer, depending upon the population studied. This group of women may also consider prenatal diagnosis in view of their personal suffering and intent not to have a child subject to the same set of problems.

The second group of women are of Ashkenazi Jewish ancestry. These women have about a 2 percent risk of harboring two common mutations in BRCA1 (185delAG and 5382insC) and one in BRCA2 (6174delT) that account for the majority of breast cancers in this ethnic group. Regardless of a family history of breast or ovarian cancer, the lifetime risk of breast cancer among Jewish female mutation carriers was 82 percent in a study of 1,008 index cases. Breast cancer risk by 50 years of age among mutation carriers born before 1940 was 24 percent but 67 percent for those born after 1940. Lifetime ovarian cancer risks were 54 percent for BRCA1 and 23 percent for BRCA2 mutation carriers. It can easily be anticipated that with identification of mutations for more and more serious/fatal monogenic genetic disorders (including cardiovascular, cerebrovascular, connective tissue and renal disorders, among others), prospective parents may well choose prenatal diagnosis in an effort to avoid at least easily determinable genetic disorders. Discovery of the high frequency (28 percent) of a mutation (T to A at APC nucleotide 3920) in the familial adenomatous polyposis coli gene among Ashkenazi Jews with a family history of colorectal cancer is also likely to be followed by thoughts of avoidance through prenatal diagnosis. This mutation has been found in 6 percent of Ashkenazi Jews. Because of the ability to determine whether a specific cancer will develop in the future, given identification of a particular mutation, much agonizing can be expected for many years. These quandaries will not and cannot be resolved in rushed visits to the physician’s office as part of preconception or any other care. Moreover, developing knowledge about genotype–phenotype associations and many other aspects of genetic epidemiology will increasingly require referral to clinical geneticists.

**Anticipation**

In 1991 the first reports appeared of dynamic mutations resulting from the unstable expansion of trinucleotide repeats. Thus far, 17 such disorders with these unstable repeats have been described (Table 1.6). All disorders described thus far are autosomal dominant or X-linked, except for Friedreich ataxia, which is autosomal recessive and also unique in having intronic involvement. Typically for these disorders (except for Friedreich ataxia), the carrier will have one normal allele and a second expanded allele.

These disorders (except for Friedreich ataxia) are also generally characterized by progressively earlier manifestations and/or more severe expression with succeeding generations. This genetic mechanism, called anticipation, is associated with further expansion of the specific triplet repeat but there are also disorders with anticipation and no apparent dynamic mutations (Box 1.3). Indeed, these disorders characteristically have a direct relation between the number of repeats and the severity of disease and an inverse relation between the number of repeats and age of onset. These aspects of anticipation weigh heavily in preconception counseling when it becomes clear that the relatively mild-to-moderate status of a mother with myotonic muscular dystrophy, for example, is likely to result in an affected child with severe congenital myotonic muscular dystrophy. More recent studies have shown that triplet size in this disorder correlates significantly with muscular disability as well as mental and gonadal dysfunction. These authors also noted that triplet repeat size did not correlate with the appearance of cataract, myotonia, gastrointestinal dysfunction and cardiac...
Table 1.6 Dynamic mutations with triplet repeat expansion

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chromosome</th>
<th>Repeat sequence</th>
<th>Size in normal</th>
<th>Size in carrier</th>
<th>Size in affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dentatorubral pallidoluysian atrophy</td>
<td>12p12-13</td>
<td>CAG</td>
<td>7–34</td>
<td>–</td>
<td>49–75</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>Xq27.3</td>
<td>CGG</td>
<td>5–54</td>
<td>50–200</td>
<td>200 to &gt;2000</td>
</tr>
<tr>
<td>Fragile XE</td>
<td>Xq27.3</td>
<td>GCC</td>
<td>6–25</td>
<td>116–133</td>
<td>200 to &gt;850</td>
</tr>
<tr>
<td>Friedreich ataxia</td>
<td>9q13</td>
<td>GAA</td>
<td>7–40</td>
<td>50–200</td>
<td>200 to &gt;1200</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>4p16.3</td>
<td>CAG</td>
<td>6–36</td>
<td>–</td>
<td>35–121</td>
</tr>
<tr>
<td>Kennedy disease (spinal bulbar muscular atrophy)</td>
<td>Xq11-12</td>
<td>CAG</td>
<td>12–34</td>
<td>–</td>
<td>40–62</td>
</tr>
<tr>
<td>Machado–Joseph disease</td>
<td>14q32.1</td>
<td>CAG</td>
<td>13–36</td>
<td>–</td>
<td>68–79</td>
</tr>
<tr>
<td>Myotonic dystrophy type 1</td>
<td>19q13.3</td>
<td>CTG</td>
<td>5–37</td>
<td>–</td>
<td>50 to &gt;2000</td>
</tr>
<tr>
<td>Myotonic dystrophy type 2</td>
<td>3q21.3</td>
<td>CCTG</td>
<td>&lt;44</td>
<td>–</td>
<td>75–11,000</td>
</tr>
<tr>
<td>Spino cerebellar ataxia type 1</td>
<td>6p22-23</td>
<td>CAG</td>
<td>6–39</td>
<td>–</td>
<td>41–81</td>
</tr>
<tr>
<td>Spino cerebellar ataxia type 2</td>
<td>12q24.1</td>
<td>CAG</td>
<td>15–29</td>
<td>–</td>
<td>35–59</td>
</tr>
<tr>
<td>Spino cerebellar ataxia type 6</td>
<td>19p13</td>
<td>CAG</td>
<td>4–16</td>
<td>–</td>
<td>21–27</td>
</tr>
<tr>
<td>Spino cerebellar ataxia type 7</td>
<td>3p21.1</td>
<td>CAG</td>
<td>4–18</td>
<td>–</td>
<td>37–130</td>
</tr>
<tr>
<td>Spino cerebellar ataxia type 8</td>
<td>13q21</td>
<td>CTG</td>
<td>16–37</td>
<td>–</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Spino cerebellar ataxia type 10</td>
<td>22q13-pter</td>
<td>ATTCT</td>
<td>10–22</td>
<td>–</td>
<td>&gt;19,000</td>
</tr>
<tr>
<td>Spino cerebellar ataxia type 12</td>
<td>5q31-33</td>
<td>CAG</td>
<td>7–28</td>
<td>–</td>
<td>66–78</td>
</tr>
<tr>
<td>Spino cerebellar ataxia type 17</td>
<td>6q27</td>
<td>CAG</td>
<td>27–44</td>
<td>–</td>
<td>&gt;45</td>
</tr>
</tbody>
</table>

