

Genetic Counseling and Genetic Screening

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CHAPTER 6

Frequency of Genetic Disease 138	Autosomal Trisomy 140	Psychological Defenses 144
Chromosomal Abnormalities 138	Autosomal Deletions or Duplications 142	Genetic Screening 145
Single-Gene Disorders 139	Sex Chromosomal Abnormalities 142	Screening Neonates 145
Polygenic/Multifactorial Disorders 139	Genetic History 143	Screening Adults 146
Teratogenic Disorders 140	Genetic Counseling 143	Screening for Cystic Fibrosis 146
Clinical Spectrum of Chromosomal Abnormalities 140	Communication 143	Follow-Up of Cystic Fibrosis Test Results 149
	Nondirective Counseling 144	Alerting Relatives 149

KEY ABBREVIATIONS

American College of Medical Genetics	ACMG
American College of Obstetricians and Gynecologists	ACOG
Congenital bilateral absence of the vas deferens	CBAVD
Cystic fibrosis	CF
Deoxyribonucleic acid	DNA
Gap Junction B	GJB
Health Resources and Services Administration	HRSA
Intelligence quotient	IQ
Mean corpuscular volume	MCV
Transmembrane conductance regulator	CFTR
Uniparental disomy	UPD

Approximately 3 percent of liveborn infants have a major congenital anomaly. About one half of these anomalies are detected at birth; the remainder becomes evident later in childhood or, less often, adulthood. Although nongenetic factors may cause malformations, genetic factors are usually responsible. In addition, more than 50 percent of first-trimester spontaneous abortions and at least 5 percent of stillborn infants have chromosomal abnormalities (see Chapter 24). Given such a pivotal role for genetic factors, medical genetics becomes integral to the practice of modern obstetrics.

This chapter considers the principles of genetic counseling and genetic screening. Disorders amenable to genetic screening and prenatal diagnosis are enumerated.

FREQUENCY OF GENETIC DISEASE

Phenotypic variation—normal or abnormal—may be considered in terms of several etiologic categories: (1) chromosomal abnormalities, numeric or structural; (2) single-gene or mendelian disorders; (3) polygenic and multifactorial disorders, polygenic implying an etiology resulting from cumulative effects of more than one gene and multifactorial implying interaction as well with environmental factors; and (4) teratogenic disorders, caused by exposure to exogenous factors (e.g., drugs) that deleteriously affect an embryo otherwise destined to develop normally. Principles of these mechanisms are reviewed elsewhere in detail.¹

Chromosomal Abnormalities

From surveys of liveborn neonates, it is well established that the incidence of chromosomal aberrations is 1 in 160. Table 6-1 shows the incidence of individual abnormalities.² The chromosomal abnormality that generates the most attention is autosomal trisomy. Autosomal trisomy usually arises as a result of abnormalities of meiosis, nondisjunction producing a gamete with 24 rather than the expected 23 chromosomes. This results in a zygote having 47 chromosomes. This error most commonly occurs during maternal meiosis, and is associated with the well-known maternal age effect. Table 6-2 shows the year-to-year increase in frequency of Down syndrome and other aneuploidies.³ Another calculation has shown that the progressive increase with advancing maternal age plateaus around age 45, but this is of relatively little clinical significance.⁴ The frequency is about 30 percent higher in midpregnancy than at term, reflecting lethal-

Table 6-1. Chromosomal Abnormalities in Newborn Infants

TYPE OF ABNORMALITY	INCIDENCE
Numeric aberrations	
Sex chromosomes	
47,XYY	1/1,000 MB
47,XXY	1/1,000 MB
Other (men)	1/1,350 MB
47,X	1/10,000 FB
47,XXX	1/1,000 FB
Other (females)	1/2,700 FB
Autosomes	
Trisomies	
13–15 (D group)	1/20,000 LB
16–18 (E group)	1/8,000 LB
21–22 (G group)	1/800 LB
Other	1/50,000 LB
Structural aberrations	
Balanced	
Robertsonian	
t(Dq; Dq)	1/1,500 LB
t(Dq; Gq)	1/5,000 LB
Reciprocal translocations and insertional inversions	1/7,000 LB
Unbalanced	
Robertsonian	1/14,000 LB
Reciprocal translocations and insertional inversions	1/8,000 LB
Inversions	1/50,000 LB
Deletions	1/10,000 LB
Supernumeraries	1/5,000 LB
Other	1/8,000 LB
Total	1/160 LB

LB, live births; MB, male births; FB, female births.
Pooled data tabulated by Hook and Hamerton.²

ity throughout pregnancy.⁵ Some trisomies, for example, No. 16, arise almost exclusively in maternal meiosis, usually maternal meiosis I. For a few chromosomes, there is a relatively higher frequency of errors at meiosis II (e.g., trisomy 18), and in yet others, errors in paternal meiosis are not uncommon (e.g., trisomy 2). Autosomal trisomy can also recur, the recurrence risk being approximately 1 percent following either trisomy 18 or 21. This suggests that genetic factors perturb meiosis, a phenomenon that serves as justification for prenatal screening after one aneuploid conception.

In addition to numeric abnormalities, structural chromosomal abnormalities occur. In a balanced interchange (translocation) between 2 or more chromosomes, individuals are phenotypically normal. However, such individuals are at increased risk for offspring with unbalanced gametes. This topic is also discussed in Chapter 24 in the context of repeated pregnancy loss.

Single-Gene Disorders

Approximately 1 percent of liveborn infants are phenotypically abnormal as a result of a single-gene mutation. Mendelian disorders thus account for 40 percent of the congenital defects seen in liveborn infants.

Table 6-2. Maternal Age and Chromosomal Abnormalities (Live Births)*

MATERNAL AGE	RISK FOR DOWN SYNDROME	RISK FOR ANY CHROMOSOME ABNORMALITIES
20	1/1,667	1/526 [†]
21	1/1,667	1/526 [†]
22	1/1,429	1/500 [†]
23	1/1,429	1/500 [†]
24	1/1,250	1/476 [†]
25	1/1,250	1/476 [†]
26	1/1,176	1/476 [†]
27	1/1,111	1/455 [†]
28	1/1,053	1/435 [†]
29	1/1,100	1/417 [†]
30	1/952	1/384 [†]
31	1/909	1/385 [†]
32	1/769	1/322 [†]
33	1/625	1/317 [†]
34	1/500	1/260
35	1/385	1/204
36	1/294	1/164
37	1/227	1/130
38	1/175	1/103
39	1/137	1/82
40	1/106	1/65
41	1/82	1/51
42	1/64	1/40
43	1/50	1/32
44	1/38	1/25
45	1/30	1/20
46	1/23	1/15
47	1/18	1/12
48	1/14	1/10
49	1/11	1/7

*Because sample size for some intervals is relatively small, confidence limits are sometimes relatively large. Nonetheless, these figures are suitable for genetic counseling.

[†]47,XXX excluded for ages 20 to 32 (data not available).

Data from Hook³ and Hook et al.⁵

The human genome has now been sequenced and shown to contain approximately 25,000 human genes. In addition, post-transcriptional modifications result in perhaps three times as many proteins (gene products). Perturbation of each gene (deoxyribonucleic acid [DNA] sequence) or protein should theoretically result in a mendelian disorder. However, function is known for only a few thousand genes. Moreover, even the most common single gene (mendelian) disorder is individually rare except in its predominate ethnic group: cystic fibrosis (CF) 1 in 2,500 whites of European or Ashkenazi Jewish origin; sickle cell anemia in blacks; β -thalassemia in Greeks and Italians; α -thalassemia in Southeast Asians; and Tay-Sachs disease, CF, Canavan disease, and familial dysautonomia in Ashkenazi Jews.

