

Genetic Counseling: Preconception, Prenatal, and Perinatal

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The time is fast approaching when virtually all the culprit genes and their mutations for >7,000 rare monogenic disorders¹ will be known. Thus far, causal single genes and their mutations have been determined for 5,673 genetic disorders,² enabling preimplantation genetic testing or prenatal genetic diagnosis. These advances using chromosomal microarrays, whole-exome sequencing and even whole-genome sequencing together with fetal imaging and noninvasive prenatal testing, expand the era in which all couples have the option of avoiding or preventing having children with irreversible, irremediable, crippling, or lethal monogenic disorders. Primary care physicians, and those in all medical specialties, will need to inform their patients of this key option. This imperative is already partly in current practice. Missing is the requirement of physicians to request and obtain the precise name of the genetic disorder in question or an existing DNA report on a family member, for prospective parents to benefit from available options.

Increasingly, couples are seeking prenatal diagnosis for adult-onset genetic disorders in which mutations have been determined. Huntington disease prenatal diagnosis has been in the vanguard for many years, but now there are requests for adult-onset dominantly transmissible disorders including breast and other malignancies,

frontotemporal dementia, neurodegenerative disorders, and cardiomyopathies. The remarkable advances in genetics provide a cogent need to confer and refer. Physicians should not invite legal purview for a failure to inform, offer, refer, or provide genetic testing.

In context, couples at risk for having progeny with abnormalities expect to be informed about their risks and options, optimally during preconception counseling. Their concerns are serious, given the significant contribution of genetic disorders to morbidity and mortality in children and adults.

The burden of genetic disorders and congenital malformations

A conservative estimate for the world population prevalence of rare diseases (71.9–80 percent considered as genetic) is 3.5–5.9 percent, equating to 263–446 million individuals affected at any point in time.^{3,4} In India, which has a quarter of the world's neonatal deaths (an estimated 753,000 in 2013), about 9 percent were due to congenital anomalies.⁵ An estimated 7.9 million infants worldwide are born each year with a major congenital malformation according to a report in 2013.⁶ The likelihood of having a child with a congenital malformation varies from 2 to 10 percent⁷ due to multiple factors

that complicate efforts to accurately diagnose and determine the incidence or prevalence of congenital anomalies or genetic disorders. Box 1.1 lists 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. Of the >7,000 rare genetic disorders, about 1 in 12 to 1 in 16 individuals are affected,¹ aware or unaware. Given a world population of 7.6 billion, an estimated 473 million are likely to have a rare disease.¹

More than 4,331 genes with phenotype-causing mutations have been identified, including 6,739 phenotypes with a known molecular basis.² Severe intellectual disability is considered to be largely genetic in origin^{8,9} with a global prevalence between 0.5 and 1.0 percent.¹⁰ Despite continuing progress in the discovery of genes causally related to neurodevelopmental delay,¹¹ in less than 40 percent of cases is there a definitive recognition of cause. The European Organization for Rare Diseases maintained that about 30 percent of all patients with a rare disease died before the age of 5 years.¹² In the United States in 2013–2014,

Box 1.1 Factors that influence estimates of the incidence or prevalence in the newborn of a congenital malformation (CM) or genetic disorder

- Availability and use of expertise in prenatal diagnostic ultrasound and MRI
- Accuracy of diagnosis
- Age at diagnosis
- Case selection, bias, and ascertainment
- Congenital hypothyroidism
- Consanguinity
- Definitions of major and minor congenital anomalies
- Diagnostic DNA analysis
- Duration of follow-up
- Economic level in developed or developing world
- Environmental toxins
- Family history
- Frequency, inclusion, and exclusion of stillbirths, fetal deaths, and elective pregnancy termination
- Frequency of certain infectious diseases
- Frequency of *de novo* gene mutations
- History of recurrent spontaneous abortion
- *In vitro* fertilization
- Incidence and severity of prematurity
- Infertility
- Intracytoplasmic sperm injection
- Later manifestation or onset of disorder
- Maternal age
- Maternal alcohol abuse
- Maternal diabetes and gestational diabetes
- Maternal diet
- Maternal epilepsy, lupus erythematosus and other illnesses
- Maternal fever or use of hot tub in the first 6 weeks of pregnancy
- Maternal folic acid supplementation
- Maternal grandmother's age
- Maternal obesity
- Maternal serum screening for chromosome abnormalities
- Maternal smoking
- Maternal-specific susceptibility genes
- Maternal use of medication
- Mortality rates decreasing
- Multiple pregnancy rate
- Necropsy
- Noninvasive prenatal testing using cell-free fetal DNA for chromosomal abnormalities and monogenic disorders
- Parent with a congenital abnormality or genetic disorder
- Paternal age
- Previous affected child
- Previous maternal immunization/vaccination
- Season of the year
- Training and expertise in examination of newborns
- Use of chromosomal analysis
- Use of chromosomal microarray
- Use of whole-exome sequencing
- Use of whole-genome sequencing
- Use of death certificates
- Use of registry data

congenital malformations, deformations, and chromosomal abnormalities accounted for the most infant deaths – 4,746 (20.4 percent) out of 23,215 – in any category of causation.¹³

Incidence and prevalence of genetic disorders and congenital malformations

Estimates of aneuploidy in oocytes and sperm reach 25 percent and 3–4 percent, respectively.^{14, 15} Estimates, especially for oocytes, vary widely (see Chapter 2). The effect of maternal age, among other factors, is important. At 25 years, early thirties, and >40 years of age, the rate of aneuploidy approximates 5 percent, 10–25 percent, and 50 percent, respectively.^{15–19} Estimates of aneuploidy and structural chromosomal abnormalities in sperm vary from 7 to 14 percent.²⁰ Not surprisingly, then, about one in 13 conceptions results in a chromosomally abnormal conceptus,²¹ while about 50 percent of first-trimester spontaneous abortions are associated with chromosomal anomalies.²² One study of blastocysts revealed that 56.6 percent were aneuploid. Moreover, these blastocysts produced *in vitro* from women of advanced maternal age also revealed mosaicism in 69.2 percent.²³ Similar results have been reported by others.²⁴ Clinically significant chromosomal defects occur in 0.65 percent of all births; an additional 0.2 percent of babies are born with balanced structural chromosome rearrangements that have implications for reproduction later in life (see Chapters 11 and 13). Between 5.6 and 11.5 percent of stillbirths and neonatal deaths have chromosomal defects.²⁵

Congenital malformations with obvious structural defects are found in about 2 percent of all births.²⁶ This was the figure in Spain among 710,815 livebirths,²⁷ with 2.25 percent in Liberia,²⁸ 2.03 percent in India,²⁹ and 2.53 percent among newborn males in Norway.³⁰ The Mainz Birth Defects Registry in Germany in the 1990–1998 period reported a 6.9 percent frequency of major malformations among 30,940 livebirths, stillbirths, and abortions.³¹ Pooled data from 12 US population-based birth defects surveillance systems, which included 13.5 million livebirths (1999–2007), revealed that American Indians/Alaska natives had a ≥ 50 percent greater prevalence for seven congenital malformations (including anotia or microtia, cleft lip, trisomy 18, encephalocele, limb-reduction

defect).³² Factors that had an impact on the incidence/prevalence of congenital malformations are discussed later.

Over 25,500 entries for genetic disorders and traits have been catalogued.² 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).³³ Baseline birth prevalence of rare single-gene disorders for multiple countries are shown in Figure 1.1, which highlights the contribution of consanguinity-associated disorders.³⁴ Polygenic disorders occurred at a rate of 46.4 in 1,000 (Table 1.1). A key study of homozygosity in consanguineous patients with an autosomal recessive disease showed that, on average, 11 percent of their genomes were homozygous.³⁵ Each affected individual had 20 homozygous segments exceeding 3 cM.

At least 3–4 percent of all births are associated with a major congenital defect, intellectual disability, or a genetic disorder, a rate that doubles by 7–8 years of age, given later-appearing and/or later-diagnosed genetic disorders.^{36, 37} If all congenital defects are considered, Baird et al.³³ 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.³⁸ The bicuspid aortic valve is the most common congenital cardiac malformation and in the final analysis may cause higher mortality and morbidity rates than all other congenital cardiac defects.³⁹ About 27 percent suffer cardiovascular complications requiring surgery.^{40, 41} Mitral valve prolapse affects 2–3 percent of the general population, involving more than 176 million people worldwide.⁴² A Canadian study of 107,559 patients with congenital heart disease reported a prevalence of 8.21 per 1,000 livebirths, rising to an overall prevalence of 13.11 per 1,000 in adults.⁴³ The authors concluded that adults now account for some two-thirds of the prevalence of congenital heart disease. Categorical examples of factors associated with an increased risk of congenital heart disease or malformations in the fetus are shown in Box 1.1. A metropolitan Atlanta study (1998–2005) showed an overall

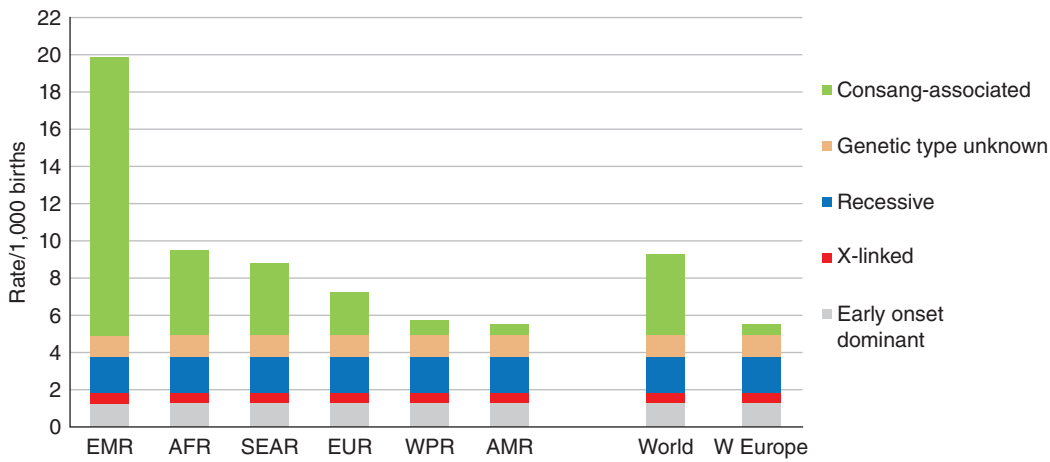


Figure 1.1 Total baseline birth prevalence of rare single-gene disorders by World Health Organization (WHO) region, highlighting the important contribution of consanguinity to monogenic disorders.
Source: Blencowe et al. 2018.³⁴ Reproduced with permission from Springer.

Table 1.1 The frequencies of genetic disorders in 1,169,873 births, 1952–1983³⁴.

Category	Rate per million livebirths	Total births (percent)
A		
Dominant	1,395.4	0.14
Recessive	1,665.3	0.17
X-linked	532.4	0.05
Chromosomal	1,845.4	0.18
Multifactorial	46,582.6	4.64
Genetic unknown	1,164.2	0.12
Total	53,175.3	5.32 ^a
B		
All congenital anomalies 740–759 ^b	52,808.2	5.28
Congenital anomalies with genetic etiology (included in section A)	26,584.2	2.66
C		
Disorders in section A plus those congenital anomalies not already included	79,399.3	7.94

^aSum is not exact owing to rounding.
^bInternational Classification of Disease numbers.
Source: Blencowe et al. 2018.³⁴ With permission from Elsevier.

prevalence of 81.4 per 10,000 for congenital heart disease among 398,140 livebirths,⁴⁴ similar to a Belgian study of 111,225 live and stillborn infants ≥26 weeks of gestation with an incidence of 0.83 percent, chromosome abnormalities excluded.⁴⁵ A EUROCAT registry study found an increasing prevalence of severe congenital heart defects (single ventricle, atrioventricular septal defects, and tetralogy of Fallot) possibly due to increasing

obesity and diabetes.⁴⁶ In a study of 8,760 patients with autism spectrum disorders and 26,280 controls, a statistically significant increase in the odds of concurrent congenital heart disease (odds ratio [OR] 1.32) was noted.⁴⁷ Atrial septal defects and ventricular septal defects were most common. 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 Kaplan⁴⁸ 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 newer genetic technologies, including chromosomal microarray, whole-exome sequencing, next-generation sequencing, and whole-genome sequencing, have helped unravel the causes of an increasing number of isolated or syndromic congenital heart defects.^{49,50} Identified genetic causes include monogenic disorders in 3–5 percent of cases, chromosomal abnormalities in 8–10 percent, and copy number variants in 3–25 percent of syndromic and 3–10 percent of isolated congenital heart defects.^{49,51} A next-generation sequencing study indicated that 8 percent and 2 percent of cases were due to *de novo* autosomal dominant and autosomal recessive pathogenic variants, respectively.⁵²

Pregestational diabetes in 775 of 31,007 women was statistically significantly associated with sacral agenesis (OR 80.2), holoprosencephaly (OR 13.1), limb reduction defects (OR 10.1), heterotaxy (12.3), and severe congenital heart defects (OR 10.5–14.9).⁵³

Maternal obesity is associated with an increased risk of congenital malformations.^{54–65} The greater the maternal body mass index (BMI), the higher the risk, especially for congenital heart defects,^{59,60,62,65} with significant odds ratios between 2.06 and 3.5. In a population-based case-control study, excluding women with pre-existing diabetes, Block et al.⁶⁶ 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). A Swedish study focused on 1,243,957 liveborn singletons and noted 3.5 percent with at least one major congenital abnormality.⁶⁴

These authors used maternal BMI to estimate risks by weight. The risk of having a child with a congenital malformation rose steadily with increasing BMI from 3.5 percent (overweight) to 4.7 percent (BMI ≥ 40). Our own^{67,68} and other studies⁶⁹ have implicated the prediabetic state or gestational diabetes as contributing to or causing the congenital anomalies in the offspring of obese women. In this context, preconception bariatric surgery seems not to reduce the risks of congenital anomalies.^{61,70–72} It appears that folic acid supplementation attenuates but does not eliminate the risk of spina bifida when associated with diabetes mellitus⁷³ or obesity⁷⁴ (see Chapter 10). In contrast, markedly underweight women reportedly have a 3.2-fold increased risk of having offspring with gastroschisis,⁷⁴ in all likelihood due to smoking and other acquired exposures.^{75,76} Indeed, a study of 173,687 malformed infants and 11.7 million unaffected controls, when focused on maternal smoking, yielded significant odds ratios up to 1.5 for a wide range of major congenital malformations in the offspring of smoking mothers.⁷⁷ 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.⁷⁸ A Californian population-based study (1995–2012) recorded a prevalence for gastroschisis of 2.7 cases per 10,000 livebirths.⁷⁵