*a* Variable ranges reported and overlapping sizes may occur.

*b* Mutation may not involve an expansion.

*c* Expansion involves four nucleotides.

*d* Expansion involves five nucleotides.

---

**Box 1.3 Selected genetic disorders with anticipation**

**Disorders with anticipation**

See Table 1.6 of disorders with trinucleotide repeats (exception: Friedreich ataxia)

**Disorders with suspected anticipation**

Adult-onset idiopathic dystonia

Autosomal dominant acute myelogenous leukemia

Autosomal dominant familial spastic paraplegia

Autosomal dominant polycystic kidney disease (PKD1)

Autosomal dominant rolandic epilepsy

Behçet syndrome

Bipolar affective disorder

Charcot–Marie–Tooth disease

Crohn disease

Dyskeratosis congenita

Facioscapulohumeral muscular dystrophy

Familial adenomatous polyposis

Familial amyloid polyneuropathy

Familial breast cancer

Familial chronic myeloproliferative disorders

Familial intracranial aneurysms

Familial pancreatic cancer

Familial paraganglioma

Familial Parkinson disease

Familial primary pulmonary hypertension

Familial rheumatoid arthritis

Graves disease

Hereditary nonpolyposis colorectal cancer

Hodgkin and non-Hodgkin lymphoma

Holt–Oram syndrome

Lattice corneal dystrophy type I (LCDI)

Li–Fraumeni syndrome

Ménière disease

Obsessive-compulsive spectrum disorders

Oculodentodigital syndrome

Paroxysmal kinesigenic dyskinesia (PKD)

Restless legs syndrome

Schizophrenia

Total anomalous pulmonary venous return

Unipolar affective disorder
DNA mutation analysis has clarified few genotype-phenotype associations but extensive databases will help. Notwithstanding this limitation, mutation analysis does provide precise prenatal diagnosis opportunities and detection of affected fetuses with compound heterozygosity. Simple logic might have concluded that genotype at a single locus might predict phenotype. For monogenic disorders, this is frequently not the case. In the autosomal dominant Marfan syndrome (due to mutations in the chromosome 15 fibrillin gene), family members with the same mutation may have severe ocular, cardiovascular and skeletal abnormalities, while siblings or other close affected relatives with the same mutation may have mild effects in only one of these systems. In Gaucher disease with one of the common Ashkenazi Jewish mutations, only about one-third of homozygotes have significant clinical disease. At least two-thirds have mild or late-onset disease or remain asymptomatic. Compound heterozygotes for this disorder involving mutations L444P and N370S have included a patient with mild disease first diagnosed at 73 years of age, while another requiring enzyme replacement therapy was diagnosed at the age of 4 years.

In CF, a strong correlation exists between genotype and pancreatic function but only a weak

### Table 1.7 Examples of imprinting and human disease

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Chromosomal location</th>
<th>Parental origin</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelman syndrome</td>
<td>15q11-q13</td>
<td>Maternal</td>
<td>383</td>
</tr>
<tr>
<td>Autism</td>
<td>15q11-q13</td>
<td>Maternal</td>
<td>384</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome</td>
<td>11p15.5</td>
<td>Paternal</td>
<td>385-387</td>
</tr>
<tr>
<td>Birk Barel mental retardation syndrome</td>
<td>8q24</td>
<td>Maternal</td>
<td>388</td>
</tr>
<tr>
<td>Congenital hyperinsulinism</td>
<td>11p15</td>
<td>Maternal</td>
<td>389</td>
</tr>
<tr>
<td>Congenital myotonic muscular dystrophy</td>
<td>19q13.3</td>
<td>Maternal</td>
<td>390</td>
</tr>
<tr>
<td>Early embryonic failure</td>
<td>21</td>
<td>Maternal</td>
<td>391</td>
</tr>
<tr>
<td>Familial paraganglioma</td>
<td>11q23</td>
<td>Paternal</td>
<td>392</td>
</tr>
<tr>
<td>Hereditary myoclonus-dystonia</td>
<td>7q21</td>
<td>Maternal</td>
<td>393</td>
</tr>
<tr>
<td>Intraterine and postnatal growth restriction</td>
<td>7</td>
<td>Maternal</td>
<td>394</td>
</tr>
<tr>
<td>Intraterine growth restriction or miscarriage</td>
<td>16</td>
<td>Maternal</td>
<td>395</td>
</tr>
<tr>
<td>Mental retardation and dysmorphism</td>
<td>14</td>
<td>Paternal</td>
<td>396</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>15q11-q13</td>
<td>Paternal</td>
<td>397</td>
</tr>
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<td>Progressive osseous heteroplasia</td>
<td>20q13.3</td>
<td>Paternal</td>
<td>399</td>
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<td>Pseudohypoparathyroidism</td>
<td>20q13.3</td>
<td>Paternal</td>
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<tr>
<td>Rett syndrome</td>
<td>Xq28</td>
<td>Paternal</td>
<td>400, 401</td>
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<td>Russell-Silver syndrome</td>
<td>7p11.2</td>
<td>Maternal</td>
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<tr>
<td>Short stature</td>
<td>14</td>
<td>Maternal</td>
<td>403</td>
</tr>
<tr>
<td>Transient neonatal diabetes</td>
<td>6q22-q23</td>
<td>Paternal</td>
<td>404-406</td>
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### Table 1.8 Selected monogenic disorders with established germline mosaicism