Polygenic/Multifactorial Disorders

Another 1 percent of neonates are abnormal but show a normal chromosomal complement and have not osten-

sibly undergone mutation at a *single* genetic locus. It can be deduced that several different genes are involved (polygenic/multifactorial inheritance).¹

Disorders in this etiologic category include most common malformations limited to a single organ system. These include hydrocephaly, anencephaly, and spina bifida (neural tube defects); facial clefts (cleft lip and palate); cardiac defects; pyloric stenosis; omphalocele; hip dislocation; uterine fusion defects; and club foot. After the birth of one child with such anomalies, the recurrence risk in subsequent progeny is 1 to 5 percent.¹ This frequency is less than would be expected if only a single gene were responsible but greater than that for the general population. The recurrence risks for malformations are also 1 to 5 percent for offspring of affected parents. That recurrence risks are similar for both siblings and offspring diminishes the likelihood that environmental causes are the exclusive etiologic factor because it is highly unlikely that households in different generations would be exposed to the same teratogen. Further excluding environmental factors as exclusive etiologic agents are observations that monozygotic twins are much more often concordant (similarly affected) than dizygotic twins, despite the fact that both types of twins share a common intrauterine environment.

The above-mentioned observations are best explained on the basis of polygenic/multifactorial inheritance. Although more than one gene is involved, only a few genes are necessary to produce the number of genotypes necessary to explain recurrence risks of 1 to 5 percent. That is, large numbers of genes and complex mechanisms need *not* be invoked. Polygenic/multifactorial etiology can thus plausibly be assumed responsible for liveborn infants having an anomaly of a single organ system without a chromosomal abnormality or a mendelian mutation (Table 6-3).

Table 6-3. Polygenic/Multifactorial Traits*

Hydrocephaly (excepting some forms of aqueductal stenosis and Dandy Walker syndrome)
Neural tube defects (anencephaly, spina bifida, encephalocele)
Cleft lip, with or without cleft plate
Cleft lip (alone)
Cardiac anomalies (most types)
Diaphragmatic hernia
Pyloric stenosis
Omphalocele
Renal agenesis (unilateral or bilateral)
Ureteral anomalies
Posterior urethral valves
Hypospadias
Müllerian fusion effects
Müllerian aplasia
Limb reduction defects
Talipes equinovarus (clubfoot)

*Relatively common traits considered to be inherited in polygenic/multifactorial fashion. For each, normal parents have recurrence risks of 1 to 5 percent after one affected child. After two affected offspring, the risk is higher.

Teratogenic Disorders

The perhaps 20 proved teratogens are reviewed in Chapter 8. Although many other agents are suspected teratogens, the quantitative contribution of known teratogens to the incidence of anomalies seems relatively small (with the possible exception of alcohol).

CLINICAL SPECTRUM OF CHROMOSOMAL ABNORMALITIES

Offering a few generalizations concerning chromosomal disorders may be helpful to the obstetrician, who may encounter abnormal fetuses or infants during prenatal genetic studies or at delivery. In this section, we briefly review the clinical and cytogenetic features characteristic of the common numeric chromosomal abnormalities. Standard genetic texts, some geared for the obstetricians-gynecologist,¹ cover the broader spectrum of rare (often mosaic) trisomies and autosomal duplication or deficiency syndromes.

Autosomal Trisomy

TRISOMY 21

Trisomy 21 (Down syndrome, mongolism) is the most frequent autosomal chromosomal syndrome, occurring in 1 of every 800 liveborn infants (Table 6-1). The relationship of Down syndrome to advanced maternal age is well known (Table 6-2). Consistent with this maternal age effect, approximately 95 percent of cases arise in maternal meiosis, usually meiosis I. Characteristic craniofacial features include brachycephaly, oblique palpebral fissures, epicanthal folds, broad nasal bridge, a protruding tongue, and small, low-set ears with an overlapping helix and a prominent antihelix (Fig. 6-1). The mean birth weight in Down syndrome, 2,900 g, is decreased but less so than in other autosomal trisomies. At birth, Down syndrome infants are usually hypotonic. Other features include iridial Brushfield spots, broad short fingers (brachymesophalangia), clinodactyly (incurving deflections resulting from an abnormality of the middle phalanx), a single flexion crease on the fifth digit, and an unusually wide space between the first two toes. A single palmar crease (simian line) is not pathognomonic, being present in only 30 percent of individuals with trisomy 21 and in 5 percent of normal individuals. Relatively common internal anomalies include cardiac lesions and duodenal atresia. Cardiac anomalies and increased susceptibility to both respiratory infections and leukemia contribute to reduced life expectancy. However, mean survival extends into the fifth decade.

Patients with Down syndrome who survive beyond infancy invariably exhibit mental retardation. However, the degree of retardation is not as severe as that of most other chromosomal aberrations. Mean intelligence quotient (IQ) ranges approximately from 25 to 70; 46/47,+21 mosaicism should be suspected if Down syndrome cases show IQs in the 70 to 80 range. Women with Down



Figure 6-1. An infant with trisomy 21. (From Simpson JL, Elias S: *Genetics in Obstetrics and Gynecology*, 3rd ed. Philadelphia, WB Saunders Company, p 24, with permission.)

syndrome are fertile. Although relatively few trisomic mothers have reproduced, about 30 percent of their offspring are also trisomic. Men are not considered fertile.

Several cytogenetic mechanisms may be associated with Down syndrome, the actual cause of which involves triplication of a small portion of chromosome 21, namely, band q22. Triplication may be caused either by the presence of an entire additional chromosome 21 or the addition of only band q22. Of all cases of Down syndrome, 95 percent have primary trisomy (47 instead of the normal 46 chromosomes) (Fig. 6-2). It is these cases that show the well-known relationship to both maternal age effect and to errors in maternal meiosis.

Structural chromosomal abnormalities—translocations—show no association to parental age. They may be either sporadic or familial. The translocation most commonly associated with Down syndrome involves chromosomes 14 and 21. With translocation Down syndrome, one parent may have the same translocation (rearrangement), that is, 45,t(14q;21q). Empiric risks are approximately 10 percent for offspring of female robertsonian translocation heterozygotes and 2 percent for offspring of male translocation heterozygotes. A potential concern is that diploid (46,XX or 46,XY) cases actually show uniparental disomy (UPD), both chromosomes originating from the same parent. In 65 Robertsonian translocation carriers [44 t(13q;14q), 11 t(14q;21q), 4 t(14q;22q), 6 others], only 1 UPD case was observed (0.6 percent).⁶ The authors also surveyed 357 inherited and 102 de novo published cases, and concluded overall UPD risk for UPD 14 or 15 was 3 percent.