The surveillance system of the National Network of Congenital Anomalies of Argentina reported a 2009–2016 study of 1,663,610 births with 702 born with limb reduction defects.⁷⁹ The prevalence was 4.22/10,000 births. In 15,094 stillbirths, the prevalence rose to 30.80/10,000. A Chinese study of 223 newborn deaths in a neonatal intensive care unit noted that 44 (19.7 percent) had a confirmed genetic disorder.⁸⁰ The National Perinatal Epidemiology Centre in Ireland in a study of fatal fetal anomalies recorded 2,638 perinatal deaths, 939 (36 percent) having a congenital anomaly, 43 percent of which were chromosomal.⁸¹ More than a single anomaly was noted in 36 percent (333 of 938) of their cases. These numbers led to a significant genetic disease burden and have accounted for 28–40 percent of hospital admissions in North America, Canada, and England.^{82–84} Notwithstanding their frequency, the causes of about 60 percent of congenital malformations remain obscure.^{85,86}

The effect of folic acid supplementation, via tablet or food fortification, on the prevalence of neural tube defects (NTDs), is now well known to reduce the frequency of NTDs by up to 70 percent^{87,88} (see Chapter 10). 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.⁸⁹

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.⁹⁰ In a prospective study of infants weighing 401–1,500 g between 1998 and 2007, a congenital malformation was noted in 4.8 percent of these very low birthweight infants. The mean gestational age overall was 28 weeks and the mean birthweight was 1,007 g.⁹¹ A surveillance study of births, stillbirths, and fetuses for malformations in a single center with 289,365 births over 41 years noted 7,020 (2.4 percent) with one or more congenital abnormalities.⁹² 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).⁹³ 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). A California Twin Registry study of 20,803 twin pairs found an overall prevalence of selected anomalies of 38 per 1,000 persons.⁹⁴

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.⁹⁵ 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). Ethnicity, too, has a bearing on the prevalence of

cardiovascular malformations. In a New York State study of 235,230 infants, some 2,303 were born with a cardiovascular malformation. The prevalence among non-Hispanic white (1.44 percent) was higher than in non-Hispanic black individuals (1.28 percent).⁹⁶ However, racial/ethnic disparities clearly exist for different types of congenital defects.⁹⁷

Congenital hypothyroidism is associated with at least a fourfold increased risk of congenital malformations, and represents yet another factor that may influence incidence/prevalence rates of congenital anomalies and neurodevelopment.^{98,99} A French study of 129 infants with congenital hypothyroidism noted that 15.5 percent had associated congenital anomalies.¹⁰⁰ Nine of the infants had congenital heart defects (6.9 percent).

Women with epilepsy on 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.¹⁰¹ A Cochrane Epilepsy Group Registry meta-analysis of 31 studies of pregnant women on anticonvulsants concluded with increased, but variable RR of congenital malformations of 2.01–5.69, the latter figure being for valproate.¹⁰²

There have been reports of an increased risk of congenital malformations following the use of assisted reproductive technology (ART) and negated by other studies.¹⁰³ A 2018 report using a Centers for Disease Control and Prevention (CDC) database of 11,862,780 livebirths (2011–2013) retrospectively analyzed the 71,050 pregnancies conceived by ART. Infants conceived by ART had an increased risk (77/10,000 vs. 25/10,000), an OR of 2.14.¹⁰³ The cause(s) of this increase – whether due to the ART or the patients' genetic predisposition – remains to be determined.

Lupo et al.¹⁰⁴ in a population-based registry study of over 10 million children in the United States assessed the association of cancer and congenital malformations. They reported that compared to children without congenital anomalies:

- children with chromosomal anomalies ($n = 539,567$) were 11.6 times more likely to be diagnosed with cancer and
- children with nonchromosomal congenital anomalies were 2.5 times more likely to have cancer before 18 years of age.

Congenital malformations and infant morbidity and mortality

The leading cause of infant death in the United States in 2014 was congenital malformations, deformations, and chromosomal abnormalities, accounting for 20.4 percent of 4,748 total infant deaths.¹³ Survival is clearly dependent on the severity or lethality of the congenital defect. The CDC assessed mortality rates for infants born with trisomy 13 and trisomy 18. 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 18.¹⁰⁵ An international registry study (2019) from 18 countries revealed prevalence rates of 0.55 and 1.07 per 10,000 births for trisomies 13 and 18, respectively. Death in the first week of life occurred in 45 percent and 42 percent for trisomy 13 and trisomy 18, respectively. Reported mortality rates were 87 percent and 88 percent at 1 year for each of these trisomies.¹⁰⁶ 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.¹⁰⁷ A Scottish study focusing on the survival of 6,153 infants with congenital anomalies up to the age of 5 years noted the following survival rates: chromosomal anomalies (48 percent), NTDs (72 percent), respiratory system anomalies (74 percent), congenital heart disease (75 percent), nervous system anomalies (77 percent) and Down syndrome (84 percent).¹⁰⁸ The survival rate among males with congenital defects was 84 percent, compared with 97 percent in those born unaffected.³⁰ Liu et al.¹⁰⁹ 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 Down syndrome, a more detailed discussion follows.

Down syndrome

The availability of prenatal diagnosis and maternal serum screening for chromosomal abnormalities

has also affected the birth frequency of Down syndrome. 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 Down syndrome.¹¹⁰ A later report from the Paris Registry of Congenital Anomalies (2001–2005) noted a “fairly stable prevalence of Down syndrome (7.1 per 10,000 livebirths) over time.”¹¹¹ A Scottish study aimed to assess the impact of prenatal diagnosis on the prevalence of Down syndrome from 1980 to 1996. Both births and pregnancy terminations were included. Pregnancy terminations for Down syndrome rose from 29 percent to about 60 percent.¹¹² In contrast, the prevalence of Down syndrome 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.¹¹³ In the United States, a prevalence rate of 8.27 per 10,000 was reported in 2013 with an estimated 250,700 individuals.^{114, 115} In Europe, the 2009–2012 prevalence rate was 10.2 per 100,000 livebirths.¹¹⁶ In Japan, the estimated prevalence rate approximates 22 per 10,000 births.¹¹⁷ Many more babies with Down syndrome are born to women under rather than over 35 years of age. There is some evidence that the risk of having Down syndrome offspring in very young mothers is increased,^{118–121} but not in twin pregnancies.¹²²

The special problems and associated defects in Down syndrome are well known, as is the increasing life expectancy. Studies from Japan,¹²³ Denmark,¹²⁴ England,¹²⁵ Australia,¹²⁶ and Canada¹²⁷ highlight the increased life expectancy with Down syndrome. Baird and Sadovnick¹²⁷ reported a large study of 1,610 individuals with Down syndrome identified in more than 1,500,000 consecutive livebirths in British Columbia from 1908 to 1981. They constructed survival curves and a life table for Down syndrome (Table 1.2) and for the general population.¹²⁸ Their estimates show that 44.4 percent and 13.6 percent of liveborn individuals with Down syndrome will survive to 60 and 68 years, respectively, compared with 86.4 percent and 78.4 percent of the general population. In another report,¹²⁹ the authors have analyzed the causes of death in Down syndrome, highlighting congenital defects and cardiovascular and respiratory illnesses as the most important. A UK population

Table 1.2 Life expectancy with Down syndrome, between 1908–1981, to age 68 years.

Age	Total	Survival at start of age interval (percent)
5	1,020	81.05
10	841	78.40
20	497	75.34
30	91	72.12
40	136	69.78
50	57	60.68
55	31	53.96
60	16	44.44
68	1	13.57

Source: Baird and Sadovnick 1989.¹²⁷ With permission from John Wiley and Sons.

prevalence study noted a median life expectancy of 58 years in 2011.¹³⁰

Additional studies of mortality rates in individuals with Down syndrome revealed that those up to about 35 years of age were little different from others with intellectual disability. Thereafter, however, mortality rates in Down syndrome doubled every 6.4 years, compared with 9.6 years for other intellectually disabled individuals.¹²⁹ Life tables constructed by these authors indicated a life expectancy of 55 years for a 1-year-old patient with Down syndrome and mild/moderate developmental delay and a life expectancy of 43 years for a 1-year-old patient with Down syndrome more profoundly affected.

A study from the CDC focused on the death certificates of 17,897 individuals with Down syndrome born between 1983 and 1997.¹³¹ These authors reported that the median age at death for those with Down syndrome increased from 25 years in 1983 to 49 years in 1997 (Figure 1.2).

A 2009 Australian study found an overall survival figure for Down syndrome of 90 percent to at least 5 years of age.¹³² The known comorbidities of Down syndrome^{116, 133–149} and earlier onset Alzheimer disease¹³³ cast a longer shadow. In individuals with Down syndrome over 40 years of age, increasing neuropsychological dysfunction and loss of adaptive skills have been noted.¹⁴⁹ Between 50 and 70 percent develop Alzheimer disease by 60 years of age,¹³⁹ and up to 84 percent of those with dementia develop seizures.¹³⁶ People

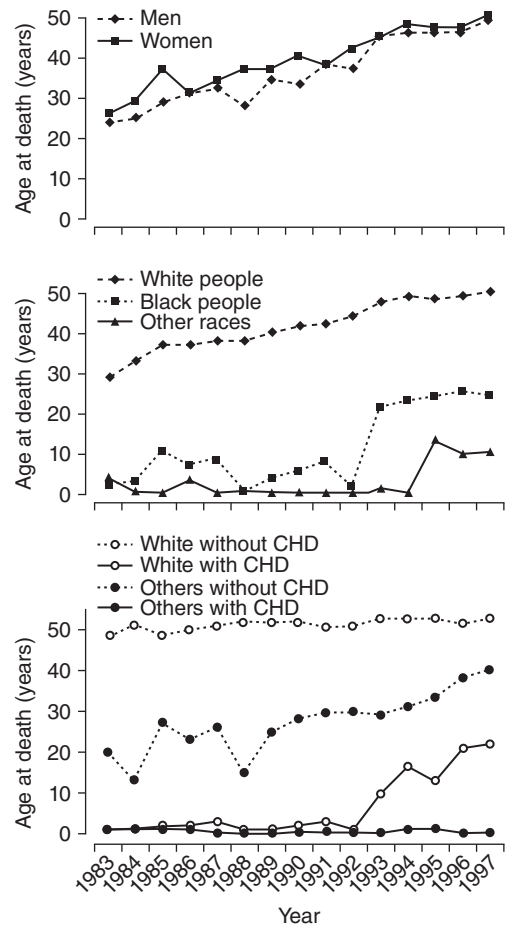


Figure 1.2 Median age at death of people with Down syndrome by sex (upper), by racial group (middle), and with or without congenital heart defects (CHD) by racial group (lower).

Source: Yang et al. 2002.¹³¹ Reproduced with permission of Elsevier.

with Down syndrome who are APOE ϵ 4 carriers and/or have multiple comorbid disorders are at an increased risk of both dementia and death.¹⁵⁰ A French study between 1979 and 1999 found a sixfold decreased risk of death from urological cancer in those with Down syndrome.¹⁴⁶ People with Down syndrome have an overall decreased incidence of solid tumors.¹⁵¹

Table 1.3 reflects the common associated defects and complications that occur in Down syndrome, some of which can be anticipated, monitored, prevented, and treated.^{132–165} A EUROCAT population-based register study between 2000 and 2010 in 12 countries analyzed 7,044 livebirths and

Table 1.3 Defects and complications associated with Down syndrome^{132–165}.

<i>Defect or complication</i>	<i>Prevalence (percent)</i>
Neurologic	
Intellectual disability	100
Hypotonia	100
Alzheimer disease and dementia	68–80
Sleep disorders	65
Autism	7–16
Hearing impairment	
Conductive	84
Sensorineural	2.7
Mixed	7.8
Epilepsy	5–13
Psychiatric disorders	11–30
ADHD	34
Moyamoya disease	3.8
Unexplained regression	Unknown
Heart	
Mitral valve prolapse	57
Congenital heart disease	44
Aortic valve regurgitation	17
Pulmonary hypertension	1.2–5.2
Respiratory	
Airway problems	>16
Immune system	
Susceptibility to infection	100
Juvenile rheumatoid-like arthritis	1.2
Gastrointestinal	
Congenital defects of the gastrointestinal tract	6
Celiac disease	5.4
Dysphagia	55
Endocrine/metabolic	
Overweight/obesity	23–70
Hypothyroidism	50
Diabetes mellitus	1.4–10.6
Hyperthyroidism	1–3
Ophthalmologic	
Eye disorders ^a	80
Cataract	17–29
Keratoconus	8–10
Hematologic/oncologic	
Leukemia	2–3 (>20-fold excess)
Testicular cancer	Standardized incidence ratio of 2.9
Transient myeloproliferative disorder	<10 (20–30% risk of AML)
Retroperitoneal teratoma	Increased
Anemia	2.6–10.5
Musculoskeletal	
Atlantoaxial instability	10–30
Osteoarthritis/low bone density	8–28
Atlantoaxial subluxation	1–2
Dental	
Tooth agenesis	54

Table 1.3 (Continued)

Defect or complication	Prevalence (percent)
Orthodontic problems	±all
Periodontal disease	±all
Dermatologic	
Hidradenitis suppurativa	2
Dermatologic disorders	1.9–39.2
Urinary tract	
Urinary tract anomalies	3.2

^aIncludes strabismus, nystagmus, refractive errors, glaucoma, and lens opacities.

fetal deaths with Down syndrome. That report¹⁵² noted that 43.6 percent of *births* with Down syndrome had congenital heart disease while 15 percent had another congenital malformation. The National Society of Genetic Counselors published valuable guidelines for communicating both prenatal and postnatal diagnoses of Down syndrome.¹⁶⁶

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 offspring with a genetic disorder is unacceptably high.¹⁶⁷ The goal is to reduce the risk of an adverse outcome to pregnancy and to secure the health of mother and fetus. Both the American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists recommend preconception counseling several times during a woman's reproductive lifespan.¹⁶⁸ 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 indications for prenatal diagnosis. When couples are at risk for having a child with a serious or fatal disorder, common experience shows that those with risks between 10 and 25 percent or even greater most often avoid pregnancies unless prenatal diagnosis is available. The advent of prenatal diagnosis has made it possible 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. Prenatal genetic studies are used in Western society virtually exclusively for the detection of defects generally characterized by irreparable intellectual disability and/or irremediable serious to fatal genetic disease. Sadly, at present, the ideal goal of prevention or treatment, rather than abortion after prenatal detection of a fetal defect, is achieved only rarely, with the exception of NTDs. Preimplantation genetic testing (see Chapter 2) does, however, provide an important option that avoids abortion.