<table>
<thead>
<tr>
<th>Disorder</th>
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</tr>
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<tbody>
<tr>
<td>Achondrogenesis type II</td>
<td>AD</td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>AD</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Albright hereditary osteodystrophy</td>
<td>AD</td>
</tr>
<tr>
<td>α-Thalassemia mental retardation syndrome</td>
<td>X-L</td>
</tr>
<tr>
<td>Amyloid polyneuropathy</td>
<td>AD</td>
</tr>
<tr>
<td>Aniridia</td>
<td>AD</td>
</tr>
<tr>
<td>Apert syndrome</td>
<td>AD</td>
</tr>
<tr>
<td>Becker muscular dystrophy</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Cantu syndrome</td>
<td>AD</td>
</tr>
<tr>
<td>Central hypoventilation syndrome</td>
<td>AD</td>
</tr>
<tr>
<td>Cerebellar ataxia with progressive macular dystrophy (SCA7)</td>
<td>AD</td>
</tr>
<tr>
<td>Charcot–Marie–Tooth disease type 1B</td>
<td>AD</td>
</tr>
<tr>
<td>Coffin–Lowry syndrome</td>
<td>X-L dom</td>
</tr>
<tr>
<td>Congenital contractural arachnodactyly</td>
<td>AD</td>
</tr>
<tr>
<td>Conrad–Hunnermann–Happle syndrome</td>
<td>X-L dom</td>
</tr>
<tr>
<td>Cowden disease</td>
<td>AD</td>
</tr>
<tr>
<td>Danon disease (lysosome-associated membrane protein-2 deficiency)</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Dejerine–Sotos syndrome (HNSN III) with stomatocytosis</td>
<td>AD</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>X-L</td>
</tr>
<tr>
<td>EEC syndrome (ectrodactyly, ectodermal dysplasia, orofacial clefts)</td>
<td>AD</td>
</tr>
<tr>
<td>Epidermolysis bullosa simplex</td>
<td>AR</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>AR</td>
</tr>
<tr>
<td>Facioscapulohumeral muscular dystrophy</td>
<td>AD</td>
</tr>
<tr>
<td>Factor X deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>Familial focal segmental glomerulosclerosis</td>
<td>AD</td>
</tr>
<tr>
<td>Familial hypertrophic cardiomyopathy</td>
<td>AD</td>
</tr>
<tr>
<td>Fibrodysplasia ossificans progressiva</td>
<td>AD</td>
</tr>
<tr>
<td>Fragile X syndrome (deletion type)</td>
<td>X-L</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Herlitz junctional epidermolysis bullosa</td>
<td>A rec</td>
</tr>
<tr>
<td>Holt–Oram syndrome</td>
<td>AD</td>
</tr>
<tr>
<td>Hunter syndrome</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td>X-L dom</td>
</tr>
<tr>
<td>Karsch–Neugebauer syndrome</td>
<td>AD</td>
</tr>
<tr>
<td>Lesch–Nyhan syndrome</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Lissencephaly (males); “subcortical band heterotopia” (almost all females)</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia I</td>
<td>AD</td>
</tr>
<tr>
<td>Myotubular myopathy</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>AD</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>AD</td>
</tr>
<tr>
<td>Oculocerebrorenal syndrome of Lowe</td>
<td>X-L</td>
</tr>
<tr>
<td>Ornithine transcarbamylase deficiency</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Osteocraniosenosis</td>
<td>AD</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>AD</td>
</tr>
<tr>
<td>Otopalatodigital syndrome</td>
<td>X-L dom</td>
</tr>
<tr>
<td>Pseudoachondroplasia</td>
<td>AD</td>
</tr>
<tr>
<td>Severe combined immunodeficiency disease</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Spondyloepimetafysial dysplasia</td>
<td>AD</td>
</tr>
</tbody>
</table>
association has been noted with the respiratory phenotype \(^{412}\) (see Chapter 17). Although individuals who are homozygous for the common CF mutation (ΔF508) can be anticipated to have classic CF, those with the less common mutation (R117H) are likely to have milder disease. \(^{413}\) On occasion, an individual who is homozygous for the “severe” ΔF508 mutation might unexpectedly exhibit a mild pancreatic-sufficient phenotype. Illustrating the complexity of genotype–phenotype associations is the instance noted by Dork et al. \(^{414}\) of a mildly affected ΔF508 homozygote whose one chromosome 7 carried both the common ΔF508 mutations and a cryptic R553Q mutation. Apparently, a second mutation in the same region may modify the effect of the common mutation, permitting some function of the chloride channel \(^{415}\) and thereby ameliorating the severity of the disease.

The extensive mutational heterogeneity in hemophilia A \(^{416}\) is related not only to variable clinical severity but also to the increased likelihood of anti-factor VIII antibodies (inhibitors) developing. Miller et al. \(^{417}\) found about a fivefold higher risk of inhibitors developing in hemophilic males with gene deletions compared with those without deletions.