Other structural rearrangements resulting in Down syndrome include t(21q;21q), t(21q;21q), and translocations involving chromosome 21 and other acrocentric chromosomes (13 to 15) or G (21 to 22). In t(21q;21q), normal

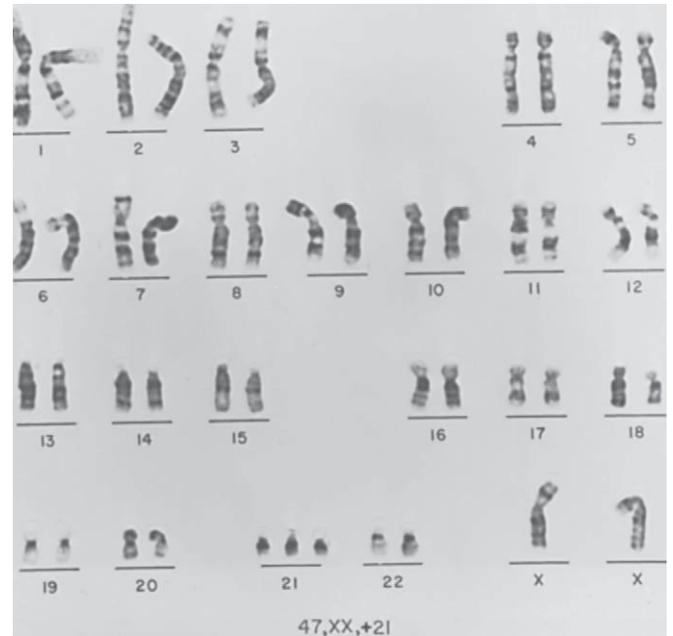


Figure 6-2. Karyotype of a trisomy 21 cell. Trypsin-Giemsa (GTG) banding. (From Simpson JL, Elias S: *Genetics in Obstetrics and Gynecology*, 3rd ed. Philadelphia, WB Saunders Company, with permission.)

gametes do not ordinarily form. Thus, only trisomic or monosomic zygotes are produced, the latter presumably appearing as preclinical embryonic losses. Parents having the other translocations have a low empiric risk of having offspring with Down syndrome.

TRISOMY 13

Trisomy 13 occurs in about 1 per 20,000 live births. Intrauterine and postnatal growth restrictions are pronounced, and developmental retardation is severe. Nearly 50 percent of affected children die in the first month, and relatively few survive past 3 years of age. Characteristic anomalies include holoprosencephaly, eye anomalies (microphthalmia, anophthalmia, or coloboma), cleft lip and palate, polydactyly, cardiac defects, and low birth weight. Other relatively common features include cutaneous scalp defects, hemangiomas on the face or neck, low-set ears with an abnormal helix, and rocker-bottom feet (convex soles and protruding heels).

Trisomy 13 is usually associated with nondisjunction (primary) trisomy (47,+13). As in trisomy 21, a maternal age effect exists, and most cases are maternal in origin. Translocations are responsible for less than 20 percent of cases, invariably associated with two group D (13 to 15) chromosomes joining at their centromeric regions (robertsonian translocation). If neither parent has a rearrangement, the risk for subsequent progeny is not increased. If either parent has a balanced 13q;14q translocation, the recurrence risk for an affected offspring is increased but only to 1 to 2 percent. The exception is homologous 13q;13q parental translocation, which carries the same dire prognosis as 21q;21q translocation.

TRISOMY 18

Trisomy 18 occurs in 1 per 8,000 live births. Among liveborn infants, girls are affected more often than boys (3:1). Among stillborns and abortuses, however, the sex distribution is more equal.

Facial anomalies characteristic of trisomy 18 include microcephaly, prominent occiput, low-set and pointed “fawn-like” ears, and micrognathia. Skeletal anomalies include overlapping fingers (V over IV, II over III), short sternum, shield chest, narrow pelvis, limited thigh abduction or congenital hip dislocation, rocker-bottom feet with protrusion of the calcaneum, and a short dorsiflexed hallux (“hammer toe”). Cardiac and renal anomalies are common.

Mean birth weight is 2,240 g. Fetal movement is feeble, and approximately 50 percent develop distress during labor. The mean survival is months. Liveborn infants show pronounced developmental and growth retardation. Trisomy 18 is not uncommonly detected among stillborn infants.

Approximately 80 percent of trisomy 18 cases are caused by primary nondisjunction (47,XX,+18 or 47,XY,+18). Errors usually arise in maternal meiosis, frequently meiosis II. Recurrence risk is about 1 percent.

OTHER AUTOSOMAL TRISOMIES

All autosomes show trisomies, but usually these end in abortuses. In addition to numbers 13, 18, and 21, only a few other trisomies are detected in liveborns (8, 9, 14, 16, and 22), and here often in mosaic forms. All cases show mental retardation, various somatic anomalies, and intrauterine growth restriction. The extent of retardation and the spectrum of anomalies vary.

Monosomy has been claimed for trisomy 21,⁷ although undetected mosaicism is always different to exclude.

Autosomal Deletions or Duplications

Deletions or duplications of portions of autosomes also exist. There are numerous types. All are characterized by mental retardation and somatic anomalies, but specific features vary.

In counseling, one should initially exclude parental chromosomal rearrangements like a balanced translocation or inversion (see Chapter 7). If the deletion is sporadic, the recurrence risk is no greater than that for any other couple of comparable parental ages.

Sex Chromosomal Abnormalities**MONOSOMY X (45,X)**

45,X individuals account for approximately 40 percent of gonadal dysgenesis cases ascertained by gynecologists. The incidence of 45,X in liveborn girls is about 1 in 10,000. Because monosomy X accounts for 10 percent of all first-trimester abortions, it can be calculated that more

than 99 percent of 45,X conceptuses must end in early pregnancy loss. The error usually (80 percent) involves loss of a paternal sex chromosome.

Gonadal dysgenesis is often associated with an abnormal sex chromosomal constitution. Associated complements include not only monosomy X but structural abnormalities of the X chromosome. Mosaicism is frequent, usually involving a coexisting 45,X cell line. Both the long arm and the short arm of the X chromosome contain determinants necessary for ovarian differentiation and for normal stature, as discussed in detail elsewhere.¹

45,X individuals not only have streak gonads but invariably are short (<150 cm). Growth hormone treatment increases the final adult height 6 to 8 cm. Various somatic anomalies exist: renal and cardiac defects, skeletal abnormalities like cubitus valgus and clinodactyly, vertebral anomalies, pigmented nevi, nail hypoplasia, and a low posterior hairline. Performance IQ is lower than verbal IQ, but overall IQ should be considered normal. Adult-onset diseases include hypertension and diabetes mellitus. Sybert^{8,9} provides guidelines for evaluation and clinical management.

KLINEFELTER SYNDROME

Boys with two or more X chromosomes have small testes, azoospermia, elevated follicle-stimulating hormone and luteinizing hormone levels, and decreased testosterone. The most frequent chromosomal complement associated with this phenotype—Klinefelter syndrome—is 47,XXY; 48,XXXY and 49,XXXXY are less common.

Mental retardation is uncommon in 47,XXY Klinefelter syndrome, but behavioral problems and receptive language difficulties are common. Mental retardation is invariably associated with 48,XXXY and 49,XXXXY. Skeletal, trunk, and craniofacial anomalies occur infrequently in 47,XXY but are commonly observed in 48,XXXY and 49,XXXXY. Regardless of the specific chromosomal complement, patients with Klinefelter syndrome all have unquestioned male phenotypes. The penis may be hypoplastic, but hypospadias is uncommon. With intracytoplasmic sperm injection and other assisted reproductive technologies, siring a pregnancy is now possible. Simpson et al.^{10,11} provides guidelines on evaluation and clinical management.