All couples or individuals concerned about the risks of genetic disorders in their offspring should seek genetic counseling before conceiving. For the more common indications for prenatal diagnosis (such as recognized carriers, a positive result on a noninvasive prenatal test [see Chapters 6–8] or advanced maternal age), the well-informed obstetrician should be able to provide the necessary information.^{169, 170} However, a salutary observation in one study revealed that 43.3 percent of patients referred for amniocentesis exclusively for advanced maternal age had additional mostly unrecognized genetic risks, or significant concerns regarding one or more genetic or congenital disorders.¹⁷¹ Neither a questionnaire in the physician's office nor limited consultation time is likely to reveal many of these disorders. It is now vital that patients understand the importance of determining the *name* of a genetic disorder in the near or extended family. Since at least 6,739 monogenic phenotypes now have known genes,² prenatal diagnosis or preimplantation genetic testing is available for avoidance or prevention.

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 an increased risk of having children with genetic disease and to know which options pertain to their particular situation. The physician and genetic counselor have 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.

As Kessler¹⁷² 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 comorbidities, 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 explosive growth of information and data available in numerous gene databases stemming from gene discovery presents an overwhelming challenge for physicians and genetic counselors. Meeting the demand for excellence is best accomplished in tandem with a geneticist and team where possible. One important example concerns sudden unexpected death before 45 years of age.^{173–175} A wide range of arrhythmia syndromes and cardiomyopathies with many known genes allow "molecular autopsies."¹⁷⁶ Where DNA was not obtained from inevitable autopsies, recovery of analyzable material can be achieved from retained tissue blocks. Pathologists increasingly recognize the importance of retaining tissue (e.g. liver) for freezing without preservative.

Another challenge is the growing list of syndromes or conditions due to discovery of an expanding long list of culprit neurodevelopmental genes and their pathogenic variants,^{177, 178} a significant number being due to *de novo* variants.¹⁷⁹ The KBG syndrome serves as a typical example, with characteristic dysmorphic features, macrodontia of upper central incisors, skeletal abnormalities, short stature, and intellectual disability, confirmed by pathogenic variants in the *ANKRD11* gene.¹⁸⁰

Recognition that highly variable phenotypes exemplified by the 22q11 deletion syndrome and confounded by changes with increasing age can make the family history difficult to interpret.^{181–183}

Certain phenotypes may emerge as a consequence of environmental exposure or gene mutation, interpretation being further compounded by the presence or absence of ischemic encephalopathy at birth.^{184, 185} Microcephaly serves as an ideal example with multiple known single genes and viruses (such as Zika) (see Chapter 34).^{186–188} Online Mendelian Inheritance in Man (OMIM) has over 900 phenotype entries and almost 800 genes linked for microcephaly with variable expressivity.¹⁸⁸

A not infrequent challenge is to determine whether a brain injury (hypoxia) or a genetic disorder was the cause of intellectual disability, presenting as cerebral palsy.^{184, 185} Typical cerebral

palsy mimics include hereditary spastic paraplegia, dystonic disorders, and choreic movement disorders.¹⁸⁹ Multiple genes are known for the cerebral palsy mimics.^{189–191}

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.¹⁹² That study focused on a review of 12,093 “genetic events” involving potentially avoidable cases of Down syndrome, 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.¹⁹³ Other physicians, too, have been found lacking in the necessary knowledge and communication skills.^{184, 194–198} Given the importance of genetic considerations in all specialties, these problems can be anticipated to become increasingly problematic, more especially in family practice.^{198, 199}

After the prenatal diagnosis of a serious genetic disorder, the geneticist/genetic counselor 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 and other comorbidities in Down syndrome 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 availability, options, and risks of elective abortion (see Chapter 32), as well as the possibility of adoption.

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 and 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 prenatal diagnosis and to explain the techniques and requirements for obtaining amniotic fluid or chorionic villi, 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.²⁰⁰

Gordis et al.²⁰¹ 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.²⁰² 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 refer.^{184, 203–205}

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,²⁰⁶ as have others.^{207, 208}

Simple language, an adequate allocation of time, care, and sensitivity are keys to successful genetic counseling. Technical jargon, used with

distressing frequency,²⁰⁹ is avoided only through conscious effort. How an issue requiring a decision is framed²¹⁰ and the nature of the language used²¹¹ may influence the patient's choice.²¹² 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 patient's 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, negligible, sometimes, more often than not)²¹³ are choices a counselor must make. Clearly, the simpler the better and the more likely the information will be 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,²¹⁴ epididymal sperm aspiration,²¹⁵ and preimplantation genetic testing) (see Chapter 2).

Empathy

Empathy embodies the ability to not only understand the perspectives and emotions of others but to communicate that understanding.^{216, 217} 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 anxiety²¹⁸ 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 counselees.

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. Or worse still, after a long history of infertility, pregnancy is achieved only to find that the fetus has aneuploidy.

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.²¹⁹

Beyond the qualifications and factual knowledge of the counselor is the person who is key to successful and effective counseling. A compassionate 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 nonverbal characteristics. Staring at a computer screen while counseling conveys deep insensitivity and engenders no trust.

Essential prerequisites for the empathetic genetic counselor include the following:

- 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).
- Vocalize the realization of the psychologic pain and distress the person or couple has experienced (e.g. recurrent pregnancy loss followed by multiple *in vitro* fertilization (IVF) efforts and subsequently a successful pregnancy with a fetal defect).
- Acknowledge the coping that has been necessary, including the stress a couple might have to endure, despite sometimes conflicting feelings.
- 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).
- Fulfill the patient's need for hope and support and actively avoid any thoughtless comments¹⁷² that may erode these fundamental prerequisites. Well-intentioned statements are frequently perceived in a very different way.²⁰⁶

It is self-evident that empathy would engender greater patient satisfaction and may well be correlated with clinical competence.²²⁰

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.²²¹ 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 partner in such cases.²²²

Guilt is not only the preserve of the obligate carrier. Affected parents inevitably also experience guilt on transmitting their defective genes.^{223, 224} Frequently, parents express guilt about an occupation, medication, or illegal drug that they feel has caused or contributed to their child's problem. Kessler et al.²²⁴ 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. "Survivor guilt" is increasingly recognized, as the new DNA technologies are exploited. Experience with Huntington disease and adult polycystic kidney disease^{225–231} confirm not only survivor guilt with a new reality (a future) but also problems in relationships with close family members. Huggins et al.²²⁸ found that about 10 percent of individuals receiving low-risk results experienced psychologic difficulties.

Guiding principles for 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^{232–234} and surveyed international guidelines.²³⁵

Accurate diagnosis

Clinical geneticists, obstetricians, or pediatricians are frequently the specialists most confronted by patients seeking guidance because of genetic diseases in their families. Given the huge advances made in the recognition of thousands of culprit genes for genetic disorders seen in virtually all specialties, all physicians need to be aware of precise molecular diagnosis tests for monogenic disorders, and the opportunities for avoidance of recurrence. A previous child or a deceased sibling or parent may have had the disease in question. The genetic counseling process depends on an accurate diagnosis. Information about the exact previous diagnosis is important not only for the communication of subsequent risks but also for precise future options. Now whole-exome or genome sequencing and the

demonstrated potential diagnostic yield of 25–52 percent for previously undiagnosed patients with severe intellectual disability^{236–240} introduce clinical demands to be up to date and well informed. It is not sufficient to know that the previous child had a mucopolysaccharidosis; exactly which type and even subtype must be determined because each may have different enzymatic deficiencies or genotypes (see Chapter 23). A history of limb-girdle muscular dystrophy will also not facilitate prenatal diagnosis because there are eight dominant types (1A–1H), at least 23 autosomal recessive types (2A–2W),²⁴¹ and many are still to be molecularly identified. Similarly, a history of epilepsy gives no clear indication of which genes are involved.²⁴² Birth of a previous child with craniosynostosis requires precise determination of the cause (~20 percent recognized as genetic)²⁴³ before risk counseling is provided. Mutations in at least 13 genes are clearly associated with monogenic syndromic forms of craniosynostosis.^{244–246} Moreover, a chromosomal abnormality may be the cause.

Awareness of genetic heterogeneity and of intra- and inter-family phenotypic variation of a specific disorder (e.g. tuberous sclerosis)²⁴⁷ is also necessary. The assumption of a particular predominant genotype as an explanation for a familial disorder is unwarranted. The common adult dominant polycystic kidney disease caused by mutations in the *ADPKD1* gene has an early-infancy presentation in 2–5 percent of cases.²⁴⁸ Moreover, mutations in the *ADPKD2* gene may result in polycystic kidney disease and perinatal death²⁴⁹ and, further, should not be confused with the autosomal recessive type caused by mutations in the *ARPKD* gene. Awareness of contiguous gene syndromes, such as tuberous sclerosis and polycystic kidney disease (*TSC2-PKD1*) is important, especially with the availability of microarrays.

Instead of simply accepting the patient's naming of the disease (e.g. muscular dystrophy or a mucopolysaccharidosis), or that a test result was normal (or not), the counselor must obtain and document confirmatory data. The unreliability of the maternal history, in this context, is remarkable, a positive predictive value of 47 percent having been documented.²⁵⁰ 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.²⁵¹

Myotonic muscular dystrophy type 1 (DM), the most common adult muscular dystrophy, with an incidence of about 1 in 8,000,²⁵² 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 in the *DMPK* gene 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 and earlier onset to the number of triplet repeats was not long in coming²⁵² (see Chapter 14). 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 when originating through maternal transmission. However, at least one exception has been noted.²⁵³ 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.²⁵⁴ Rare cases also exist in which complete reversal of the mutation occurs with spontaneous correction to a normal range of triplet repeats.^{255–262}

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 consistent with the overwhelming consensus of opinion that governs genetic counseling. Nondirective

genetic counseling has been endorsed by medical geneticists,²⁶³ as well as by the World Health Organization Expert Committee on Genetic Counseling,²⁶⁴ and in a multinational study focused on the attitudes of genetic counselors.^{265, 266} In an analysis of nondirective genetic counseling, Kessler²⁶⁷ proffered 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. Indeed there are some who believe that nondirective counseling is neither possible nor desirable.^{268, 269} Not unexpectedly, significant differences in counseling techniques mirror the divergent views of counselors on the goals, content, and process of genetic counseling. Kessler²⁶⁷ 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 has ameliorated many of these issues.

Michie et al.²⁷⁰ studied nondirectiveness in genetic counseling. They defined directiveness as advice and expressed views about or selective reinforcement of counselees' behavior, thoughts, or emotions. As expected, they concluded that genetic counseling as currently practiced was not characterized, either by counselors, counselees, or a standardized rating scale they used, as uniformly nondirective.

Clarke²⁷¹ 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. In 1970²⁷² it was emphasized

that the offer of prenatal diagnosis was not associated with any explicit or implicit commitment to abort. Clarke²⁷¹ further opined that "nondirective 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,²⁷³⁻²⁷⁵ and rightly so. He regarded reproductive choice as part of the "1980s consumerism model of clinical genetics."²⁷⁶ 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.²⁷⁶ 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 judgments about what types of people are worthy of life."²⁷⁶ Others have reported that people's decision-making processes are more rational than they might appear to be.²⁷⁷ Simms²⁷⁸ 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."²⁷⁹

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.²⁸⁰ A breach of this principle, supported by some,²⁸¹ 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.²⁸²

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.^{283, 284} The difficulty lies mainly in trying to remain impartial while aiming to prevent the occurrence of genetic disease. Personality characteristics of the counselor may well influence the counseling provided.²⁸⁵ The optimistic counselor may unwittingly color the texture of counseling provided in contrast to the depressed counselor. Hsia²⁸⁶ validly observed that optimistic counselors may tell anxious individuals not to worry, whereas pessimistic ones might unwittingly exaggerate the significance of even small risks. 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.²⁸⁷

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."²⁸⁸ 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 15-year experience offering predictive counseling for Huntington disease, the Canadian authors emphasized the importance of preparation for receiving test results.²⁸⁹ In a study of counseling following prenatal diagnosis of Klinefelter syndrome, Marteau et al.²⁹⁰ found that pregnancy was almost two-and-a-half times more likely to continue when counseling was provided by a geneticist.

Ever-increasing genetic testing using microarrays and whole-exome sequencing introduced the

counseling challenge following determination of secondary findings. This issue of possible genomic uncertainty should be addressed prior to any sample being obtained. The American College of Medical Genetics and Genomics (ACMG) have a list of 59 actionable disorders which geneticists are directed to communicate because of potential health and life-saving opportunities (see Chapter 14). Patients may opt out of this potential directive counseling, and clearly have the right not to know.²⁹¹ More difficult, however, are discoveries of variants of uncertain or unknown significance (VOUS) (see Chapter 14). Recognition, for example, in a newborn with epileptic encephalopathy, macrosomia, hypotonia, hypoglycemia, and dysmorphic facies of unknown compound heterozygous, instead of known homozygous mutations²⁹² in the *HERC1* gene, would pose a serious challenge to remain nondirective regarding future recurrence risks and options. Further complicating nondirectiveness is the realization that pathogenic variants may occur in disease-free individuals.²⁹³

Fortunately, it is very uncommon to have two parents with totally opposing views regarding the option of an abortion of an affected fetus. A counseling experience with a couple, both of whom were FBI agents, brought this issue into stark relief. The emotional exchange and the vested positions of the parties invited the "nondirective directive" to return home for their decision making while ensuring that they were in the possession of all necessary facts upon which rationality could trump.