Given the history of a previously affected offspring with a genetic disorder, the preconception visit serves as an ideal time to refocus on any putative diagnosis (or lack thereof) and to do newly available mutation analyses when applicable.

**Mosaicism**

Mosaicism is a common phenomenon (witness the normal process of X-inactivation and tissue differentiation) that results in functional mosaicism in females. Mosaicism might occur in somatic or germline cells. Its recognition is important, because a disorder may not be due to a new dominant mutation, despite healthy parents. Erroneous counseling could follow, with the provision of risks very much lower than would be the case if germline mosaicism existed. After the birth to healthy parents of a child with achondroplastic dwarfism, random risks of one in 10,000 might be given for recurrence. However, germline mosaicism has been described after the birth of a second affected child. \(^{418}\) Similarly, the birth of a male with Duchenne muscular dystrophy (DMD), no family history and no detectable mutation on DNA analysis of maternal peripheral leukocytes might lead to counseling based on spontaneous mutation rates. Once again, germline mosaicism is now well recognized in mothers of apparently sporadic sons with achondroplastic dwarfism, random risks of one in 10,000 might be given for recurrence.

Table 1.8 Continued

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal-coloboma syndrome</td>
<td>AD</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>AD</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>X-L dom</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>AD</td>
</tr>
<tr>
<td>von Hippel-Lindau disease</td>
<td>AD</td>
</tr>
<tr>
<td>von Willebrand disease (type 2b)</td>
<td>X-L rec</td>
</tr>
<tr>
<td>Waardenburg syndrome</td>
<td>AD</td>
</tr>
<tr>
<td>Wiskott–Aldrich syndrome</td>
<td>X-L rec</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; X-L rec, X-linked recessive; X-L dom, X-linked dominant.

The extensive mutational heterogeneity in hemophilia A is related not only to variable clinical severity but also to the increased likelihood of anti-factor VIII antibodies (inhibitors) developing. Miller et al. found about a fivefold higher risk of inhibitors developing in hemophilic males with gene deletions compared with those without deletions.

Given the history of a previously affected offspring with a genetic disorder, the preconception visit serves as an ideal time to refocus on any putative diagnosis (or lack thereof) and to do newly available mutation analyses when applicable.
patient with somatic cell mosaicism is likely to have some signs, although possibly subtle, of the disorder in question, while those with germline mosaicism are not expected to show any signs of the disorder. Examples of somatic and gonadal mosaicism include autosomal dominant osteogenesis imperfecta, Huntington disease and spinocerebellar ataxia type 2. Lessons from these and the other examples quoted for germline mosaicism indicate a special need for caution in genetic counseling for disorders that appear to be sporadic.

Very careful examination of both parents for subtle indicators of the disorder in question is necessary, particularly in autosomal dominant and sex-linked recessive conditions. The autosomal dominant disorders are associated with 50 percent risks of recurrence, while the sex-linked disorders have 50 percent risk for males and 25 percent risk for recurrence in families. Pure germline mosaicism would likely yield risks considerably lower than these figures, such as 7–14 percent for females with gonadal mosaicism and X-linked DMD. A second caution relating to counseling such patients with an apparent sporadic disorder is the offer of prenatal diagnosis (possibly limited) despite the inability to demonstrate the affected status of the parent.

Chromosomal mosaicism is discussed in Chapter 6 but note can be taken here of a possibly rare (and mostly undetected) autosomal trisomy. A history of subfertility with mostly mild dysmorphic features and normal intelligence has been reported in at least 10 women with mosaic trisomy 18.

Genetic counseling when the fetus is affected

The fateful day when the anxious, waiting couple hears the grim news that their fetus has a malformation or genetic disorder will live on in their memories forever. Cognizance of this impact should inform the thoughts, actions and communications of the physician called on to exercise consummate skill at such a poignant time. Couples may have traveled the road of hope and faith for many years, battling infertility only to be confronted by the devastating reality of a fetal anomaly. With hopes and dreams so suddenly dashed, doubt, anger and denial surface rapidly. The passionate physician will need to be fully armed with all the facts about the defect or be ready to obtain an immediate expert clinical genetics consultation for the couple.

Care should be taken in selecting a quiet, comfortable, private location that is safe from interruption. Placek and Eberhardt, in reviewing the literature, noted consensus recommendations in breaking bad news that included the foregoing and sitting close enough for eye contact without physical barriers. Identifying a support person if the partner cannot/will not attend the consultation is important and knowledge of available resources is valuable. All of the above points are preferences that have been vocalized by parents receiving bad news about their infants.

Almost all couples would have reached this juncture through maternal serum screening, an ultrasound study or amniocentesis/CVS for maternal age, for established known carriers, because of a previously affected child, being an affected parent or having a family history of a specified disorder. Not rarely, an anxious patient insists on a prenatal study. On one such occasion, the patient stated, “My neighbor had a child with Down syndrome,” only to discover from the requested amniocentesis study that her fetus also had a serious abnormality. Physicians are advised not to dissuade patients away from prenatal diagnosis but rather to inform them about the risks of fetal loss balanced against the risk of fetal defects, distinctly different from recommendations for accepted indications.

Recognition of a fetal abnormality by imaging, molecular or cytogenetic study may reveal, for the first time, the genetic disorder in an asymptomatic parent. Robyr et al. described 20 such parents with disorders including spinal muscular atrophy, DiGeorge syndrome, osteogenesis imperfecta, arthrogryposis and Noonan-like syndrome.