**POLYSOMY X IN GIRLS
(47,XXX; 48,XXXX; 49,XXXXX)**

About 1 in 800 liveborn girls has a 47,XXX complement. 47,XXX individuals are more likely to show mental retardation than are individuals in the general population, and they show IQs 10 to 15 points lower than their sibs. However, the absolute risk for mental retardation does not exceed 5 to 10 percent, and even then, IQ is usually 60 to 80. Most 47,XXX patients have a normal reproductive system. The theoretical risk of 47,XXX women delivering an infant with an abnormal chromosomal complement is 50 percent, given one half

maternal gametes carrying 24 chromosomes (24,XX). Empiric risks are much less. Somatic anomalies are not unusually considered increased in 47,XXX individuals, although anomalies may occur and have been observed in prenatally detected cases.¹² However, 48,XXXX and 49,XXXXX individuals are invariably retarded and more likely to have somatic malformations than 47,XXX individuals.

POLYSOMY Y IN BOYS (47,XYY AND 48,XXYY)

Presence of more than one Y chromosome is another frequent chromosomal abnormality in liveborn boys (1 in 1,000). 47,XYY men seem more likely than 46,XY boys to be tall and display sociopathic behavior. One estimate is that 1 percent of 47,XYY men will be incarcerated compared with 0.1 percent of 46,XY men. 47,XXYY men usually have normal male external genitalia.

GENETIC HISTORY

Obstetrician/gynecologists must attempt to determine whether a couple, or anyone in their family, has a heritable disorder or is at increased risk for abnormal offspring. To address this question, some obstetricians find it helpful to elicit genetic information through the use of questionnaires or checklists that are often constructed in a manner that requires action only to positive responses. Figure 6-3 reproduces a form that has been modified from that recommended by the American College of Obstetricians and Gynecologists (ACOG).

One should inquire into the health status of first-degree relatives (siblings, parents, offspring), second-degree relatives (nephews, nieces, aunts, uncles, grandparents), and third-degree relatives (first cousins, especially maternal). Adverse reproductive outcomes such as repetitive spontaneous abortions, stillbirths, and anomalous liveborn infants should be pursued. Couples having such histories should undergo chromosomal studies in order to exclude balanced translocations (see Chapter 24). Genetic counseling may prove sufficiently complex to warrant referral to a clinical geneticist, or it may prove simple enough for the well-informed obstetrician to manage. If a birth defect exists in a second-degree relative (uncle, aunt, grandparent, nephew, niece) or third-degree relative (first cousin), the risk for that anomaly will usually not prove substantially increased over that in the general population. For example, identification of a second- or third-degree relative with an autosomal recessive trait places the couple at little increased risk for an affected offspring, an exception being if the patient and her husband are consanguineous. However, a maternal first cousin with an X-linked recessive disorder could identify a couple at increased risk for a similar occurrence.

Parental ages should also be recorded. Advanced maternal age (Table 6-2) warrants discussion irrespective of a physician's personal convictions regarding pregnancy termination, as knowledge of an abnormality may affect obstetric management. Ethnic origin should be recorded

because certain genetic diseases are increased in selected ethnic groups (see below). Such queries apply for both gamete donors as well as couples achieving pregnancy by natural means.

Advanced *maternal* age confers increased risk for aneuploidy. This probably does not hold for advanced *paternal* age. A few studies indicate an increased frequency of aneuploidy in sperm in the sixth and seventh decades. However, risks are only marginally increased above background, and there remains no indication that a liveborn pregnancy risk is increased.

By contrast, a *paternal* age effect exists for single gene mutation, most relevantly de novo autosomal dominant mutations. A pregnancy sired by a man in his sixth decade or beyond carries perhaps a 1 percent increase, owing to the cumulative effects of single gene mutations at many loci. Unfortunately, prenatal testing is not applicable because hundreds of different loci could be involved. There is no evidence of a *maternal* age effect for single gene disorders.

GENETIC COUNSELING

Although genetic counseling may require referral to a clinical geneticist, it is impractical for obstetricians to refer all patients with genetic inquiries. Indeed, obstetricians performing diagnostic procedures such as amniocentesis must counsel their patients before such a procedure. Therefore, salient principles of the genetic counseling process are described.

Communication

Pivotal to counseling is communicating in terms that are readily comprehensible to patients. It is useful to preface remarks with a few sentences recounting the major causes of genetic abnormalities, such as cytogenetic, single-gene, polygenic/multifactorial ("complex"), and environmental (teratogens) causes. Writing unfamiliar words and using tables or diagrams to reinforce important concepts is helpful. Repetition is essential. Allow the couple not only to ask questions but to talk with one another to formulate their concerns.

Written information (letters or brochures) can serve as a couple's permanent record, allaying misunderstanding and assisting in dealing with relatives. Preprinted forms describing common problems (e.g., advanced maternal age) have the additional advantage of emphasizing that the couple's problem is not unique. More complicated scenarios require a letter.

Irrespective of how obvious a diagnosis may seem, confirmation is always obligatory. Accepting a patient's verbal recollection does not suffice, nor would accepting a diagnosis made by a physician not highly knowledgeable about the condition. The anomalous individual may need to be examined by the appropriate authority; examining first-degree relatives may be required as well to detect subtle findings, for example, of an autosomal dominant disorder like neurofibromatosis or Marfan syndrome. If a definitive diagnosis cannot be made, the physician should

Prenatal Genetic Screen

Name _____ Patient# _____ Date _____

1. Will you be 35 years or older when the baby is due? Yes ___ No ___
2. Have you, the baby's father, or anyone in either of your families ever had any of the following disorders?
 Down syndrome (mongolism) Yes ___ No ___
 Other chromosomal abnormality Yes ___ No ___
 Neural tube defect, i.e., spina bifida (meningomyelocele or open spine), anencephaly Yes ___ No ___
 Hemophilia Yes ___ No ___
 Muscular dystrophy Yes ___ No ___
 Cystic fibrosis Yes ___ No ___
 If yes, indicate the relationship of the affected person to you or to the baby's father: _____
3. Do you or the baby's father have a birth defect? Yes ___ No ___
 If yes, who has the defect and what is it? _____
4. In any previous marriages, have you or the baby's father had a child born, dead or alive, with a birth defect not listed in question 2 above? Yes ___ No ___
5. Do you or the baby's father have any close relatives with mental retardation? Yes ___ No ___
 If yes, indicate the relationship of the affected person to you or to the baby's father: _____
 Indicate the cause, if known: _____
6. Do you, the baby's father, or a close relative in either of your families have a birth defect, any familial disorder, or a chromosomal abnormality not listed above? Yes ___ No ___
 If yes, indicate the condition and the relationship of the affected person to you or to the baby's father: _____
7. In any previous marriage, have you or the baby's father had a stillborn child or three or more first-trimester spontaneous pregnancy losses? Yes ___ No ___
 Have either of you had a chromosomal study? Yes ___ No ___
8. If you or the baby's father is of Jewish ancestry, have either of you been screened for Tay-Sachs disease, Canavan disease, or cystic fibrosis? Yes ___ No ___
 If yes, indicate who and the results: _____
9. If you or the baby's father is black, have either of you been screened for sickle cell trait? Yes ___ No ___
 If yes, indicate who and the results: _____
10. If you or the baby's father is of Italian, Greek, or Mediterranean background, have either of you been tested for β -thalassemia? Yes ___ No ___
 If yes, indicate who and the results: _____
11. If you or the baby's father is of Philippine or Southeast Asian ancestry, have either of you been tested for α -thalassemia? Yes ___ No ___
 If yes, indicate who and the results: _____
12. Irrespective of ethnic group, have you or the baby's father been screened for cystic fibrosis? Yes ___ No ___
13. Excluding iron and vitamins, have you taken any medications or recreational drugs since becoming pregnant or since your last menstrual period? (include nonprescription drugs)
 If yes, give name of medication and time taken during pregnancy: _____
14. Have you currently been taking folic acid supplements? Yes ___ No ___

Figure 6-3. Questionnaire for identifying couples having increased risk for offspring with genetic disorders. (Modified from a form recommended by the American College of Obstetricians and Gynecologists: Antenatal Diagnosis of Genetic Disorders. Technical Bulletin No. 108. Washington, DC, ACOG, 1987.)

not hesitate to say so. Proper counseling requires proper diagnosis.