Incidental detection by ultrasound, for example, of a hypoplastic thymus,²⁹⁴ following a maternal-age indicated amniocentesis of a 22q11.2 deletion provides another quandary when one parent with a few signs is found to harbor the same microdeletion. Certainty about the future phenotype would be unwise,²⁹⁵ with the discussion about pregnancy termination requiring definitive nondirectiveness.

Concern for the individual

The ethical principles of beneficence, respect for autonomy, non-maleficence, and justice (see Chapter 37) underscore the approach to all patients. They are the focus of our concern, not the interests of the state. Although germs and genes occupy the province of the public health authorities, genetic

privacy is paramount. This attitude permeates the genetic counseling encounter where many challenging issues will be raised, including the frequent controversial issue of abortion.

Communication 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 intellectually deficient child, the physician should explore the consequences for the interrelationships of the couple, the effects on their other children, the suffering of the affected child, the possible social stigma,²¹⁹ and the economic and other societal implications, as well as the need for contraception. Some may 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. However, our concern is for the individual, whose priorities, needs, and choices remain paramount. In the physician/counselor–patient relationship, concern for the individual should always override 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 lethal or severe disorders such as anencephaly or trisomy 13. O'Connell et al. have described the profoundly emotional journey and the adaptive grieving process of four mothers who, after prenatal diagnoses of anencephaly, continued their pregnancies to delivery.²⁹⁶ 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 (see Chapters 29 and 30). The availability of adoption should always be discussed.

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.

The counseling session provides an opportunity to also contribute to the overall psychological health of the patient. Counselors should therefore spend significant time helping patients to apply the information to their lives and should not be wholly focused on communicating genetic information.²⁹⁷

Truth in counseling

Since the time of Hippocrates, physicians have often withheld the truth from their patients and, as Katz²⁹⁸ 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, Lantos²⁹⁹ 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."

Situations have arisen in genetic counseling where facts have been distorted, de-emphasized, or even hidden. Obstetricians opposed to abortion of an abnormal fetus have been known to provide incorrect or misleading information. That position is simply amoral, and flies in the face of the ethical principles of autonomy and beneficence. A physician or genetic counselor visiting their religious beliefs on a patient is totally unacceptable. In one medico-legal case, the mother had a 25 percent risk of having a second child with severe intellectual disability and microcephaly. The obstetrician purposefully delayed the required ultrasound study to 28 weeks of gestation, after which pregnancy termination was impermissible. The state court, in

addition to finding that physician negligent, levied a hefty punitive fine as well.

The enormous increase in DNA testing, including prenatal studies, has led to a corresponding increase in questions of nonpaternity. Prevalence estimates of nonpaternity vary widely,^{300–302} with a meta-analysis noting a median of 4 percent in 17 studies.³⁰¹ Discovery of a potential chromosomal abnormality (e.g. an inversion), a microdeletion or a microduplication, or concerning DNA variant, may unexpectedly reveal nonpaternity. This observation may rest on a Y-chromosome karyotypic difference, haplotypes,³⁰³ or a Y-deletion not found in the fetal DNA. A microarray may yield consanguinity (from runs of homozygosity) when the male partner is clearly not related (see Chapter 13). A biallelic DNA variant in the fetus may not be reflected in the putative allele of the “father of the fetus.” Once the nonpaternity has been discovered the question arises about informing the male partner, and telling the truth.

Much has been written about this dilemma.^{300, 304–308} Of course this potential family crisis could possibly be avoided when obtaining informed consent, at which time it should be made clear that paternity will be confirmed routinely if prenatal testing for other reasons is performed. Pregnant women given that information may decide to forego any testing.

The challenge providers face is the morality of nondisclosure, the potential for not only serious harm to the family unit but also, in some cultures, abandonment or potential serious injury or death to the mother.³⁰⁴ Some have argued that clinical significance should determine whether disclosure should occur.³⁰⁰ Where an inheritance pattern and explanation is necessary, for example, communication will be needed. In those circumstances the provider would be advised to first meet with the mother. However, clinical significance may not be immediately apparent. Avci recounts the poignant case of a 55-year-old father in kidney failure planning to receive a kidney transplant from his 35-year-old son.³⁰⁴ The HLA matching pointed to nonpaternity. The physician in that case met with the parents and son, confabulating that tests on the son indicated that being a donor was highly risky for him! The position taken by this physician would be justifiable according to well regarded ethicists,³⁰⁹ and in accord with the

principle of beneficence. Other ethicists disagree, and maintain that veracity is an ethical principle^{310, 311} and rather than a moral rule, it is a *prima facie* obligation.^{304, 309} Like confidentiality, truth too is not absolute.

The paternalistic approach overrides all personal choices with the aim of protecting or benefitting the patient. Since this would occur without the patient’s full knowledge or consent, it would be ethically unacceptable and in conflict with the principle of autonomy.³¹⁰ The Kantian philosophy holds that lying is always wrong, regardless of circumstances.³¹¹

In today’s world, the question of nonpaternity disclosure automatically invites legal purview.^{305, 306} Withholding information from the “father” directly violates the physician–patient “contract,” and establishes a cause of action for malpractice. On the other hand, a woman attending genetic counseling alone (not infrequent) could maintain her rights to privacy,³¹² the breach of which would inevitably end up in court. Much of enacted legislation in many states in the United States is focused on disclosures to third parties and not on the issue of concealing genetic information from a contracted party.³⁰⁵

Clearly, 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 testing^{313, 314} 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.

Confidentiality and trust

Genetic counseling and testing always reveals much more about the patient’s health status and often reveals risk information applicable to other family members. Ethical codes of practice enunciated by the American Medical Association (AMA) Code of Medical Ethics,³¹⁵ the American Society of

Human Genetics,³¹⁶ the National Society of Genetics Counselors,³¹⁷ and the President's Commission for the study of Ethical Problems in Medicine³¹⁸ have uniformly declared that it is impermissible to disclose confidential information without consent. While patient confidentiality was always thought of as inviolate, all^{315–318} recognize exceptional circumstances. However, the promulgation of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (2003)³¹⁹ permits disclosures of health information if the individual to be warned is the subject of a threat of physical harm. This position harkens back to the infamous *Tarasoff* case in which an individual disclosed to his psychotherapist his intention to murder a former girlfriend who had spurned his affections.³²⁰

Much of the disclosure quandaries arise as a consequence of advances in the analysis of DNA. Relatives of a proband who is determined to be a carrier of a serious monogenic disorder or is actually affected, once informed, may be able to take life-saving measures (e.g. long QT syndrome, colon cancer). For colorectal cancer there is evidence that over 50 percent of families at risk do not receive the necessary information.^{321, 322} Those in their reproductive years could choose options that include prenatal genetic diagnosis or preimplantation genetic testing. There are also relatives who exercise their right not to know, especially for degenerative neurological disorders for which no cure or effective therapy exists. 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 AMA has affirmed the importance of keeping genetic information confidential.³¹⁵

Geneticists and genetic counselors may argue that they have no patient relationship with relatives in question. There is, however, a moral imperative to care. Practical issues inevitably supervene. If the patient is unwilling to transmit the information, the provider is stymied and cannot be expected to launch a search for the relative(s). Given the wide dispersal of families, frequently noted limited intrafamilial communication,³²³ caregivers are left with the requirement to indicate in writing the need and importance for the patient to transmit the vital information.

Next-generation sequencing discovery of secondary findings applicable to the patient may also be of potential importance to close relatives (e.g. a mutation in *BRCA1* or *BRCA2*). In noncohesive noncommunicating families (sadly common), all good intentions may then come to naught. Some have argued that providers *may* owe a duty of care to relatives,³²⁴ even though an international consensus holds that individuals have a moral obligation to communicate genetic information to their family members.³²⁵ In France, a law requires direct disclosure to relatives about genetic risks of any serious disease that can affect their health.³²⁶

However, faced with an intractable patient, some guidance about disclosure is reflected in a statement issued by the American Society of Human Genetics in 1998.³¹⁶ 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.³²⁷

Timing of genetic counseling

Today, more than ever before, genetic counseling before conception or marriage³²⁸ may provide opportunities for carrier detection, prenatal diagnosis, preimplantation genetic testing, or the presentation of other important options noted earlier. This is the time to review the family history, although it is startling that so many couples know so little about their relatives. 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 folic acid supplementation against the occurrence of an NTD^{329, 330} (see Chapter 10), 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.^{279, 331, 332} 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^{203–205} to couples with increased risks of having children with genetic disorders. 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 session³³³ (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. Frets³³⁴ 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, having 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.³³⁵

Counselee education

Hsia et al.³³² emphasized that genetic counseling is an educational process in which the counselee acquires a set of facts and options. Fraser's²⁶³ 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^{335–339} 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 could effectively communicate the critical importance of preconception and prenatal care.

Duty to recontact

The enormous expansion of genetic testing, including expanded carrier testing, chromosomal microarrays, whole-exome sequencing, and whole-genome analysis, has further emphasized the continuing responsibility of communicating results. That obligation extends well after a clinical visit, given that the information may

inform a patient's risks or affect reproductive decisions.^{336, 337}

Mersch et al.³⁴⁰ reported that among 1.45 million people who received genetic testing for hereditary cancer risks between 2006 and 2016, further communications were necessary since 6.4 percent had unique variants reclassified. Some 7.7 percent of VOUS were reclassified and 8.7 percent were upgraded. As an aside, following genetic research and new meaningful results, an ethical duty to inform the patient has become apparent.³⁴¹

In a study by Carrieri et al. most patients viewed recontact as desirable.³⁴² However, a range of barriers to implementation have been raised, including a lack of resources, potential negative psychological consequences, unclear operational definitions of contacting, policies that prevent healthcare professionals from recontacting, difficulties locating patients, intrusion into privacy, and a violation of a patient's interests and right not to know.^{343–346}

To obviate any concern that failure to recontact could be construed as negligence,³⁴⁶ patients need to be told as part of the informed consent for testing of their responsibility to be in contact, either annually or when childbearing is planned or in progress or if a relevant change has occurred in their family history. This is especially the case when sequencing or a chromosomal microarray reveals a VOUS. We have for decades appended a statement in our post-genetic counseling letter to the referring physician and the patient alike about the need to remain in contact. There is indeed a duty to recontact, but that duty is reciprocal, despite the objections of some.³⁴⁷

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 lawsuit³⁴⁸ 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.³⁴⁹ 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.”³⁵⁰ Clearly, recommendations for recontact should be recorded in clinical notes and echoed in letters to referring physicians and patients alike. Initial ACMG guidelines regarding recontacting³⁵¹ were revised in 2008³⁵² and framed as “points to consider” in 2018.³⁵³ These were the points:

1. Recontact is fundamentally a shared responsibility among the ordering healthcare provider, the clinical testing laboratory, and the patient.
2. As part of the informed consent process, the patient or family should be advised that:
 - a) Changes in interpretation of clinical genomic test results are possible and recontact may be important for patient care.
 - b) If the patient's medical history or family history changes, the patient should make the healthcare provider aware.
 - c) Important times for the patient to request an update are at life cycle junctures such as pre-conception planning, pregnancy, and changes in family history information, including sudden unexpected death or the diagnosis of a major health issue in the person originally tested or a close relative.
 - d) When seeking an updated variant interpretation, the patient or family should contact the provider who ordered the test, the clinical geneticist who interpreted the test result with the patient, and/or the clinical testing laboratory for an update on a result with an uncertain interpretation. Alternatively, the patient can request their primary care or specialty provider to contact a genetics provider.
 - e) The patient or family has a right to decline recontact.
 - f) The patient or family should register with the healthcare facility patient portal if available.
 - g) It is the patient's obligation to provide updated contact information over time.
3. The ordering provider should emphasize, through discussion and in written explanation to the patient, that the ordering provider cannot promise that recontact regarding a revised interpretation will occur unless the patient initiates the recontact.
4. The discussion regarding recontact should be documented in the medical record. The patient or family ideally will be given a copy of the recontact policy.

5. The ordering provider should inform the patient of the specific tests performed and which laboratory performed the analysis, typically by providing a copy of the test report. The patient should be encouraged to keep the report with their important health information. The test report should be entered into the electronic health record (EHR) and should be provided to the referring physician.

6. The responsibility to inform the ordering physician of variant reclassification or discovery of a new gene–disease relationship rests with the clinical laboratory.

7. Medical geneticists need to inform referring providers that, even if the patient is referred to a medical geneticist for counseling regarding test results, the ordering physician will remain the primary contact for the laboratory.

8. If contacted by the laboratory with an updated result, the ordering physician should make reasonable efforts to recontact the patient.

Do no harm

The classic exhortation *primum non nocere* (first, do no harm) is as pertinent to clinical genetics as it is to medicine in all specialties. Attention to this principle arises particularly in the context of predictive genetic diagnosis, possible for a rapidly escalating number of neurodegenerative disorders (e.g. Huntington disease, frontotemporal dementia, Machado–Joseph disease), cardiovascular and other serious disorders including multiple endocrine neoplasia type 2B, and breast, colon, and other malignancies. Published recommendations and guidelines³⁵⁴ urge rigorous pretest and post-test genetic counseling. Many factors impact the attempt at risk communication and prediction. Patients who attend for genetic counseling invariably have their own, possibly tentative idea, about their personal risks. Their perception of risks will vary according to their family history, educational level, socioeconomic status, psychological state of mind, life experience, gender, health status, language ability, culture, IQ, and comprehension of mathematics.^{355–359} Those who initially thought their personal risks or risks of having an affected child were 50 percent and are informed that the risk only approximates 10 percent may be relieved and not even opt for any testing. Others may be startled to hear that all couples face a 3–4 percent

risk on average for bearing a child with a birth defect, intellectual disability, or genetic disorder.

The inherent harm that could potentially be done by predictive testing is the potential for demoralization and depression with possible suicidal consequences (see later discussion). 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. A single consultation is inadvisable for a couple (or individual) considering predictive testing. During the counseling session with full information transfer, an assessment of emotional health should be made. For many, a consultation with a psychologist or psychiatrist would be wise before a follow-up visit to determine the decision to test or not, and to obtain informed consent.