Not infrequently, second-trimester ultrasound studies reveal fetal abnormalities of uncertain etiology. For example, on one (legal) case, sequential observations noted prominent lateral cerebral ventricles, multiple thoracic hemivertebrae and intrauterine growth restriction. Amniocyte chromosome studies were normal. The parents were not counseled about the potential for mental retardation despite no definitive diagnosis. The child was born with holoprosencephaly with marked psychomo-
tor delay. Diagnostic uncertainty must be shared with parents at risk.

**Decision making**

The presence of both parents for the consultation concerning possible elective abortion for a fetal defect is critical in this situation. All the principles governing the delivery of genetic counseling and discussed earlier apply when parents need to decide whether or not to continue their pregnancy. A brief explanation of some of the key issues follows, culled from over 45 years of experience in this very subject.

Doubt and disbelief crowd the parental senses in the face of such overwhelming anxiety. Was there a sample mix-up? How accurate is this diagnosis? How competent is the laboratory? Have they made errors in the past? How can we be certain that there has been no communication failure? Is there another couple with the same name? There are endless questions and endless doubts. Each and every one needs to be addressed carefully, slowly and deliberately, with painstaking care to provide the necessary assurance and reassurance. Needless to say, the clinical geneticist must have thoroughly checked all the logistics and potential pitfalls before initiating this consultation. Errors have indeed occurred in the past.

The central portion of the communication will focus on the nature of the defect and the physician or counselor providing the counseling should be fully informed about the disorder, its anticipated burden, the associated prognosis, life expectancy and the possible need for lifetime care. A clear understanding of the potential for pain and suffering is necessary and an exploration concerning the effect on both parents and their other children is second only to a discussion about the potential effects on the child who is born with the condition in question. Any uncertainties related to diagnosis, prognosis, pleiotropism or heterogeneity should emerge promptly. Questions related to possible future pregnancies should be discussed, together with recurrence risks and options for prenatal diagnosis.

The question concerning a repeat prenatal study is invariable, at least if not stated then certainly in the mind of the parents. There are occasions when a repeat test might be appropriate, especially if there is a failure to reconcile cytogenetic or molecular results with expected high-resolution ultrasound observations. Maternal cell contamination (see Chapter 6), while extremely unlikely in almost all circumstances, requires exclusion in some others. Some prenatal diagnoses may not easily be interpretable and a phenotype may not be predictable with certainty. A de novo supernumerary chromosome fragment in the prenatal cytogenetic analysis (see Chapter 6) is a key example that can mostly be settled by a chromosomal microarray study. The sensitive counselor should offer a second opinion to anxious parents facing an uncertain prenatal diagnosis. The “compleat physician” anticipates virtually all of the patient’s questions, answers them before they are asked and raises all the issues without waiting for either parent to vocalize them.

Occasionally, it is apparent that there are powerful disparate attitudes to abortion between the spouses. Such differences would best be considered during the preconception period, rather than for the first time when faced with a serious fetal defect. Resolution of this conflict is not the province of the physician or counselor, nor should either become arbitrator in this highly charged and very personal dispute, in which religious belief and matters of conscience may collide. The physician’s or counselor’s duty is to ensure that all facts are known and understood and that the pros and cons of various possible scenarios are identified in an impartial manner. A return appointment within days should be arranged. Questions of paternity have also suddenly emerged in this crisis period and can now be settled, sometimes with painful certainty.

**Elective abortion: decision and sequel**

Among the greatest challenges clinical geneticists and genetic counselors face is the consultation in which the results of prenatal studies indicating a serious fetal defect are communicated to parents for the first time. The quintessential qualities a counselor will need include maturity, experience, warmth and empathy, sensitivity, knowledge, communication skill and insight into the psychology of human relationships, pregnancy and grieving. Ample time (with follow-up visits) is critical. The principles and prerequisites for counseling discussed earlier apply fully in these circumstances and the fact that this is a parental decision, not a
Genetic Disorders and the Fetus

The importance of continuing follow-up visits with couples who have terminated pregnancy for fetal defects cannot be overemphasized. In an important study on the psychosocial sequelae in such cases, White-van Mourik et al. showed the long-range effects (Table 1.9). Displays of emotional and somatic symptoms 1–2 years after abortion were not rare and included partners. Although some couples grew closer in their relationships, separations, especially because of failed communication, increased irritability and intolerance, were noted in 12 percent of the 84 patients studied. Marital discord in these circumstances has been noted previously. At least 50 percent of couples admitted to having problems in their sexual relationship. In addition, many couples indicated changed behavior toward their existing children, including overprotectiveness, anxiety,

<table>
<thead>
<tr>
<th>Feeling</th>
<th>Women (%)</th>
<th>Men (%)</th>
<th>Women after 24 months (%)</th>
<th>Men after 24 months (%)</th>
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<tbody>
<tr>
<td>Sadness</td>
<td>95</td>
<td>85</td>
<td>60</td>
<td>47</td>
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<tr>
<td>Depression</td>
<td>79</td>
<td>47</td>
<td>12</td>
<td>6</td>
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<td>Anger</td>
<td>78</td>
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<td>Fear</td>
<td>77</td>
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<td>Guilt</td>
<td>68</td>
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<td>7</td>
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<tr>
<td>Failure</td>
<td>61</td>
<td>26</td>
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<td>Shame</td>
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<td>Vulnerability</td>
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<td>Relief</td>
<td>30</td>
<td>32</td>
<td>16</td>
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<td>Isolation</td>
<td>27</td>
<td>20</td>
<td>11</td>
<td>6</td>
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<tr>
<td>Numbness</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Panic spells</td>
<td>20</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Withdrawal</td>
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<td>12</td>
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<table>
<thead>
<tr>
<th>Somatic symptom</th>
<th>Women (%)</th>
<th>Men (%)</th>
<th>Women after 24 months (%)</th>
<th>Men after 24 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crying</td>
<td>82</td>
<td>50</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Irritable</td>
<td>67</td>
<td>38</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>No concentration</td>
<td>57</td>
<td>41</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Listlessness</td>
<td>56</td>
<td>17</td>
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<td>Sleeplessness</td>
<td>47</td>
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<td>Tiredness</td>
<td>42</td>
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<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>31</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nightmares</td>
<td>24</td>
<td>7</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>17</td>
<td>–</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Headaches</td>
<td>9</td>
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irritability and consequent guilt and indiffer-
ence.430 Women with secondary infertility and
those younger than 21 years of age (or immature
women) had the most prolonged emotional, physi-
cal and social difficulties.430