Nondirective Counseling

In genetic counseling, one should provide accurate genetic information yet ideally dictate no particular course of action. Of course, completely nondirective counseling is probably unrealistic. For example, a counselor's unwitting facial expressions may expose his or her unstated

opinions. Merely offering antenatal diagnostic services implies approval. Despite the difficulties of remaining truly objective, one should attempt to provide information and then support the couple's decision.

Psychological Defenses

If not appreciated, psychological defenses can impede the entire counseling process. Anxiety is low in couples counseled for advanced maternal age or for an abnormal-

ity in a distant relative. So long as anxiety remains low, comprehension of information is usually not impeded. However, couples who have experienced a stillborn infant, an anomalous child, or multiple repetitive abortions are more anxious. Their ability to retain information may be hindered.

Couples experiencing abnormal pregnancy outcomes manifest the same grief reactions that occur after the death of a loved one: denial, anger, guilt, bargaining, and resolution. One should pay deference to this sequence by not attempting definitive counseling immediately after the birth of an abnormal neonate. The obstetrician should avoid discussing specific recurrence risks for fear of adding to the immediate burden. By 4 to 6 weeks, the couple has begun to cope and is more receptive to counseling.

An additional psychological consideration is that of parental guilt. One naturally searches for exogenous factors that might have caused an abnormal outcome. In the process of such a search, guilt may arise. Conversely, a tendency to blame the spouse may be seen. Usually, guilt or blame is not justified, but occasionally the “blame” is realistic (e.g., in autosomal dominant traits). Fortunately, most couples can be assured that nothing could have prevented a given abnormality in their offspring.

Appreciating the psychological defenses described earlier helps one to understand the failure of ostensibly intelligent and well-counseled couples to comprehend genetic information.

GENETIC SCREENING

Genetic screening implies routine monitoring for the presence or absence of a given condition in apparently normal individuals. Screening is now offered routinely for all individuals of certain ethnic groups to identify those individuals heterozygous for a given autosomal recessive disorder (Table 6-4). Ultrasound screening for fetal abnormalities during pregnancy is reviewed in Chapter 9.

Screening Neonates

One could theoretically screen neonates for many other genetic disorders. Screening is actually recommended for relatively few disorders because prerequisites essential for initiating screening programs are not usually met. Widespread testing is ordinarily performed only if an abnormal finding would alter clinical management. In the United States, neonates have long been mandated in all states to be screened for phenylketonuria and hypothyroidism, which are amenable either to dietary or hormonal treatment, respectively. The number of disorders for which neonates are screened varies state by state. In the United States, most commonly mandated are selected inborn errors of metabolism that include galactosemia (diet treatment), sickle cell anemia (early administration of antibiotics), and 21-hydroxylase adrenal hyperplasia (cortisol administration).

Table 6-4. Genetic Screening in Various Ethnic Groups

ETHNIC GROUP	DISORDER	SCREENING TEST
All ethnic groups	Cystic fibrosis	DNA analysis of selected panel of 23 CFTR mutations (alleles present in 0.1 percent of the general U.S. population)
Black	Sickle cell anemia	Mean corpuscular volume <80 percent, followed by hemoglobin electrophoresis
Ashkenazi Jewish	Tay-Sachs disease	Decreased serum hexosaminidase-A or DNA analysis for selected alleles
Cajuns	Canavan disease	DNA analysis for selected alleles
	Familial dysautonomia	DNA analysis for selected alleles
French-Canadians Mediterranean people (Italians, Greek)	Tay-Sachs disease	DNA analysis for selected alleles
	β -Thalassemia	DNA analysis for selected alleles
Southeast Asians (Filipinos, Chinese, African, Vietnamese, Laotian, Cambodian, Filipino)	α -Thalassemia	Mean corpuscular volume (MCV) <80 percent, followed by hemoglobin electrophoresis if iron deficiency excluded
		MCV < 80 percent, followed by hemoglobin electrophoresis if iron deficiency excluded

CFTR, cystic fibrosis transmembrane conductance regulator.

Other disorders are mandated less commonly, usually using mass spectrometry. The March of Dimes recommends screening for 30 disorders as well as for deafness. This organization's web site provides state-by-state information (www.marchofdimes.com/professionals/580.asp). Disorders explicitly enumerated by the ACOG and the U.S. Health Resources and Services Administration (HRSA) include not only phenylketonuria, hypothyroidism, galactosemia, sickle cell anemia, and adrenal hyperplasia (see earlier) but also biotinidase deficiency, congenital toxoplasmosis, CF (postnatal), homocystinuria, maple syrup urine disease, and medium chain acyl-CoA dehydrogenase deficiency. The ACOG and HRSA note that although possible, to screen for disorders of fatty acid oxidation, organic acids, and urea cycle, there is less experience.

Considerable recent attention is being given to screening for deafness. More than 70 genes related to hearing are already known. Mutations in gap junction B (*GJB2*), the gene that codes connexin 26, and the neighboring gene *GJB6* (connexin 30) account for 50 percent of deafness in the newborn.¹³ The heterozygote frequency for *GJB2* alone is 3 percent in North American whites.¹⁴

An accepted principle is that screening is not attempted for neonates with untreatable disorders. Thus, neonatal screening is not recommended for chromosomal abnormalities, Tay-Sachs disease, and Duchenne muscular dystrophy.

Screening Adults

The ACOG recommends population screening for selected disorders, seeking asymptomatic heterozygotes in families in which no affected individual has been born.¹⁵⁻¹⁹ These autosomal recessive disorders are amenable to prenatal diagnosis and are listed in Table 6-4.

TAY SACHS DISEASE

The prototype for screening is Tay-Sachs disease, an autosomal recessive disorder for which Ashkenazi Jewish individuals are at increased risk. The ACOG cites a heterozygote frequency of 1 in 30.¹⁵ In the United States, Jewish individuals may be uncertain whether they are of Ashkenazic or Sephardic descent (90 percent are Ashkenazi); thus, obstetricians should screen all Jewish couples, as well as couples in which only one partner is Jewish. Other conditions for which genetic screening is recommended in Jewish couples are Canavan disease,¹⁸ familial dysautonomia,¹⁹ and CF (see later). In all of these disorders, the carrier frequency is about 1 in 30. Ashkenazi Jewish individuals may also elect to be screened for other disorders: Gaucher disease, Nieman-Pick disease, Bloom syndrome, Fanconi anemia C, and mucopolidosis.¹⁹ Carrier frequencies for these disorders vary from 1 in 15 (Gaucher disease) to 1 in 127 (mucopolidosis IV). Heterozygote detection rates for each condition are 95 to 99 percent, the efficiency reflecting only a few mutations being responsible for each disorder. In aggregate, the likelihood of an Ashkenazi Jewish individual being heterozygous for one of the autosomal recessive disorders listed in this section is 1 in 4.¹⁹

Screening usually involves molecular testing for common selected mutations. In Tay Sachs disease, molecular testing in Ashkenazi Jews detects 94 percent of heterozygotes, whereas more laborious biochemical analysis (based on ratio of hexosaminidase A to total hexosaminidase – A plus B) detects 98 percent.¹⁵ If only one partner is Ashkenazi, the ACOG^{15,19} suggests screening that individual first. In low-risk populations (e.g., non-Ashkenazi Europeans), carrier frequency is only 1 in 300.¹⁵ Because molecular heterogeneity is so prevalent, biochemical testing is necessary in testing individuals who are not Ashkenazi Jews.