Many at risk of developing Huntington disease choose not to be tested. In a study of 733 individuals who did not wish to learn if they harbored this fatal flaw, 66 percent pointed to lack of a cure or treatment, and 66 percent to the inability to undo information provided.³⁶⁰ Only 12–17 percent of those at risk in North America and Europe pursue testing.^{360–364} Family and extended family repercussions may occur as a consequence of a choice not to be tested in the face of a 50 percent risk.^{365–367} Some family members may hold the untested who proceed to have children morally irresponsible.

There is of course the right of every person not to know their genetic status as potential carrier of a serious genetic disorder. It is not the duty of a counselor to state or hint that it is a moral imperative to have a predictive test. Rather, the responsibility is to provide a perspective on the testing, the various options, and the disparate pros and cons.

Predictive testing of children younger than 18 years of age is proscribed except in life-threatening disorders (e.g. long QT syndrome, multiple endocrine neoplasia type 2B). 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.

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 juvenile Huntington disease at 18 months of age and diagnosed at the age of 3 years.³⁶⁸ These cases pose challenging ethical, moral, and legal questions, but both prenatal and preimplantation genetic testing (see Chapter 2) are now well accepted in the Western world.³⁶⁹⁻³⁷¹ Certainly rigorous recommendations and guidelines are in place for the prenatal diagnosis and the preimplantation genetic testing for Huntington disease,³⁶⁹ which would apply equally to other neurodegenerative disorders and serious/fatal adult-onset disorders.

In general, the post-prenatal testing behavior of the mother is not likely to escape the average paternal observer. In a study of 54 women whose fetal risks of being affected were 50 percent (that included spouses of an affected partner), after an initial unaffected pregnancy, 10 percent chose not to have prenatal testing in a subsequent pregnancy.³⁷²

Prenatal diagnosis is not recommended for couples who do not intend to terminate a pregnancy if the fetus is affected.³⁷³ A contrary view holds that diagnosis of a fetal genetic disorder may well inform the subsequent management of labor and delivery. Continuation of that pregnancy would likely remove the autonomous right of that child to decide to be tested or not.³⁷⁴ In a review of 15 such pregnancies, one guideline was to recommend that couples should not disclose the diagnosis in order to protect the confidentiality and autonomy of the future child.³⁷⁴

Clearly, there are extraordinarily difficult circumstances related to planned childbearing 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 of personal risk in childbearing, 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.³⁷⁵ Physicians also need to reorient their practices so that women of childbearing age understand that to optimize the chance of having a healthy child,³³⁵ prenatal care is best initiated before conception and not after the second missed menstrual period, as is still anachronistically practiced so widely.

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*),³⁷⁶ 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. For colorectal cancer there is evidence that over 50 percent of families at risk do not receive the necessary information.³⁷⁷⁻³⁷⁹ A salutary lesson is provided in the study of 43 families with at least one sudden unexplained death.³⁸⁰ Identification of a 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 legal 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.³⁸¹ From the judicial opinions in these cases³⁸² we learned that: (i) moral duty is not equal to legal duty; (ii) the duty to one's family members of avertible risk serves the interests of justice; (iii) given precedents of third party disclosures in the fields of psychiatry and infectious disease, there has been a willingness to extend the duty to warn.

Sudden death as a consequence of a monogenic disorder invokes specific responsibilities not only by the pathologist performing the autopsy but also the geneticist or genetic counselor, if involved with the family. Determination of the cause of sudden death, if not clearly obvious, may be ascribed to an arrhythmia. Cost issues aside, there is the need to consider gene sequencing for the long QT syndrome, the Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. At the very least, a tissue sample should be frozen without preservative for subsequent DNA studies. Where cardiac pathology points to a cardiomyopathy, similar considerations pertain. Counseling of next of kin in such cases is important, more especially since they may face a 50 percent personal risk. On occasion, a patient at high risk may refuse to be informed about a specific genetic test result. However, if that result implicates a specific disorder that not only places that individual at risk but as a consequence may cause harm to others, the ethical imperative would demand communication of that unwanted information.³⁸³

Important legal precedents serve as further guidance. In the *Pate v. Threlkel* case (1987),³⁸⁴ the mother of Heidi Pate was diagnosed and treated for the autosomal dominant form of medullary thyroid cancer. Three years later, the same diagnosis was made for Heidi. She sued her mother's physicians asserting that they had had a duty to warn her and her siblings. The Florida Supreme Court held that

a reasonably prudent physician had a legal duty to warn of a genetically transferable disease.

The case *Safer v. Estate of Pack*³⁸⁵ followed a similar theme. The father of Donna Safer was diagnosed in 1956 and surgically treated for colon cancer associated with multiple polyposis. Despite a total colectomy, he died when Donna was only 10 years of age. Subsequently, at the age of 36 years, she was diagnosed with metastatic colon cancer due to autosomal dominant multiple polyposis. She sued her father's surgeon's estate (he died in 1969) for not warning *him* of the genetic nature and transmissibility of that cancer. The Appellate Court in New Jersey decided that a physician had a duty to warn those known to be at risk of a genetic disorder and went on to state that duty may not always be satisfied by warning the patient.³⁸⁶ About 5 years later, in 2001, the New Jersey Legislature enacted a broad genetic privacy law³⁸⁷ that without consent a physician is prohibited from disclosure of genetic information.^{386, 388}

A failure to make a diagnosis of the fragile X syndrome in the symptomatic daughter of Kimberly Molloy was followed by her giving birth to a son with this disorder. She sued the three physicians who treated her daughter (*Molloy v. Meier*).³⁸⁹ The Minnesota Supreme Court (2004) concluded that physicians owed a duty to a third party and that legal action was permissible for the failure to warn.³⁸⁹

More recently, and in the United Kingdom, the duty to warn came into sharp focus. A man with Huntington disease expressly forbade his doctor from informing his daughter of his diagnosis. She subsequently (and accidentally) learned of the diagnosis when she was already pregnant. She sued her father's physicians (*ABC v. St. Georges Healthcare NHS Trust*)³⁹⁰ for failure to inform her, claiming she would have terminated her pregnancy. The High Court denied the claim, holding that there was no duty of care. However, the Court of Appeal (2017) overturned this decision, indicating that clinicians may owe a duty to warn a patient's relatives.³⁹¹

The foregoing cases, including the decision by the UK Court of Appeal, made it clear that confidentiality in genetics is not absolute^{324, 392, 393} with some exceptions.

Following the ruling of the Court of Appeal, the case returned to the High Court for trial, where

the decision was against the claimant (ABC).³⁹¹ Notwithstanding that ruling the Court “introduced a novel legal duty of care owed by doctors to third parties in certain circumstances.”³⁹¹

Earlier, the UK General Medical Council regarded the transfer of genetic information as justified if failure to do so exposes others to a risk of death or serious harm.^{324, 394} The Joint Committee on Genomics in Medicine concurred³⁹³ and advised that if a breach of confidentiality is to be made, consent for disclosure should be sought, discussion should be held with professional colleagues (e.g. ethics committee), and disclosure should be kept to a minimum, and all actions documented.³⁹⁵ Internationally, many authors have opined and wrestled with these issues and mostly saw the necessity of communicating with relatives of the proband.^{396–400}

Preconception genetic counseling

It is an anachronism that preconception genetic counseling in the 21st century, despite being recognized as important, is not widely practiced.^{401, 402} 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.”⁴⁰³ It is now possible to prenatally diagnose *all monogenic disorders* in which the culprit gene is known. Since 6,739 have phenotypes thus far with recognized single genes,² it is very important for the physician to obtain and record the exact name of the genetic disorder(s) in the family. A history of “muscular dystrophy,” given numerous types, would, for example, not be useful. Patients need a brief explanation as to why they need to obtain the precise information, and the physician’s request documented. Review of medical records, photographs (e.g. previous stillbirths), and pertinent autopsy reports, radiographs, brain scans, and chromosome or other special laboratory reports may be necessary, as well as referral for genetic counseling. 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 childbearing 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 supplementation for the 70 percent avoidance of NTDs (see Chapter 10) and about diabetic control, management of obesity, cessation of illicit drugs, medications, smoking and alcohol. Referral to other specialists (e.g. neurologists), for tailoring medication requirements to safer and possibly less teratogenic agents (e.g. epilepsy, acne), 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 interaction 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 previously functioned in the United States as an expected standard of care, which requires that a prospective mother be informed of her increased 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. Now, given the very low procedural risks, all women should be offered

routine prenatal genetic studies that focus on chromosomal analysis and α -fetoprotein (see Chapter 17). Advances in fetal imaging and low risks of fetal loss following amniocentesis (0.1–0.4 percent) or CVS (0.2–0.4 percent)^{404, 405} (see Chapter 9) have led to the policy change. The advent of noninvasive prenatal testing (see Chapters 6 and 7) has further decreased the need for CVS or 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.⁴⁰⁶ The authors found that an additional age-related risk of nonchromosome 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.

Pregnancy outcomes related to maternal age were reported in a Danish study of 369,516 singleton cases.⁴⁰⁷ Pregnancies were followed from 11–14 weeks to delivery or termination and the age groups (20–34, 35–39, and ≥ 40 years) compared. Adverse outcomes included chromosomal abnormalities, congenital malformations, miscarriage, stillbirth, and delivery prior to 34 weeks of gestation. Women ≥ 40 years had a 3.83 percent risk of chromosomal abnormality, compared with 0.56 percent in the younger age group. Other significant results were an odds ratio of 3.1 for miscarriage (1.68 percent vs. 0.42 percent) and an odds ratio of

1.66 (2.01 percent vs. 1.21 percent) for birth < 34 weeks of gestation.

Paternal age

Paternal age has trended upwards in the United States, England, and elsewhere in recent years.^{408, 409}

The current consensus view is that a male ≥ 40 years of age at the time of conception is defined as being of advanced age.⁴¹⁰ Advanced paternal age (≥ 40) in the United States for childbearing in the 35- to 49-year-old category has risen from 42.8/1000 to 69.1/1000 from 1980–2015.⁴¹¹ This probably reflects increased divorce/remarriage rates and the increased use of assisted reproductive technologies.⁴⁰⁹ Advanced paternal age is associated with increased infertility and miscarriage rates,^{409, 412–415} as well as an increased risk of 0.3–0.5 percent of *de novo* autosomal dominant mutations that result in severe phenotypes.^{416–421} Professional societies and others whose guidelines suggest that sperm donors be less than 50 years of age,^{422, 423} might now reconsider given both new and established data.

Well-established data exist for a number of autosomal dominant disorders in the offspring of older fathers⁴⁰⁸ (Table 1.4), with achondroplasia having a relative risk of 12. The causes are *de novo* mutations estimated to accumulate to 420 over a 20-year period.⁴⁰⁸ An Israeli psychiatric disease registry study of 87,907 births, showed a 2.96-fold relative risk of schizophrenia among the offspring of fathers over 50 years of age compared with those aged 20–24 years.⁴²⁴ A Swedish National Birth Registry study of the entire population of

Table 1.4 Single-gene dominant disorders in offspring that are associated with advanced paternal age and relevant to prenatal diagnosis.

Clinical condition	Gene	Population risk	Relative risk	Adjusted risk
Achondroplasia	<i>FGFR3</i>	1/15,000	12	1/1,250
Apert syndrome	<i>FGFR2</i>	1/50,000	9.5	1/5,263
Crouzon syndrome	<i>FGFR2</i>	1/50,000	8	1/6,250
Pfeiffer syndrome	<i>FGFR2</i>	1/100,000	6	1/16,666
Wilms tumor	<i>WT1</i>	1/10,000	2.1	1/4,761
Bilateral retinoblastoma	<i>RB1</i>	1/15,000	5	1/3,000
Neurofibromatosis 1	<i>NF1</i>	1/3,000	2.9	1/1,034
Osteogenesis imperfecta	<i>COL1A1/2</i>	1/10,000	2.5	1/4,000
Polycystic kidney disease	<i>PKD1/2</i>	1/1,000	1.2	1/833
Thanatophoric dysplasia	<i>FGFR3</i>	1/20,000	3.18	1/6,290

Source: Yatsenko et al.⁴⁰⁸ Reproduced with permission of Springer Nature.

births (2,615,081) between 1973 and 2010 examined the link between autism and paternal age.⁴²⁵ The authors observed a statistically significant 3.45-fold greater likelihood of autism for fathers age at conception of >45 years compared to fathers in the 20–24 age group. They also reported a 13.1-fold greater likelihood of developing attention deficit hyperactivity disorder and a 2.07-fold risk of psychosis. In a California study of 5,121 spontaneous abortions between 6 and 20 weeks of pregnancy, fathers over 50 years of age had double the likelihood of associated pregnancy loss.⁴¹⁵ A prospective Danish study of 23,821 pregnancies showed that fathers >50 years of age had associated risks of fetal death almost twice that of younger fathers.⁴²⁶

A Swiss population study found that the proportion of younger fathers was uniformly different between those with and without Down syndrome offspring. Young fathers had an almost twofold increased odds for siring a child with trisomy 21.⁴²⁷ The authors stated the need for confirmation of their findings.

Paternal age should garner more attention during genetic counseling,⁴²⁸ especially with the availability of molecular analysis of multiple genes susceptible to *de novo* mutations in both noninvasive prenatal testing (see Chapter 8) and prenatal diagnosis (see Chapter 14).

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. In addition, it deprives them of the option of preimplantation genetic testing for those disorders with known mutations. Failure to make an early diagnosis of a genetic disorder during the first 5 years of life is common. 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.⁴²⁹ Such delay has become

problematic given that the *NF1* gene and genes for many other monogenic disorders are routinely sequenced for a precise diagnosis.