Grief counseling becomes part of the consulta-
tion after elective termination, in which full recog-
nition of bereavement is necessary. The psychology
of mourning has been thoroughly explored by both
Parkes433 and Worden.434 Worden emphasized how
important it is for a bereaved individual to com-
plete each of four stages in the mourning process.
1. Acceptance of the loss.
2. Resolving the pain of grieving.
3. Adjusting to life without the expected child.
4. Placing the loss in perspective.

The importance of allowing parents the option of
holding the fetus (or later, the child), when appro-
priate, is well recognized.435,436 These authors have
also called attention to the complex tasks of
mourning for a woman who is faced with one
defective twin when pregnancy reduction or birth
might occur.

Notwithstanding anticipated loss and grief,
Seller et al.,436 reflecting our own experience,
emphasized that many couples recover from the
trauma of fetal loss “surprisingly quickly.” Insinu-
ation of this reality is helpful to couples in consul-
tations both before and after elective termination.
Moreover, couples’ orientation toward the griev-
ing process achieves an important balance when
they gain sufficient insight into the long-term emo-
tional, physical, economic and social consequences
they might have needed to contemplate if prenatal
diagnosis had not been available.

Testing the other children
Invariably, parents faced with the news of their
affected fetus question the need to test their other
children. Answers in the affirmative are appropri-
te when diagnosis of a disorder is possible. Carrier
detection tests, however, need careful considera-
tion and are most appropriately postponed until
the late teens, when genetic counseling should be
offered. Given the complex dilemmas and far-
reaching implications of testing asymptomatic
children for disorders that may manifest many
years later, parents would best be advised to delay
consideration of such decisions while in the midst
of dealing with an existing fetal defect. In later
consultations, the thorny territory of predictive
genetic testing of children can be reviewed at
length.437–440 Fanos437 emphasized that testing ado-
lescents “may alter the achievement of develop-
mental tasks, including seeking freedom from
parental figures, establishment of personal iden-
tity, handling of sexual energies and remodeling
of former idealizations of self and others.” Fanos
also emphasized that parental bonding may be
compromised by genetic testing when the child’s
genetic health is questionable. Parents may react to
the possible loss or impairment of a child by devel-
oping an emotional distance, recognized as the
vulnerable child syndrome.441 Other aspects,
including interference with the normal develop-
ment of a child’s self-concept, introduce issues of
survivor guilt or increase levels of anxiety already
initiated by family illnesses or loss.441 Predictive
testing of children for later-manifesting neurode-
generative or other disorders would rarely be rec-
ommended, except in circumstances in which early
diagnosis could offer preventive or therapeutic
benefit.

Perinatal genetic counseling
A similar spectrum of issues and concerns is faced
after the detection and delivery of a child with a
genetic disorder or an anomaly. Pregnancy with a
defective fetus may have been continued from the
first or second trimester or a diagnosis may be
made in the third trimester or at the delivery of a
living or stillborn child. The principles and pre-
requisites for genetic counseling discussed earlier
apply equally in all these circumstances.442 Special
attention should be focused on assuaging aspects
of guilt and shame. Difficult as it may be for some
physicians,443,444 close rapport, patient visitation
and sincerity are necessary at these times, even
when faced with commonly experienced anger. A
misstep by the physician in these circumstances
in failing to continue (it is to be hoped) the
rapport already established during pregnancy care
provides the spark that fuels litigation in relevant
cases.

Despite anger, grief and the gamut of expected
emotions, the attending physician (not an inex-
perienced healthcare provider) should take care to
urge an autopsy when appropriate. Diagnosis of certain disorders (e.g. congenital nephrosis) can be made by promptly collected and appropriately prepared renal tissue for electron microscopy, if mutation analysis (see Chapters 10 and 23) is unavailable. In circumstances in which parents steadfastly withhold permission for autopsy (which is optimal), magnetic resonance imaging could provide some useful acceptable alternative when fetal anomalies are expected. The autopsy is the last opportunity parents will have to determine causation, which may ultimately be critical in their future childbearing plans and also for their previous children. A formal protocol for evaluating the cause of stillbirth or perinatal death is important (Box 1.4) to secure a definitive diagnosis, thereby laying the foundation for providing accurate recurrence risks and future precise prenatal diagnosis. In addition, in the face of known or suspected genetic disorders in which mutation analysis now or in the future may be critical, care should be taken to obtain tissue for DNA banking or for establishing a cell line. Later, parents may return and seriously question the failure of the physician to secure tissues or DNA that would have been so meaningful in future planning (e.g. X-linked mental retardation, spinal muscular atrophy).

Psychologic support is important for couples who have lost an offspring from any cause, a situation compounded by fetal or congenital abnormality. The birth (or prenatal detection) of twins discordant for a chromosomal disorder is not rare, given the increased frequency of multiple pregnancy associated with advanced maternal age and the use of assisted reproductive techniques. Pregnancy reduction (see Chapter 28) or the death of one twin or delivery of both evokes severely conflicting emotions that may well affect the mother’s care for the surviving child. Considerable psychologic skill must be marshaled by physicians if meaningful care and support are to be provided.