THALASSEMIAS

In Italians and Greeks, screening for β -thalassemia is indicated.¹⁶ This might rely initially on mean corpuscular volume (MCV), which will also screen for α -thalassemia in Southeast Asians, Filipinos, and Africans.¹⁶ MCV of greater than 80 percent excludes heterozygosity for α - or β -thalassemia. Values less than 80 percent are more likely to reflect iron deficiency anemia than thalassemia heterozygosity; thus, tests to exclude the former are indicated. If iron deficiency is not found, hemoglobin electrophoresis showing elevated hemoglobin A2 and hemoglobin F will confirm β -thalassemia. DNA-based testing is necessary to detect α -globin deletions, which cause α -thalassemia.¹⁶

ACOG has recently recommended that detection of sickle cell trait (heterozygosity) be determined using the same regimen as that for β -thalassemia – MCV <80% followed by hemoglobin electrophoresis if iron deficiency is excluded. Solubility tests previously used to detect sickle cell trait (SA) are now considered less sensitive, and do not detect other abnormal hemoglobins (e.g., hemoglobin C, β -thalassemia).^{19a}

Screening for Cystic Fibrosis

Since 2001, screening for CF has been recommended by the ACOG and American College of Medical Genetics (ACMG),^{20,21} with guidelines modified by ACOG in late 2005.²² Severely affected individuals show pulmonary and pancreatic disease. Mean life expectancy is only 30 years and has increased only marginally over the last decades.²³ In the United States a significant portion of lung transplants and heart lung transplants are for CF. The disorder usually is manifested early in childhood, 10 to 20 percent being detected at birth because of meconium ileus. Increasing accumulation of viscous secretions progressively leads to chronic respiratory obstruction. Malnutrition and poor postnatal growth arise secondary to blockage of pancreatic ducts, producing insufficient pancreatic enzymes that interfere with intestinal absorption. Almost all men with CF have azoospermia, the anatomic result of congenital bilateral absence of the vas deferens (CBAVD). Sometimes CBAVD is the only manifestation of CF. In these cases, the mutant alleles are less deleterious than those causing severe (primary and pancreatic CF). Individuals CF who do not show pancreatic insufficiency are said to have mild CF and have a median survival of 56 years.²³ Definitive diagnosis is made by the chloride sweat test, although molecular confirmation is increasingly used. Once a mutation (see later) is recognized in a given family, molecular studies are indicated to detect other heterozygotes and affected relatives.

The CF gene is relatively large (27 exons), and its gene product is a chloride channel. In whites of non-Ashkenazi European descent, about 75 percent of CF mutations are caused by the deletion of three amino acids in codon 508 ($\Delta F508$), resulting in loss of a phenylalanine residue.²⁴ About 50 percent of couples at risk for CF offspring can be identified by screening solely for this mutation, offering unequivocal prenatal

diagnosis. Detecting the remaining couples at risk for CF is more difficult. Screening only for $\Delta F508$ would not infrequently uncover couples in which one parent has the $\Delta F508$ mutation but the other does not. If one parent has $\Delta F508$ but the other does not, the actual risk of that couple having an affected child is low. However, the CF gene product (protein) cannot be assayed per se; thus, prenatal genetic diagnosis could not exclude a fetus who inherited the $\Delta F508$ from the known heterozygous parent and who inherited a deleterious, severe, but unrecognized allele from the other parent. Only molecular methods would distinguish unaffected from affected fetuses. One could exclude fetuses who inherited $\Delta F508$ from their one heterozygous parent of known genotype, but half of the excluded fetuses would be clinically normal (i.e., only heterozygous for a mutant CF allele). Distinguishing compound heterozygosity (affected) from heterozygosity with its only one mutant allele is not possible unless both parental mutations are known.

The obvious solution is to detect all other mutations within the CF locus. In Ashkenazi Jewish individuals, one other mutation (W1282X) quickly proved common,²⁵ but individual mutations have otherwise been individually rare in all ethnic groups. Figure 6-4 is an early study from the Cystic Fibrosis Foundation showing an increasing detection rate in northern European white and Ashkenazi Jewish populations as increasing numbers of CF-causing alleles are sought.²⁶ Based on these cases, sensitivity approached but did not exceed 80 or 97 percent in these two ethnic groups, respectively. Differing sensitivities exist using the now-accepted panel of mutations recommended for testing by the ACOG and ACMG in 2001^{20,21} and updated in 2005.²² This is discussed later. Irrespective, not all at-risk pregnancies are identified, a principle applicable in any screening test. Unlike case detection approaches (e.g., Pap smears, invasive testing for aneuploidy), one never expects to detect 100 percent of cases in a screening program. This might be precluded for technical, financial or diagnostic reasons.

GUIDELINES FOR CYSTIC FIBROSIS SCREENING

In 2001, recommendations for CF screening were made jointly by the ACOG, the ACMG, and the National Institutes of Health Genome Center.^{20,21} It was recommended that a panethnic mutation panel be used that includes all mutant CF alleles having a frequency of 0.1 percent in the general U.S. population.²¹ This was modified in 2004 to encompass 23 mutations (Table 6-5).²⁷ Screen-

ing for other alleles is optional. Vendors offer expanded panels of up to nearly 100 mutations, but this is still only a fraction of the 1,300 reported CF mutations. Even if the entire gene is sequenced, not all CF mutations will be identified. Those not yet identified presumably act in promoter regions or perturb post-translational modification.

The 2001 guidelines stated that one should offer CF heterozygote screening to non-Jewish whites and Ashkenazi Jews, both of which were originally estimated to have carrier frequencies of 1 in 29.^{20,21,28} In the most recent tabulation, the frequency was estimated to be 1 in 24 and 1 in 25, respectively.²² Based on this, the overall heterozygote detection rates in whites and Ashkenazi Jews can now be stated to be 88 and 94 percent, respectively.²² In other ethnic groups (Asian-Americans, Hispanics, African-Americans), the carrier frequency is lower (Table 6-6). In these ethnic groups, detection rates are also lower (Table 6-7).