Frequently, 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 disorder. For example, confined placental mosaicism (see Chapter 4) 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 (see Chapter 4), 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 the autosomal recessive Meckel–Gruber syndrome, preparatory discussions about establishing the specific mutation from each parent could reveal that the father is not a carrier of a mutation in the culprit gene. Although nonpaternity is more likely, a judicious approach would also include consideration of uniparental disomy.^{430, 431} 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 (see discussion later and Chapter 14). About 25 percent of cases of Prader–Willi syndrome are caused by maternal uniparental disomy.⁴³² Involvement of chromosomes 7, 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.^{433, 434}

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 should now be 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 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.⁴³⁵

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 a cardiac rhabdomyoma would prompt molecular analysis of the *TSC1* and *TSC2* genes for more precise future prenatal diagnosis.⁴³⁶

A parent with a genetic disorder

Physicians are now advised to determine whether a culprit gene has been found for a specific genetic disorder under discussion, since prenatal diagnosis would then be available for that couple or their children. Adult-onset genetic disorders (breast/ovarian cancer, colon cancer, hypertrophic cardiomyopathy, long QT syndrome) serve as examples where prenatal diagnosis is an option. The long-established prenatal diagnoses for both presymptomatic and symptomatic neurodegenerative disorders⁴³⁷ continue to be expanded to include disorders such as amyotrophic lateral sclerosis and frontotemporal dementia by analysis of the *C9orf72* gene.⁴³⁸ In prenatal diagnosis discussions for all adult-onset disorders, there is a natural focus on the tortured questions of personal existence and self-extinction. One example is that of 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.⁴³⁹ Mutation analysis in a subsequent pregnancy assured an unaffected fetus.⁴⁴⁰

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 have intellectual disability. This was especially evident in our series of 50 couples having prenatal diagnosis for tuberous sclerosis.⁴³⁶ 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 study⁴⁴¹ 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!

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.^{442, 443} 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.⁴⁴⁴ 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).⁴⁴⁵ An important Stockholm study of 1,089 stillbirths usefully separated causes in preterm and term/post-term births.⁴⁴⁶ Infection and intrauterine growth restriction/placental insufficiency accounted for over 44 percent of cases in about equal proportion.

The genetics of diabetes is complex with multiple types, both polygenic, multifactorial, syndromic, and monogenic in origin. The polygenic type 1 diabetes (T1DM) and type 2 diabetes (T2DM) have over 40 and 90 genes implicated, respectively. Between 1 and 5 percent of diabetes is monogenic and symptoms overlap with T1DM and T2DM diabetes.^{447, 448} Affected monogenic type patients mostly do not have islet autoantibodies, often have endogenous insulin production, and are frequently misdiagnosed.^{449, 450} Both T2DM and monogenic diabetes are often not insulin-dependent, have a family history of diabetes, and can occur in the young. Usually, insulin resistance does not occur, nor does acanthosis nigricans in monogenic diabetics, who are mostly not obese.⁴⁴⁹

Diabetes diagnosed in the first year of life is monogenic and due to K_{ATP} channel mutations.⁴⁵¹ There are multiple types of monogenic autosomal

dominant maturity-onset diabetes of the young (MODY), four subtypes predominating with mutations in *HNFI A* (52 percent), *GCK* (32 percent), *HNF4 A* (10 percent), and *HNF1 B* (6 percent).⁴⁵²

A precise preconception molecular diagnosis is important so as to direct appropriate treatment. No pharmacologic treatment is indicated for the GCK-MODY type, low dose sulfonylureas are prescribed for HNF1A-MODY and HNF4A-MODY, with high-dose sulfonylureas for K_{ATP} channel-related diabetes.⁴⁵¹

Pregestational T1DM and T2DM are associated with poorer pregnancy outcomes, including up to a fourfold higher rate of perinatal mortality.⁴⁵³ The poorer glycemic control at the time of conception and the first trimester, the higher the frequency of stillbirths, congenital abnormalities, perinatal morbidity and mortality, macrosomia, dystocia in labor, and maternal mortality.^{454–458} Obesity, with its burden of obstetric complications and congenital anomalies⁴⁵⁷ (as discussed earlier), compounds all the problems in the diabetic mother.

Pregnant women with the chronic multifactorial autoimmune disease systemic lupus erythematosus (SLE) face a host of complications. This disorder, with its predilection for women of childbearing age, is more prevalent in non-white populations and is characterized by involvement that includes renal, cardiovascular, musculoskeletal, neurological, rheumatological, and cutaneous systems.⁴⁵⁹ Adverse pregnancy outcomes include fetal death, preterm births, intrauterine growth restriction, and neonatal lupus.⁴⁶⁰ Women with anti-Ro/anti-La antibodies, the latter being specific for the diagnosis of SLE and Sjögren syndrome,⁴⁶¹ can be asymptomatic. Anti-Ro antibodies may precede the clinical manifestations of SLE by an average of 3.6 years.⁴⁶² Note, however, these antibodies are found in up to 3 percent of the general population.⁴⁶³

The prime consequences of having anti-Ro antibodies is the risk of fetal/neonatal heart block and neonatal lupus. In a study of 325 children with second- or third-degree heart block, the overall mortality rate was 17.5 percent. Death *in utero* occurred in 6 percent.⁴⁶⁴ The risk of offspring being born with congenital heart block to a mother with anti-Ro antibodies is between 0.2 and 2.0 percent, but 15–20 percent if there has been a previously affected fetus or neonate.^{464, 465} After

two affected pregnancies, the subsequent pregnancy risk is 50 percent.⁴⁶⁶ Complex therapeutic considerations include fluorinated glucocorticoids (dexamethasone and betamethasone) and maternal fetal echocardiography monitoring.^{467, 468} Neonatal lupus with congenital heart block will usually require pacemaker implantation.^{469, 470} For mothers with a previous affected pregnancy, hydroxychloroquine has been recommended as a pre-emptive treatment.^{471, 472} Fortunately, only a third of mothers carrying fetuses with complete heart block have an identified autoimmune disorder such as lupus or Sjögren disease.⁴⁷³

Certain genetic disorders may threaten maternal and fetal health in pregnancy and are discussed in detail in Chapter 31.

A history of infertility

Beyond the issues of paternal age discussed earlier, there is the evidence that structural chromosomal abnormalities, which occur in 0.25 percent of births, more frequently have their origin in paternal chromosomes. In a 2006 report, 72 percent of *de novo* unbalanced chromosomal rearrangements were of paternal origin.⁴⁷⁴ The likelihood of having a translocation doubled every 10 years after the age of 25.⁴⁷⁵ An American Cancer Society Study of 2,532 cases of hematological cancers noted that men over 35 had a 63 percent higher risk of having affected offspring when compared with those under 25.⁴⁷⁶ A small, but statistically significant increased risk of nonchromosomal congenital malformations associated with advanced paternal age was reported by the National Birth Defects Prevention Study.⁴⁷⁷ Malformations included were cleft lip, diaphragmatic hernia, right ventricular outflow tract obstruction, and pulmonary stenosis.

About 10 percent of couples have infertility. 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.⁴⁷⁸ 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 Chapters 11 and 13). Microarrays performed after routine cytogenetics on products of conception in 2,389 cases revealed significant copy number changes or whole-genome uniparental disomy in 1.6 percent and 0.4 percent of cases, respectively.⁴⁷⁹ A study of 1,300 infertile men revealed chromosomal abnormalities in 10.6 percent and Y-microdeletions in 4.0 percent.⁴⁸⁰ 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 intellectual disability and/or malformations, who could benefit from prenatal or preimplantation diagnosis.

Other examples of disorders characteristically associated with recurrent pregnancy loss or infertility include premature ovarian failure in fragile X syndrome carriers (see Chapter 16), and the X-linked disorders steroid sulfatase deficiency⁴⁸¹ and incontinentia pigmenti.⁴⁸² Thrombophilia as a significant cause remains uncertain.^{483, 484} In about 8 percent of women experiencing recurrent abortion a mutation in the *SYCP3* gene (which encodes an essential component of the synaptonemal complex, key to the interaction between homologous chromosomes) was noted.⁴⁸⁵ An extensive list of genes related to premature ovarian failure have been recognized,⁴⁸⁶ especially noteworthy in a highly consanguineous population.⁴⁸⁷ Consequently, next-generation sequencing⁴⁸⁸ or whole-exome sequencing,^{489–492} cost issues aside, would be indicated.

Although the investigation to determine the cause of male or female infertility can be extensive, several observations are pertinent here. We recognized that congenital bilateral absence of the vas deferens (CBAVD),⁴⁹³ which occurs in 1–2 percent of infertile males, is primarily a genital form of CF (see Chapter 15). Men with CBAVD⁴⁹⁴ should have CF gene analysis (sequencing, poly T variant analysis, deletion analysis). A meta-analysis concluded that among CBAVD patients, 78 percent had one recognizable *CFTR* gene mutation whereas 46 percent were noted to have two mutations.⁴⁹⁵ The mutation detection rate is likely to exceed 92 percent including large gene rearrangements.⁴⁹⁶ Of interest is the observation of Traystman et al.⁴⁹⁷ that CF carriers may be at higher risk for infertility

than the population at large. Men who test negative for a *CFTR* mutation should have the *ADGRG2* gene on the X chromosome sequenced.^{498, 499}

Some patients with CBAVD (21 percent in one study⁵⁰⁰) also have renal malformations. These patients may have a normal sweat test and thus far no recognizable mutations in the CF gene.^{500, 501} Renal ultrasound studies are recommended in all patients with CBAVD who have normal *CFTR* analyses. The partner of a male with CBAVD and a recognized mutation(s), after gene analysis, should routinely be offered sequencing and deletion analysis of the *CFTR* gene. Such couples frequently consider epididymal sperm aspiration,^{502, 503} with pregnancy induced by IVF. Precise prenatal and/or preimplantation genetic testing can be achieved only if specific mutations have been recognized.

Significant male infertility is mainly associated with XXY males (see Chapter 12), autosomal translocations, Kallman syndrome, Y-microdeletions, autosomal inversions, CBAVD, mixed gonadal dysgenesis, and X-linked and autosomal gene mutations.⁵⁰⁴ We reported a 28-year-old with azoospermia and bilateral congenital cataracts associated with a contiguous deletion including the Nance–Horan gene at Xp23.13 and implicating the *SCML1* gene.⁵⁰⁵ The global prevalence of Yq microdeletions approximates 7.5 percent in infertile males.⁵⁰⁶ Genes including *DAZ* (“deleted in azoospermia”), *YRRM* (Y chromosome RNA recognition motif),^{507, 508} and others may be deleted singly or together in the region of Yq11.23.⁵⁰⁹ 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 IVF is likely to achieve pregnancy rates between 20 and 24 percent,⁵¹⁰ a success rate not very different from the approximately 30 percent rate in a single cycle after natural intercourse at the time of ovulation.⁵¹⁰ Pregnancy follow-up data from cases culled from 35 different programs reported in a European survey⁵¹¹ and a major American study of 578 newborns showed no increased occurrence of congenital malformations.²¹⁴ However, a statistically significant increase in sex chromosome

defects has been observed.⁵¹² Prenatal diagnosis is recommended in all pregnancies following ICSI.

Even “balanced” reciprocal translocations in males may be associated with the arrest of spermatogenesis and resultant azoospermia.⁵¹³ In one series of 150 infertile men with oligospermia or azoospermia, an abnormal karyotype was found in 10.6 percent (16/180), 5.3 percent (8/150) had an AZF-c deletion, and 9.3 percent (14/150) had at least a single CF gene mutation.⁵¹⁴ This study revealed a genetic abnormality in 36/150 (24 percent) of men with oligospermia or azoospermia. A Turkish study of 1,696 males with primary infertility showed 8.4 percent with a chromosomal abnormality and 2.7 percent with a Y-chromosome microdeletion.⁵¹⁵

Rarer disorders may need to be considered in the quest to determine the cause of infertility including, for example, the blepharophimosis, ptosis, epicanthus inversus syndrome, which may respond to treatment.⁵¹⁶

In a study of 75,784 women to determine all-cause and cause-specific mortality, those with infertility had a 10 percent increased risk of death from any cause.⁵¹⁷ Death from breast cancer was more than doubled. In a major prospective Danish study, 3,356 women who had children born after frozen embryo transfer were compared with 910,291 fertile women. The incidence rate of childhood cancer was 17.5 per 100,000 for children born to fertile women, and 44.4 per 100,000 in children born after the use of frozen embryos.⁵¹⁸ The statistically significant increased risk was primarily leukemia and sympathetic nervous system tumors. The cause(s) remain unknown. A US study did not find a significant association, but had a shorter follow-up period (<5 years), follow-up loss, and incomplete maternal data.⁵¹⁹ In a retrospective study using insurance data, the records of 19,658 infertile women and 525,695 fertile women were examined to determine severe maternal morbidity.⁵²⁰ The overall incidence of severe maternal morbidity among women receiving fertility treatment was 7.0 percent compared with 4.3 percent in fertile women.

Parental carrier of a genetic disorder

Prospective healthy parents are mostly unaware of their carrier status for a chromosomal or single-gene disorder, unless their medical or

reproductive history has otherwise been informative. Studies to determine prenatal carrier status for a chromosomal disorder are recommended following a history of recurrent miscarriage, previous stillbirth, previous child with intellectual disability, or congenital abnormality, infertility, oligospermia, azoospermia, or a family history that is concerning for any of these outcomes. Chromosome analysis will mostly suffice in determining translocations, inversions, and somatic mosaicism. Chromosomal microarrays (see Chapter 13) for both parents are appropriate if no diagnosis was made for previous affected progeny, but will miss balanced translocations.

The first preconception visit is the time to establish the carrier status of a couple for either a chromosomal or monogenic disorder.⁵²¹ 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 (see discussion later). 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. Recognition of the carrier status for Duchenne muscular dystrophy (DMD) of a prospective mother at the first preconception visit should immediately include consideration of her own future health. Some two-thirds of mothers are carriers of a DMD gene mutation. As X-linked carriers they may manifest symptoms and signs of this disorder, including muscle weakness, prominent but weak calf muscles, abnormal gait, fatigue, exercise intolerance, and, of greatest importance, heart involvement.⁵²² Up to 16.7 percent of DMD carriers develop dilated cardiomyopathy, with carriers of Becker muscular dystrophy (BMD) having up to a 13.3 percent risk.⁵²³ The cardiomyopathy may also manifest with conduction defects and arrhythmias.^{522, 524–527} While most carriers become symptomatic around puberty,⁵²⁸ the risks and severity increase with age. Unfortunately, physicians are often unaware of the risks DMD carriers face,⁵²⁹ despite having elevated levels of creatine phosphokinase.⁵³⁰ In a study of 77 DMD and BMD carriers with a molecular confirmed diagnosis, 49

percent had myocardial fibrosis detected by cardiac MRI.⁵³¹ Irreversible heart failure maybe the final complication for which cardiac transplantation has been done.⁵³²

A report on 355 fragile X carrier women noted that >30 percent complained of anxiety, depression, and headaches.⁵³³ Between 20 and 30 percent of carriers experience irregular or absent menses due to primary ovarian insufficiency.⁵³⁴ This latter recognition during routine obstetric care often serves as an alert to check fragile X syndrome carrier status. We have also seen instances where recognition of carrier status has led to reversal of a putative diagnosis of parkinsonism or early dementia, instead of an actual diagnosis of the fragile X tremor ataxia syndrome manifesting in a grandfather over 60 years of age (see Chapter 16).