Supporting telephone calls from doctor and staff and encouragement to attend appointments every 6 weeks, or more frequently when appropriate, are often appreciated by patients. Review of the autopsy report and discussion with reiterative counseling should be expected of all physicians. Frequently, parents receive an autopsy report by mail without further opportunity for explanation and discussion. In one study, 27 percent failed to receive autopsy results. Providing contact with support groups whose focus is the disorder in question is also valuable. In the United States, the vast majority of these groups have combined to form the Alliance of Genetic Support Groups, which acts as a central clearinghouse and referral center.

**Box 1.4 Protocol for evaluating the cause of stillbirth or perinatal death**

1. Review genetic, medical and obstetric history.
2. Determine possible consanguinity.
3. Gently and persistently recommend that parents permit a complete autopsy.
4. Obtain photographs, including full face and profile, whole body and, when applicable, detailed pictures of any specific abnormality (e.g. of digits).
5. Obtain full-body skeletal radiographs.
6. Consider full-body magnetic resonance imaging, if autopsy is not permitted.
7. Carefully document any dysmorphic features.
8. Obtain heparinized cord or fetal blood sample for chromosomal or DNA analysis.
9. Obtain fetal serum for infectious disease studies (e.g. parvovirus, cytomegalovirus, toxoplasmosis).
10. Obtain fetal tissue sample (sterile fascia best) for cell culture aimed at chromosome analysis or biochemical or DNA studies.
11. Obtain parental blood samples for chromosome analysis, when indicated.
12. Communicate final autopsy results and conclusions of special analyses.
13. Provide follow-up counseling, including a summary letter.
Family matters

Beyond all the “medical” steps taken in the wake of stillbirth or perinatal death due to fetal defects are critical matters important to the family and its future. Active, mature and informed management is necessary in these difficult and frequently poignant situations. Regardless of the cause of the child’s defect(s), maternal guilt is almost invariable and sometimes profound. Recognition of a definitive cause unrelated to a maternal origin should be explained in early discussions and reiterated later. For autosomal recessive disorders or with even more problematic X-linked disorders, maternal “culpability” is real and not easily assuaged. The fact that we all carry harmful genes, some of which we may have directly inherited, while others may have undergone mutation, may need in-depth discussion. Mostly, it is possible and important to reassure mothers that the outcome was not due to something they did wrong. Where the converse is true, much effort will be needed for management of guilt and shame, and for planning actions that promise a better future with ways to avert another adverse outcome.

Attention to details that have a very important role in the mourning process include ensuring that the child be given a name and, in the case of the death of a defective fetus in the third trimester, that the parents’ wishes for a marked grave be determined. As noted earlier, most caretakers feel that parents are helped by both seeing and holding the baby. Although some may experience initial revulsion when the subject is mentioned, gentle coaxing and explanations about the experiences of other couples may help grieving parents. Even with badly disfigured offspring, it is possible for parents to cradle a mostly covered baby whose normal parts, such as hands and feet, can be held. Important mementos that parents should be offered are photographs, a lock of hair, the baby’s name band or clothing. Ultimately, these concrete emblems of the baby’s existence assist parents in the mourning process, although the desperate emptiness that mothers especially feel is not easily remedied. Photos may also be helpful in providing comfort for other children and for grandparents. Parents will also vary in their choice of traditional or small, private funerals. Physicians should ensure that parents have the time to make these various decisions and assist by keeping the child in the ward for some hours when necessary.

Both parents should be encouraged to return for continuing consultations during the mourning period. Mourning may run its course for 6–24 months. These consultations will serve to explore aspects of depression, guilt, anger, denial, possible marital discord and physical symptoms such as frigidity or impotence. Impulsive decisions for sterilization should be discouraged in the face of overwhelming grief. Advice should be given about safe, reliable and relatively long-term contraception. Similarly, parents should be fully informed about the consequences of having a “replacement child” very soon after their loss. That child may well become a continuing vehicle of grief for the parents, who may then become overanxious and overprotective. Subsequently, they may bedevil the future of the replacement child with constant references to the lost baby, creating a fantasy image of perfection that the replacement child could never fulfill. Such a child may well have trouble establishing his or her own identity.

The surviving children

Distraught parents frequently seek advice about how to tell their other children. Responses should be tailored to the age of the child in question, to the child’s level of understanding and against a background of the religious and cultural beliefs of the family. A key principle to appreciate is that having reached the stage of cognizance regarding the loss, a child needs and seeks personal security. Hence, the parents’ attention should be focused on love, warmth and repetitive reassurance, especially about (possibly) unstated feelings of previous wrongdoing and personal culpability. Advice about grieving together instead of being and feeling overwhelmed in front of their children is also helpful advice. Focusing on the children's thoughts and activities is beneficial rather than lapsing into a state of emotional paralysis, which can only serve to aggravate the family’s psychodynamics adversely.

The efficacy of genetic counseling

The essential goal of the communication process
Genetic Disorders and the Fetus

in genetic counseling is to achieve as complete an understanding by the counselee(s) as possible, thereby enabling the most rational decision making. Parental decisions to have additional affected progeny should not be viewed as a failure of genetic counseling. Although the physician’s goal is the prevention of genetic disease, the orientation of the prospective parents may be quite different. A fully informed couple, both of whom had achondroplasia, requested prenatal diagnosis with the expressed goal of aborting a normal unaffected fetus so as to be able to raise a child like themselves. Would anyone construe this as a failure in genetic counseling?