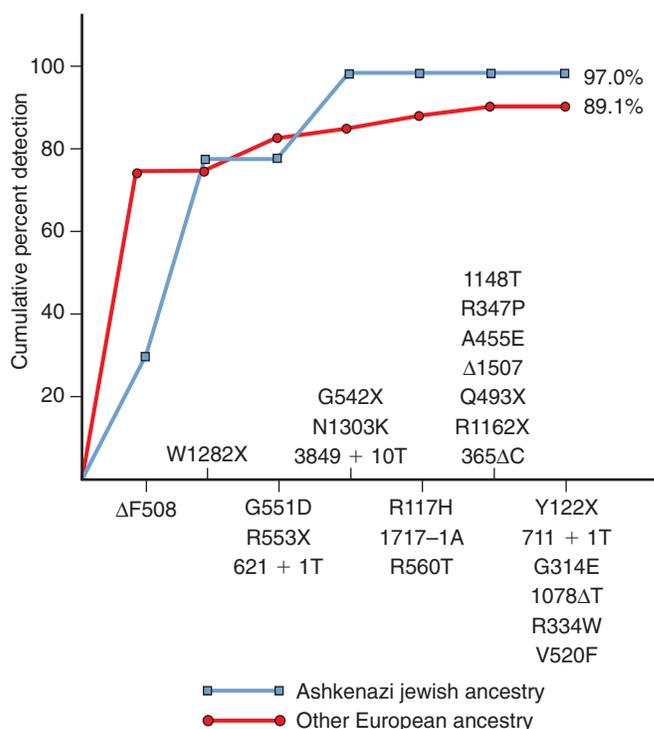


Figure 6-4. Increasing detection rate in northern European white and Ashkenazi Jewish populations as increasing numbers of CF-causing alleles are sought. (From Cystic Fibrosis Foundation Annual Report. New York, 1996.)

Table 6-5. Recommended Panel of 23 Mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Gene That Should Be Sought in Carrier Detection Programs^{33*}

$\Delta F508$	$\Delta I507$	G542X	G551D	W1282Z	N1303K
R533X	621 + 1G > T	R117H	1717 - 1G > A	A455E	R560T
R1162X	G85E	R334W	R347P	711 + 1G > T	1898 + 1G > A
2184delA	3120 + 1G > A	3849 + 10kbC > T	2789 + 5G > A	3659delC	

*The panel is applicable in all ethnic groups. If R117H is detected, status of the 5T-7T-9T polymorphism should be determined reflexly. After originally consisting of 25 mutations,²¹ two mutations were removed.²⁷ 1078delT was removed because of its rarity, whereas I148T was removed because the causative gene was actually a second mutation (3199del6) in linkage disequilibrium. However, this mutation (3199del6) is too rare to justify screening.

Table 6-6. Detecting Cystic Fibrosis (CF) Heterozygotes (23 Mutation Panel)²⁷

ETHNIC GROUP	HETEROZYGOTE CARRIER FREQUENCY	PERCENT OF HETEROZYGOTES DETECTABLE	LIKELIHOOD OF BEING HETEROZYGOUS DESPITE NEGATIVE SCREEN
Ashkenazi Jewish	1/24	94%	1/400
European non-Hispanic White	1/25	88%	1/208
Hispanic-American	1/46	72%	1/164
Black	1/65	65%	1/186
Asian	1/94	49%	1/184

Data of ACOG Committee Opinion 325 (2005).²² The current panel encompasses 23 mutations,²⁷ rather than the original 25.²¹

Table 6-7. Likelihood of Affected Fetus after Concurrent versus Sequential Screening for Cystic Fibrosis

	NON-HISPANIC EUROPEAN WHITES	ASHKENAZI JEWISH
No screening	1/2,500	1/2,304
Both partners negative (concurrent)	1/173,056	1/640,000
One partner negative, one untested (sequential)	1/20,800	1/38,400
One partner positive, one negative (concurrent)	1/832	1/1,600
One partner positive, other untested	1/100	1/96
Both partners positive	1/4	1/4

These calculations are based on the frequencies shown in Table 6-6.

Worthy of special comment is allele R117H. This allele is not uncommonly associated with CBAVD, but it is not causative for the classic (severe) CF phenotype as characterized by pulmonary, hepatic, and pancreatic complications. Recall that men with CBAVD usually have two dysfunctional CF alleles.²⁹ However, in CBAVD only one, *not both* alleles, could be $\Delta F508$ or consist of a CF allele conferring severe phenotype (pancreatic and pulmonary disease). If both alleles were $\Delta F508$ or “severe,” the phenotype would not be CBAVD but classic CF. If the other allele were R117H, a compound heterozygous male would have CBAVD ($\Delta F508/R117H$). If his spouse were heterozygous for $\Delta F508$, the likelihood would be 25 percent that any given fetus will have severe CF ($\Delta F508/\Delta F508$).

In certain circumstances, however, R117H/ $\Delta F508$ compound heterozygotes show severe CF. This arises on the basis of concurrent perturbations involving a polymorphism (5T) in intron 8 of the CF gene.²⁹ If at that portion of the CF gene there exist 5 thymines (5T), or to a lesser extent seven thymines (7T), splice-junction perturbations occur, deleting exon 8 and, hence, producing a truncated partially dysfunctional transmembrane conductance regulator (CFTR) gene product. With 5T, the CF protein (gene product) is 10 percent of normal. This is more than with $\Delta F508$ and W1282X, in which virtually no CFTR gene product is produced. With 7T, the gene product

is 50 percent of normal, and with 9T, it is 100 percent normal. Despite expressing only 10 percent gene product, however, this is enough for a 5T allele not to confer severe CF, that is, pulmonary and pancreatic disease. However, if 5T exists on the same chromosome (i.e., *cis*) as a second similarly mild mutation (specifically R117H), the two alleles in aggregate (on the same chromosome) confer the negligible low levels of CFTR as conferred by a single severe CF mutant allele like $\Delta F508$. If the CF gene (allele) on the other chromosome has a severe CF mutation, the fetus can show severe CF. To clarify:

- If 5T exists on the same chromosome as R117H and the other chromosome has a severe mutation ($\Delta F508$), severe CF will occur.
- If 7T exists on the same chromosome (*cis*) as R117H and the other chromosome has a severe mutation, the fetus is at risk only for mild CF because 7T/R117H still produces sufficient CF gene product. CBAVD can result but not severe CF (pulmonary and pancreatic disease).
- If both chromosomes show 5T (homozygosity) and neither carries another CF mutation, CBAVD may occur but not severe CF.

Given the above-mentioned information, ACOG and ACMG guidelines recommend that laboratories automatically (“reflex”) test for 5T whenever R117H is detected.^{20,21,27} If R117H is not detected, 5T/ 7T/ 9T status will not be determined. If a physician wishes to know the status of 5T polymorphisms, for example, in excluding CBAVD as a cause for male infertility, a specific request must thus be made for 5T/ 7T/ 9T testing.

IMPLEMENTING CYSTIC FIBROSIS SCREENING

How does a practitioner initiate CF screening and comply with guidelines? A few suggestions may be helpful in the office setting.

Recall that if a couple has already had a child with CF, or if there exists an affected relative, genetic screening as will be described above is *not* germane. Rather, case detection strategies then become appropriate. The index case, or the couple if the proband is unavailable, should be screened not just for the panel of 23 mutations alluded to earlier, but if uninformative, a larger panel of CF mutations. If the mutation is still not evident, family

studies to identify polymorphic loci informative for linkage analysis should be considered if prenatal genetic diagnosis is planned. Sequencing the entire gene may be desired. Sequencing might also be appropriate in evaluating a man with CBAVD if his spouse is heterozygous for a severe CF allele (e.g., $\Delta F508$) and if the molecular basis is not evident.²²

CHOOSING A PANEL

Fulfilling ACOG/ACMG guidelines for the 23 mutations is possible through several vendors. Costs are typically \$150 to \$300. Panels screening for more than the 23 mutations are not necessary in the presence of a negative family history; relatively few additional heterozygotes are detected as more alleles are sought. If an extended panel is chosen, it may be prudent to screen every patient in one's practice similarly, or make a special note to justify individual alteration in practice. Analogous reasoning applies to ethnic-specific panels.