Carrier status for women with a family history of hemophilia A or B cannot be excluded by a normal activated partial thromboplastin time or normal factor VIII or factor IX levels.⁵³⁵ A definitive molecular diagnosis combined with linkage analysis where necessary is needed, especially if prenatal or preimplantation diagnosis is sought. Determination of a pathogenic variant in the structurally complex factor VIII gene enables confirmation of carrier status.^{536, 537} Prenatal diagnosis requests for hemophilia A are uncommon, but have been provided.^{538–540} Preimplantation genetic testing (see Chapter 2) for hemophilia has also been accomplished.⁵⁴¹ Noninvasive prenatal diagnosis of hemophilia A and B in hemophilia carriers using maternal plasma and factor VIII and factor IX sequence variants has been demonstrated⁵⁴² (see Chapter 8).

We all carry a host of deleterious recessive genes (~100–300)⁵⁴³ and technical advances have enabled routine simultaneous testing of hundreds of autosomal recessive and X-linked disorders which affect about 1 in 300 pregnancies.⁵⁴⁴ Not well understood by patients is the fact that expanded carrier testing^{545–555} examines only a few common mutations in each gene analyzed. The net effect is a significant reduction in the risk of being a carrier of the gene tested. Unfortunately, the refrain heard from patients having had expanded carrier testing is “I am not a carrier.” Financial constraints prevent many couples benefitting from the extensive panel of carrier tests, leaving them with the previously required indications of ethnicity, affected offspring,

or family history. This type of limited carrier testing, which includes CF and spinal muscular atrophy, misses about 70 percent of carriers of rare disorders.⁵⁵⁶ For the most part carriers of autosomal recessive disorders are asymptomatic. An important exception are the carriers of the sickle cell disease gene mutation p.Glu6-Val in the β -globin chain of hemoglobin, who have an increased risk of both venous thromboembolism and chronic renal disease.⁵⁵⁷ This is an important realization that should lead to care and surveillance, given that about 300 million worldwide have the sickle cell trait.

Autosomal recessive disease severity when due to compound heterozygous pathogenic variants will be a consequence of the variable expression of the two alleles (e.g. CF with the p.Phe508del and the p.Arg117His alleles resulting only in CBAVD) (see Chapter 15). Gene modifiers too will affect the phenotype. Variant interpretation remains a challenge as well as increasing the need and time taken for genetic counseling given that over 1,800 autosomal recessive genes are known.⁵⁴³

Clearly, the purpose of expanded carrier screening (see Chapter 14) for healthy couples enables them to benefit from available options that include preimplantation genetic testing, routine prenatal diagnosis, adoption, donor sperm or ova, or surrogacy. This approach has proved acceptable to the American College of Obstetricians and Gynecologists, the American College of Medical Genetics and Genomics, the Society for Maternal-Fetal Medicine, and the National Society of Genetic Counselors.^{558, 559} The clinical utility and efficacy has been clearly demonstrated.^{546, 549, 551, 558}

Johansen Taber et al.⁵⁶⁰ reported on the actions and reproductive outcomes of 391 at-risk couples from a tested population of over 270,000 using a panel of 176 genetic disorders. Over 75 percent who had preconception testing, planned or acted to avoid having an affected progeny. More than 50 percent of at-risk couples terminated pregnancies. Relying on a survey study, the authors acknowledge, has limitations so far as memory, response bias, and selection (infertility problems) are concerned. In a smaller study, others⁵⁴⁹ demonstrated the clear superiority of expanded carrier screening compared with ethnicity-based testing, with over threefold detection. Punj et al. offered preconception next-generation sequencing to determine

carriers and found 12/71 couples at risk.⁵⁴⁸ Eight were carriers of hemochromatosis. These authors analyzed 728 genes in 202 individuals, 78 percent being determined to have at least one positive carrier result. In this exploratory study, which used a 148 gene-panel rather than the ACMG actionable panel of 59 genes, 3.5 percent of participants had a medically actionable variant⁵⁴⁸ (see Chapter 14). Applying their analysis to the ACMG panel, 2.9 percent had an actionable variant.

Ethnicity-based carrier testing (Table 1.5) remains the only option for large swaths of the world's population. Selective Ashkenazi Jewish mutation carrier testing, for example, for disorders listed in Table 1.5 do provide valuable but limited information, leading to options noted above. A study of 6,805 Jewish patients (Ashkenazi, Sephardi, and Mizrahi) having expanded carrier screening showed that 64.6 percent were identified as a carrier of one or more of 96 disorders⁵⁶² (Table 1.6). The authors noted that >80 percent of the reported variants would have been missed by standard Ashkenazi Jewish screening protocols. One in 16 couples were identified as joint carriers with a 25 percent risk of having an affected child. A novel, likely pathogenic variant was seen in about 2.5 percent of patients tested. A whole-exome sequencing study of 123,136 cases examined carrier rates in six ethnic groups, focusing on 415 genes associated with severe recessive disorders.⁵⁶³ These authors found that 32.6 percent (East Asian) and 62.9 percent (Ashkenazi Jewish) were variant carriers of at least one of the 415 genes. A pan-ethnic screen using these 415 genes would identify up to 2.52 percent of at-risk couples.

However, the limitations of ethnic-based carrier testing were revealed by a genetic ancestry analysis of >93,000 individuals having expanded carrier testing using a 96-gene panel.⁵⁶⁵ Nine percent of those tested had an ancestry from a lineage inconsistent with self-reported ethnicity.

Multiple published reports on preconception or prenatal expanded carrier screening using large but variable-sized gene panels overwhelmingly support this approach above ethnicity-based testing.^{545, 549, 566–572}

Although not currently required in preconception carrier screening, testing for hereditary cancer risk should be considered. A personal or family history of cancer as well as ethnicity currently

serves as an indication for screening. Autosomal dominant disorders are otherwise not usually subject to screening. In a study of 26,906 individuals in the Healthy Nevada Project screened for *BRCA*-related breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia, 1.33 percent were found to be carriers of pathogenic or likely pathogenic variants.⁵⁷³ Moreover 90 percent of carriers had not been identified previously, and only 25.2 percent had a relevant family history. These three disorders determined by screening (not family history) are not usually considered for prenatal diagnosis or preimplantation genetic testing. However, other autosomal dominant disorders with manifestations in childhood (e.g. multiple endocrine neoplasia type 2B, familial adenomatous polyposis, long QT syndrome, cardiomyopathy) do qualify for preconception, preimplantation, and prenatal testing. A study of 23,179 individuals with a family history of cancer had next-generation sequencing using a 30-gene panel.⁵⁷⁴ A total of 2,811 pathogenic variants were found in 2,698 individuals for an overall pathogenic frequency of 11.6 percent. For those of Ashkenazi Jewish descent three-quarters of the pathogenic variants in the *BRCA1* and *BRCA2* genes would have been missed if only the routine three common founder mutations were tested.

Geneticists and genetic counselors will attest to the frequent challenges they encounter faced by their patients' difficulty comprehending genetic test results, implications, and options. On the heels of the technologic advances in genetics have come commercialization in the form of direct-to-consumer (DTC) testing. Few patients are cognizant of the commercialization realities that include selling of their data, receiving misleading results, being faced with incorrect, false-positive or false-negative results, a lack of informed consent, confidentiality, and privacy.^{575–580} There is a wide spectrum of laws that govern genetic testing in most countries, with special reference to laboratory accreditation, staff certification, genetic counseling requirements, and informed consent.

In one study of identical twins there was a lack of concordance between laboratories.⁵⁸¹ In an illustrative case, the result provided was actionable, but no action was taken by the recipient of the DTC communication.⁵⁸² Ethical breaches, including testing of children, further complicate DTC practices.⁵⁸³

Table 1.5 Genetic disorders in various ethnic groups.

<i>Ethnic group</i>	<i>Genetic disorder</i>
Africans (black)	Sickle cell disease and other disorders of hemoglobin α - and β -thalassemia Glucose-6-phosphate dehydrogenase deficiency Benign familial leucopenia
Afrikaners (white South Africans)	High blood pressure (in females) Variegate porphyria Fanconi anemia
American Indians (of British Columbia)	Cleft lip or palate (or both)
Amish/Mennonites	Ellis–Van Creveld syndrome Pyruvate kinase deficiency
Armenians	Hemophilia B Familial Mediterranean fever
Ashkenazi Jews	A- β -lipoproteinemia Bloom syndrome Breast cancer Canavan disease Colon cancer Congenital adrenal hyperplasia Dysferlinopathy (limb girdle muscular dystrophy 2B) Dystonia musculorum deformans Factor XI (PTA) deficiency Familial dysautonomia Familial hyperinsulinism Fanconi anemia (type C) Galactosemia Gaucher disease (adult form) Iminoglycinuria Joubert syndrome Maple syrup urine disease Meckel syndrome Niemann–Pick disease Pentosuria Retinitis pigmentosa ⁵⁹⁰ Tay–Sachs disease Warsaw Breakage syndrome ⁵⁶¹
Chinese	Thalassemia (α) Glucose-6-phosphate dehydrogenase deficiency (Chinese type) Adult lactase deficiency

Table 1.5 (Continued)

<i>Ethnic group</i>	<i>Genetic disorder</i>
Eskimos	E1 pseudocholinesterase deficiency
Finns	Congenital adrenal hyperplasia Aspartylglucosaminuria
French Canadians	Congenital nephrosis Neural tube defects
Irish	Tay–Sachs disease Neural tube defects Phenylketonuria
Italians (northern)	Schizophrenia
Japanese and Koreans	Fucosidosis Acatlasia Dyschromatosis universalis hereditaria
Maori (Polynesians)	Oguchi disease Clubfoot
Mediterranean peoples (Italians, Greeks, Sephardic Jews, Armenians, Turks, Spaniards, Cypriots)	Familial Mediterranean fever Glucose-6-phosphate dehydrogenase deficiency (Mediterranean type) Glycogen storage disease (type III) Thalassemia (mainly β)
Norwegians	Cholestasis-lymphedema Phenylketonuria
Yugoslavs (of the Istrian Peninsula)	Schizophrenia

Table 1.6 Residual risk values for diseases in Ashkenazi Jewish populations.

<i>Disease</i>	<i>100% Ashkenazi Jewish carrier frequency</i>	<i>Detectability</i>	<i>Residual risk</i>	<i>Probability of affected fetus if parents pos/neg^a</i>
Gaucher disease	1 in 15	0.95	1 in 281	1 in 1,124
Cystic fibrosis	1 in 23	0.94	1 in 368	1 in 1,472
Tay–Sachs disease	1 in 27	0.98	1 in 1,301	1 in 5,204
Familial dysautonomia	1 in 31	>0.99	1 in 3,001	1 in 12,004
Canavan disease	1 in 55	>0.97	1 in 1,801	1 in 7,204
Glycogen storage disease type 1a	1 in 64	0.95	1 in 1,261	1 in 5,044
Hyperinsulinemic hypoglycemia	1 in 68	0.90	1 in 671	1 in 2,684
Mucopolidosis IV	1 in 89	0.95	1 in 1,761	1 in 7,044
Maple syrup urine disease	1 in 97	0.95	1 in 1,921	1 in 7,684
Fanconi anemia	1 in 100	0.99	1 in 9,901	1 in 39,604
Dihydrolipoamide dehydrogenase deficiency	1 in 107	>0.95	1 in 2,121	1 in 8,484
Niemann–Pick disease type A	1 in 115	0.97	1 in 3,801	1 in 15,204
Usher syndrome type 3	1 in 120	>0.95	1 in 2,381	1 in 9,524
Bloom syndrome	1 in 134	0.99	1 in 13,301	1 in 53,204
Usher syndrome type 1F	1 in 147	≥0.75	1 in 585	1 in 2,340
Nemaline myopathy	1 in 168	>0.95	1 in 3,341	1 in 13,364

^aOne parent is positive and one parent is negative by carrier screening.

Source: Modified from Scott et al.⁵⁶⁴

Professional organizations, aware of all these issues, have discouraged the use of DTC genetic testing. Position statements have accordingly been issued by the American College of Obstetricians and Gynecologists,⁵⁸⁴ the American College of Medical Genetics and Genomics,⁵⁸⁵ the Joint Society of Obstetricians and Gynecologists, and the Canadian College of Medical Genetics.⁵⁸⁶ A range of laws exist in Europe, with France and Germany banning DTC genetic testing.⁵⁸⁷ Serious concern has been expressed about the ethical, legal, and regulatory challenges of DTC testing in Ireland⁵⁸⁸ and Europe.⁵⁸⁹

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, sometimes revealed by expanded carrier screening⁵⁹¹ or whole-exome sequencing.⁵⁹² Such a disorder may be common (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.⁵⁹³ Venous thromboembolism is the third leading cause of cardiovascular death in the United States, and provides additional insights into the genetic basis of unprovoked pulmonary embolism. Using whole-exome sequencing in 393 affected individuals and 6,114 controls, Desch et al.⁵⁹⁴ identified four genes (*PROS1*, *STAB2*, *PROC*, *SERPINC1*) with pathogenic variants, expanding the need for genetic testing given the history of thromboembolism.

For some families, individuals with quite different apparent clinical features may, in fact, have the same disorder. Seventeen cancers in different organs in family members may not be recognized as manifestations of the same common mutation. In hereditary nonpolyposis colon/rectal cancer, various family members may suffer from other cancers including the uterus, ovary, breast, stomach, small bowel, ureter, melanoma, or salivary glands. Analysis of the five culprit genes in the proband would enable detection of the mutation, which could then be assayed in other family members at

risk. In another 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 identified (about 85 percent of cases due to *APKD1* and close to 15 percent due to *APKD2*),⁵⁹⁵ 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.⁵⁹⁶ 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 15 long QT syndrome genes.⁵⁹⁷ Other disorders in which sudden death due to a conduction defect might have occurred, with or without a family history of cataract or muscle weakness, should raise the suspicion of myotonic muscular dystrophy (see Chapter 31).