Clarke et al.\textsuperscript{456} considered three prime facets that could possibly evaluate the efficacy of genetic counseling: (1) recall of risk figures and other relevant information by the counselee(s); (2) the effect on reproductive planning; and (3) actual reproductive behavior. Their conclusions, reflecting a Western consensus, were that there are too many subjective and variable factors involved in the recall of risk figures and other genetic counseling information to provide any adequate measure of efficacy. Further, assessing reproductive intentions may prejudice the service the counselee wishes as well as the fact that there are too many confounding factors that have an impact on reproductive planning. Moreover, how many years after counseling would be required to assess the impact on reproductive planning? They regarded evaluation of reproductive plans as “a poor proxy for reproductive behavior.” In dispensing with assessments of actual reproductive behavior in the face of counseling about such risks, they pointed to the complex set of social and other factors that confound the use of this item as an outcome measure. They did, however, recommend that efficacy be assessed against the background goals of genetic counseling aimed at evaluation of the understanding of the counselee(s) of their own particular risks and options.

Evaluation of the efficacy of genetic counseling\textsuperscript{12,169} should therefore concentrate on the degree of knowledge acquired (including the retention of the counselee(s) with regard to the indicated probabilities) and the rationality of decision making (especially concerning further reproduction). Frequent contraceptive failures in high-risk families highlight the need for very explicit counseling.

Important points made by Emery et al.\textsuperscript{457} in their prospective study of 200 counselors included the demonstrated need for follow-up after counseling, especially when it is suspected that the comprehension of the counselee(s) is not good. This seemed particularly important in chromosomal and X-linked recessive disorders. They noted that the proportion deterred from having children increased with time and that more than one-third of their patients opted for sterilization within 2 years of counseling.

A number of studies\textsuperscript{457–459} document the failure of comprehension by the counselee(s). The reports do not reflect objective measures of the skill or adequacy of genetic counseling and the possible value of a summary letter to the patient of the information provided after the counseling visit. Sorenson et al.\textsuperscript{460} prospectively studied 2,220 counselees who were seen by 205 professionals in 47 clinics located in 25 states and the District of Columbia. They gathered information not only on the counselees but also on the counselors and the clinics in which genetic counseling was provided. They, too, documented that 53 percent of counselees did not comprehend their risks later, while 40 percent of the counselees given a specific diagnosis did not appear to know it after their counseling. They thoroughly explored the multiple and complex issues that potentially contributed to the obvious educational failure that they (and others) have observed. In another study of parents with a DS child, Swerts\textsuperscript{408} noted that of those who had genetic counseling, 45 percent recalled recurrence risks accurately, 21 percent were incorrect and 34 percent did not remember their risks.

The expected post-counseling letter to the referring physician with a copy (or a separate letter) to the patient plays a vital role in securing comprehension of risks and issues. Printed materials, especially covering risks, test limitations, psychologic and social aspects, enrich the counseling benefits.\textsuperscript{78} Genetic counseling can be considered successful when counselees, shown to be well informed, make careful, rational decisions regardless of whether their physicians consider their position to be ill advised. Clearly, counselees and counselors may differ in their perception of the consultation and
the degree of satisfaction.\textsuperscript{461} Notwithstanding the obvious benefits of counseling, reproductive uncertainty is often not eliminated because it is related to factors beyond the scope of counseling.\textsuperscript{462}

In considering the effectiveness of genetic counseling, Sorenson et al.\textsuperscript{460} summarized the essence of their conclusion.

In many respects, an overall assessment of the effectiveness of counseling, at least the counseling we assessed in this study, is confronted with the problem of whether the glass is half full or half empty. That is, about half of the clients who could have learned their risk did but about half did not. And, over half of the clients who could have learned their diagnosis did but the remainder did not. In a similar vein, clients report that just over half of their genetic medical questions and concerns were discussed but about half were not. The picture for sociomedical concerns and questions was markedly worse, however. And, reproduc-tively, just over half of those coming to counseling to obtain information to use in making their reproductive plans reported counseling influenced these plans but about half did not. Any overall assessment must point to the fact that counseling has been effective for many clients but ineffective for an almost equal number.

A critical analysis of the literature by Kessler\textsuperscript{463} concluded that published studies on reproductive outcome after genetic counseling reveal no major impact of counseling. Moreover, decisions made before counseling largely determined reproduction after counseling.

A more recent study of patients’ expectations of genetic counseling revealed that the majority had their expectations fulfilled, especially with perceived personal control.\textsuperscript{464} When patients’ expectations for reassurance and advice were met, they were subsequently less concerned and had less anxiety compared with when such expectations were not fulfilled.

The limited efficacy of genetic counseling revealed in the study by Sorenson et al.\textsuperscript{460} reflects the consequences of multiple factors, not the least of which are poor lay understanding of science and a lack or inadequacy of formal training of counselors in clinical genetics,\textsuperscript{465} which is no longer the case for genetic counselors, at least in the USA and Canada. Efficacy, of course, is not solely related to counselee satisfaction. Efforts to educate the public about the importance of genetics in their personal lives have been made by one of us in a series of books (translated into nine languages) over a quarter of a century.\textsuperscript{167,168,171–173,256} In addition to public education and its concomitant effect of educating physicians generally, formal specialist certification in the United States, Canada and the United Kingdom, acceptance of clinical genetics as a specialty approved by the American Medical Association and new degree programs for genetic counselors certified by the National Board of Genetic Counselors will undoubtedly improve the efficacy of genetic counseling.

References


27. Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in the earliest weeks of preg-
nancy reduces the prevalence of neural tube defects. JAMA 1989;262:2847.


41. Olafsson E, Hallgrimsson JT, Hauser WA, et al. Preg-
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