Worth emphasizing is that the above-mentioned advice is not applicable when a family member is known to have severe CF. Extended panels or even sequencing should then be undertaken in order to elucidate the molecular basis.

SCREENING CONCURRENTLY OR SEQUENTIALLY

A key decision is whether to screen both the mother and father together (concurrent) or to screen only the mother (sequential); if only the mother is screened, the father would be studied only if the mother were a carrier. Either approach is acceptable. Screening both partners obviously produces the highest detection rate, although not by much (Table 6-7). The downside is that one partner will be a carrier significantly more often (two-fold), thus generating more anxiety and requiring follow-up more often.

"OFFERING" CYSTIC FIBROSIS SCREENING

The original (2001) guidelines by the ACOG and ACMG stated that CF screening should be "offered" only to whites of European or Ashkenazi Jewish ancestry.^{20,21} It thus seemed reasonable to screen in a fashion analogous to that for Tay-Sachs disease, sickle cell anemia, β - or α -thalassemia. Initiation of a dialogue with the patient is required by the physician or a member of his or her health provider team. One should state that genetic screening is not obligatory. Patient information brochures, such as the ACOG/ACMG publication *Cystic Fibrosis Carrier Testing—The Decision is Yours*,³⁰ review inheritance of CF, variability of CF symptoms, and likelihood of detecting carrier status. This brochure explicitly states that not all CF mutations are detectable, and hence, not all affected individuals can be detected. That is, false-negative cases are unavoidable. The legal significance of this statement cannot be overemphasized.

In couples of black, Hispanic, and Asian origin, it was originally stated that CF screening should be "made available."^{20,21,28} There were no specific recommendations for distinguishing between "offer" and "made available." If applying this, perhaps a brief informative statement about CF could be followed by informing the patient

that CF screening exists. Information gained through brochures or other sources could help the undecided patient decide if she wishes to pursue.

More recently, it has become obvious that it was often unwieldy to assign a single ethnicity to a given patient.^{31,32} Moreover, ACOG has estimated that two thirds of obstetricians were offering CF screening to all pregnant patients. Thus, it is now considered reasonable to offer CF screening to all pregnant women.

DOCUMENTING COMPLIANCE

Prudent for litigious protection is adherence to a consistent plan verifying that information on screening was conveyed. This might consist of written notation on the chart. If so, retention of the written informed consent stating the patient's choice is essential. A sample consent form exists in the ACOG/ACMG patient information brochure.³³ However, retaining such a form on every patient might be burdensome, especially in offices using an electronic medical record.

Follow-Up of Cystic Fibrosis Test Results

The following scenarios could arise:

- If CF screening tests on both partners are negative, no further evaluation is required. Recall, however, that detection of 100 percent of carriers is never possible in population screening. Table 6-7 shows frequency of affected fetuses if screening is negative.
- If one partner has a CF mutation, but the other screens negative, no further evaluation is needed. The residual risk of still having a CF fetus is low but finite (Table 6-7).
- If one partner is a CF carrier and the other cannot be tested, the couple has a low but no longer inconsequential risk. In Europeans of non-Ashkenazi white origin, the residual risk is 100 (1×1 in 25×1 in 4). If Jewish, the risk is 1 in 96. Chorionic villi or amniotic fluid analysis can exclude these fetuses with the maternal mutation, assuring that they will be clinically normal.
- If both couples are heterozygous for the same or for two different deleterious alleles (compound heterozygotes), referral to a geneticist is appropriate. The risk for an unaffected fetus is 25 percent, and options for a definitive diagnosis should be presented. Useful in this regard is the ACOG/ACMG booklet, *Cystic Fibrosis Testing—What Happens if Both my Partner and I are Carriers*.³³

Alerting Relatives

Suppose a patient or her spouse has a severe CF-causing mutation, like $\Delta F508$. Relatives of your patient could well have inherited the same mutation from a common ancestor. The likelihood is 50 percent that any given sib of your patient or her partner will have the same mutation. As caring physicians, we surely wish to alert at-risk individuals; however, we have no authority to contact a relative directly. The solution is using a sample

letter, mailed not by the physician but by the patient or her spouse. This letter would inform relatives of the consequence of a CF mutation having been detected. A template for such a letter exists in the ACOG/ACMG booklet *Preconception and Prenatal Carrier Screening for Cystic Fibrosis*.³⁰

KEY POINTS

- The frequency of major birth defects is 2 to 3 percent, based on the definition of a defect causing death, a severe dysfunction, or a structural malformation requiring surgery.
- Major etiologic categories include chromosomal abnormalities (1 in 160 live births), single-gene or Mendelian disorders, polygenic/multifactorial disorders, and disorders caused by exogenous factors (teratogens).
- The frequency of autosomal trisomies is higher in midtrimester (30 percent for Down syndrome) than at term, and many trisomies are so lethal that they are found only in abortuses.
- Single-gene disorders in aggregate result in major defects in 1 percent of neonates, and additional disorders are manifested later in life. However, individual disorders are uncommon. CF occurs in 1 per 3,600 whites of northern European or Ashkenazi Jewish origin.
- Principles of genetic counseling include adequate communication, appreciation of psychological defenses, and adherence to nondirective counseling.
- Genetic screening to detect heterozygotes in the nonpregnant and, if not already evaluated, in the pregnant population is appropriate for the following autosomal recessive disorders: Tay-Sachs disease, Canavan disease, familial dysautonomia in Jewish populations; Tay-Sachs disease in Cajun and French-Canadian populations; CF in all populations; α -thalassemia in Asians; β -thalassemia in Mediterranean populations (Greek and Italians); and sickle cell disease in blacks.
- Heterozygosity for β -thalassemia and α -thalassemia can be inexpensively detected on the basis of MCV less than 80 percent followed by hemoglobin electrophoresis, once iron deficiency is excluded.
- CF is found in all ethnic groups, but the heterozygote frequency is higher in non-Hispanic whites of northern European (1 in 25) or Ashkenazi Jewish origin (1 in 24) than in other ethnic groups (black 1/65, Hispanic 1/46, Asian 1/94). The ACOG and the ACMG originally recommended that CF screening be offered to whites and “made available” to other groups. In 2005, the ACOG acknowledged the difficulty in assigning a single ethnicity and stated that

it was reasonable to offer screening to all pregnant women.

- The CF gene is large (27 exons), and more than 1,300 disease-causing mutations have been recognized. Screening is obligatory only for a specified panel of 23 mutations.
- In northern European white and Ashkenazi Jewish individuals, the heterozygote detection rate using the specified panel is 84 and 94 percent, respectively. In other ethnic groups detection rates are lower (65 percent blacks, 72 percent Hispanics, 49 percent Asian Americans).
- A couple can either both undergo CF screening simultaneously or the second partner can be screened only if the first proves to be a heterozygote. The former generates the highest detection rate, but the latter method is also acceptable.
- If the 5T polymorphism exists on the same chromosome (*cis*) on which a mild CF mutation exists (e.g., R117H), the effect is the same as if there were a single severe mutation (e.g., $\Delta F508$). Thus, if the other chromosome has a severe mutation ($\Delta F508$), severe CF will result. If both chromosomes show a 5T polymorphism or if 5T exists *trans* to a chromosome with the $\Delta F508$ mutation, the result is CBAVD.

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