Rare named disorders in a pedigree should automatically raise the question of the need for genetic counseling. We have seen instances (e.g. pancreatitis) in which, in view of its frequency, the disorder was simply ascribed to alcohol or idiopathic categories. Hereditary pancreatitis, although rare, is an autosomal dominant disorder for which several genes are known.⁵⁹⁸

Awareness of the clinical manifestations in carrier females of X-linked disorders is important given health and risk implications (Table 1.7). The pattern of inheritance of an unnamed disorder may signal a specific monogenic form of disease. For example, unexplained intellectual disability on either side of the female partner's family calls for fragile X DNA carrier testing. Moreover, unexpected segregation of a maternal premutation may have unpredicted consequences, including reversion of the triplet repeat number to the normal range.⁶⁷¹ Genetic counseling may be valuable, more especially because the phenomena

Table 1.7 Signs in females who are carriers of selected X-linked recessive disease pertinent to prenatal diagnosis.

<i>Selected disorders</i>	<i>Key feature(s) that may occur</i>	<i>Selected references</i>
Aarskog–Scott syndrome allelic with XLMR 16	Widow's peak or short stature	599
Achromatopsia	Decreased visual acuity and myopia	600
Adrenoleukodystrophy	Neurologic and adrenal dysfunction	601, 602
Alport syndrome	Microscopic hematuria and hearing impairment	603
Amelogenesis imperfecta, hypomaturation type	Mottled enamel vertically arranged	604
Arthrogryposis multiplex congenita	Club foot, contractures, hyperkyphosis	605
ATRX syndrome α -thalassemia/ID syndrome	Mild intellectual disability, hemoglobin H inclusions	599, 606
Borjeson–Forssman–Lehmann syndrome	Tapered fingers, short, widely spaced, flexed toes, mild mental retardation	607
Choroideremia ^a	Chorioretinal dystrophy	608
Chondrodysplasia punctata 1	Mild intellectual disability, possible bone defects and short stature	599
Chronic granulomatous disease	Cutaneous and mucocutaneous lesions	609–611
Cleft palate	Bifid uvula	612
Conductive deafness with stapes fixation	Mild hearing loss	613
Deafness X-linked 1 allelic with Charcot-Marie-Tooth 5	Mild high-pitch hearing loss	599
Dilated cardiomyopathy	Cardiac failure	614
Duchenne/Becker muscular dystrophy	Pseudohypertrophy, muscle weakness, cardiomyopathy/conduction defects	615–618
Dyskeratosis congenita	Retinal pigmentation	619
Ectodermal dysplasia	Variable severity of skin, hair, nails, and teeth	599
Emery–Dreifuss muscular dystrophy	Cardiomyopathy/conduction defects	620–622
Fabry disease	Angiokeratomas, corneal dystrophy, "burning" hands and feet, rhabdomyolysis	623, 624
FG syndrome	Anterior displaced anus, facial dysmorphism	625
Fragile X syndrome	Mild-to-moderate intellectual disability, behavioral aberrations, schizoaffective disorder, premature ovarian failure, fragile X tremor ataxia syndrome, women and men premutation carriers	626–628 (see Chapter 16)
G6PD deficiency	Hemolytic crises, neonatal hyperbilirubinemia	629
Hemophilia A and B	Bleeding tendency	630
Hypohydrotic ectodermal dysplasia	Sparse hair, decreased sweating	631, 632
Ichthyosis	Ichthyosis	633
KDM5C gene disease	Intellectual disability	634
Lissencephaly and agenesis of the corpus callosum	Epilepsy with subcortical band heterotopia	599
Lowe syndrome	Lenticular cataracts	635
MASA syndrome/SPG1	Mild intellectual disability, abducted thumbs	599
McLeod neuroacanthocytosis syndrome	Chorea, late-onset cognitive decline	636
Menkes disease	Patchy kinky hair, hypopigmentation	637, 638
Myopia	Mild myopia	639
Nance–Horan syndrome ^b	Posterior Y-sutural cataracts and dental anomalies	640
Norrie disease	Retinal malformations	641
Ocular albinism type 1	Retinal/fundal pigmentary changes	642

Table 1.7 (Continued)

<i>Selected disorders</i>	<i>Key feature(s) that may occur</i>	<i>Selected references</i>
Oculofaciodigital syndrome (OFD1) allelic with Simson–Galabia–Beheld syndrome 2 and Joubert syndrome	Facial dysmorphism, abnormal digits, and polycystic kidneys	599
Oligodontia	Hypodontia	643
Opitz G/BBB syndrome	Hypertelorism	644
Opitz–Kaveggia syndrome	Mild intellectual disability, hypertelorism	599
Ornithine transcarbamylase deficiency	Hyperammonemia, psychiatric/neurologic manifestations	645, 646
Ovarian cancer	Ovarian cancer	647
Pelizaeus–Merzbacher	Possible mild spasticity	648
Retinoschisis	Peripheral retinal changes	649
Retinitis pigmentosa	Night blindness, concentric reduction of visual field, pigmentary fundal degeneration, extinction of electroretinogram, cone disruption, vision loss	650, 651
MECP2-duplication syndrome	Intellectual disability, neuropsychiatric features, endocrine abnormalities	652
Simpson–Golabi–Behmel syndrome	Extra lumbar/thoracic vertebrae, accessory nipples, facial dysmorphism	653, 654
Spinal and bulbar muscular atrophy	Muscle weakness and cramps	655
Split-hand/split-foot anomaly	Mild split-hand/split-foot anomaly	656
Spondyloepiphyseal dysplasia, late onset	Arthritis	657
Ulnar hypoplasia with lobster-claw deficiency of feet	Slight hypoplasia of ulnar side of hand and mild syndactyly of toes	658
Wiskott–Aldrich syndrome ^a	Abnormal platelets and lymphocytes	659, 660
X-linked intellectual disability	Mostly intellectual disability (many genes), occasional short stature, hypertension, psychiatric symptoms	661–663
X-linked mental retardation	Short stature, hypertelorism	599, 664, 665
X-linked mental retardation (OPHN1)	Cerebellar hypoplasia, distinctive facies	666, 667
X-linked myotubular myopathy	Weakness, respiratory problems	668
X-linked protoporphyria	Life-long photosensitivity; liver disease	669
X-linked retinitis pigmentosa	Retinal changes	670

^aUncertain.

^bMay be same disorder.

of pleiotropism (several different effects from a single gene) and heterogeneity (a specific effect from several genes) may confound interpretation in any of these families.

History of a previous child with intellectual disability with a diagnosis deemed “idiopathic” or of unknown cause after chromosomal, fragile X and biochemical analyses, is no longer tenable without whole-exome sequencing^{672, 673} (see Chapter 14). Over 700 genes involved in intellectual disability of monogenic origin have been recognized.^{674, 675}

In a meta-analysis of 3,350 individuals with neurodevelopmental disorders^{676–678} the diagnostic yield was 36 percent using whole-exome sequencing. More recently, whole-exome sequencing for patients sent for a chromosomal microarray yielded diagnoses in about 27 percent of intellectual disability cases.⁶⁷⁶

Consanguinity

A wide swath of the world’s population have high rates of consanguinity (50–70 percent of births to

consanguineous parents). This especially applies to India, Pakistan, Bangladesh, the Middle East, and Africa. Medical literature is replete with examples of rare severe autosomal recessive disease in these populations. Where family history does not reveal unknown or hidden consanguinity, purposeful or incidental, significant runs of homozygosity seen on a chromosomal microarray (see Chapter 13) frequently will. In those instances, recognition of a shared gene and its mutation within a shared region may unexpectedly lead to a rare diagnosis. Not as well known, perhaps, is that shared variant homozygosity markedly reduces the fertility rate of close consanguineous couples.⁶⁷⁹

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, intellectual disability, and physical handicap was significantly higher in the offspring of consanguineous couples.^{680, 681} 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.^{681, 682} A Jordanian study also noted significantly higher rates of infant mortality, stillbirths, and congenital malformations among the offspring of consanguineous couples.⁶⁸³ A Norwegian study of first-cousin Pakistani parents yielded a relative risk for birth defects of about twofold.⁶⁸⁴ In that study, 28 percent of all birth defects were attributed to consanguinity. An observational study of 5,776 Indian newborns noted a birth defect prevalence of 11.4 per 1,000 births with a consanguinity rate of 44.74 percent.⁶⁸⁵

A study from Saudi Arabia, where the consanguinity rate exceeds 50 percent, focused on whole-exome sequencing of 2,219 families who had or had lost an affected fetus or child. The study group was constituted by 1,653 individual samples, 127 twosomes, 370 trios, 58 quads, and 11 others.⁶⁸⁶ They resolved many cases by determining known causal recessive genes and their mutations, but also discovering multiple previously unknown pathogenic variants. In addition, they recognized some genes that also had a dominant rather than recessive mode of inheritance. Their

prenatal diagnostic detection rate was 46.2 percent (30/65 cases), 87 percent of which were autosomal recessive.

Whole-exome sequencing following discovery of a fetal anomaly not resolved by karyotyping or chromosomal microarray may well provide a precise diagnosis. In a study of 102 anomalous fetuses, a definitive or probable diagnosis was made in 21 (20.6 percent).⁶⁸⁷ A similar small study of 19 families with fetal anomalies yielded candidate variants in 12 (63 percent).⁶⁸⁸ A systematic evidence-based review of exome and genome sequencing for congenital anomalies or intellectual disability on behalf of the ACMG concluded that a change in patient management was observed in nearly all studies, including an impact on reproductive outcomes.⁶⁸⁹

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.⁶⁹⁰ Abnormal or concerning prenatal ultrasound observations in pregnancies by consanguineous couples may prompt prenatal whole-exome sequencing.⁶⁹¹

Environmental exposures that threaten fetal health

Concerns about normal fetal development after exposure to medications, alcohol, 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 2 per 1,000 livebirths⁶⁹² in the United States but in certain regions and countries rates reach as high as 10 percent.^{693–695} There is a limited list of known and proven human drug teratogens⁶⁹⁶ (see Chapter 3). Maternal use of specific teratogenic medications,⁶⁹⁷ such as isotretinoin, may be missed, unless the physician expressly inquires about them.

Preconception advice to avoid heat exposure in early pregnancy is appropriate. Our observations 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.⁶⁹⁸ High fever in the very early weeks of pregnancy is a potential teratogen⁶⁹⁸ and should be avoided and treated promptly. Animal studies show that commonly used drugs enter the fetal brain.⁶⁹⁹

A report from the Spanish Collaborative Study of Congenital Malformations noted a 2.8-fold increased risk of Down syndrome in the offspring of women ≥ 35 years of age and who were taking oral contraceptives when they became pregnant.⁷⁰⁰

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:

- Knowledge of family history
- Attention to maternal health (e.g. diabetes control,^{701, 702} confirm cardiac and vascular normality)
- Decision not to have children (includes consideration of vasectomy or tubal ligation)
- Adoption
- *In vitro* fertilization
- Gamete intrafallopian tube transfer or allied techniques
- Artificial insemination by donor
- Ovum donation (includes surrogacy)
- Intracytoplasmic sperm injection
- Carrier detection tests
- Noninvasive prenatal screening by fetal DNA in the maternal circulation
- Maternal serum α -fetoprotein screening for NTDs
- Prenatal diagnosis (CVS, amniocentesis, cordocentesis, ultrasound, MRI)
- Preimplantation genetic testing

- Fetal treatment or surgery for selected disorders
- Folic acid supplementation in periconceptional period (see Chapter 10)
- Noninvasive prenatal testing (aneuploidy; monogenic disorders)
- Selective abortion

Genetic counseling as a prelude to prenatal diagnosis

The assumption that noninvasive prenatal testing for common chromosomal abnormalities (see Chapter 7) is a screening and not a diagnostic test, is unfortunately common. Many women receiving a normal report opt to avoid an amniocentesis. The vast majority will be vindicated, but some will complete pregnancy with a child having a disorder that could have been diagnosed in early gestation. Physicians and counselors are advised to remind women of this limitation, given that about half of all chromosomal abnormalities will be missed by the noninvasive screen.⁷⁰³

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 intellectual disability 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 11). 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, neither chromosomal microarrays, biochemical assays, nor DNA analyses will provide results with 100 percent certainty.

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 should 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 use of the chromosomal microarray (see Chapter 13) and whole-exome sequencing (see Chapter 14). Cautions are appropriate with special reference to VOUS (see Chapter 14), that require in addition, parental samples to determine inherited or *de novo* changes.

Other key issues to be considered by the genetic counselor and discussed when appropriate with the consultand follow.

Informed consent

Consent for minor procedures including amniocentesis and CVS has been a requirement for decades and needs no repetition. However, the advent of chromosomal microarrays (see Chapter 13) and whole-exome sequencing for prenatal diagnosis (see Chapter 14) requires additional explanations and caveats. Informed consent for

these two technologies is focused on the potential results, not sampling risks and procedures. The specific issues primarily involve the interpretation of results, their significance, the small possibility of uncertain findings, test limitations, and incidental results.

Chromosomal microarray testing adds up to 6–10 percent to a prenatal diagnosis result (see Chapter 13) beyond the 8–10 percent for routine karyotyping, and whole-exome sequencing when done after the ultrasound discovery of fetal structural abnormality adds an additional 6.2–80 percent.^{691, 704–708} This absurd range reflects very small case series, varying indications, and the presence of single or multiple fetal abnormalities. A more likely detection range would be between 8.5 and 32 percent.^{707, 708}

Prenatal diagnosis using whole-exome sequencing (see Chapter 14) is primarily focused on pregnancies in which fetal structural abnormality has been observed. A much less frequent indication would be a recent or late diagnosis of a parent with a likely monogenic disorder characterized by genetic heterogeneity. No matter the indication, the informed consent obtained incorporates and extends current practice for chromosomal microarray tests. The decision to offer whole-exome sequencing will almost inevitably come on the heels of the detection of fetal abnormality and in an atmosphere of tension and anxiety. Any center offering whole-exome sequencing will have, of necessity, established their informed consent procedure. The following list of pointers are likely to find common ground:

1. Pre- and postgenetic counseling by a geneticist or genetic counselor is a prerequisite, with strict adherence to ethical standards.^{709, 710}
2. Both parents should be in attendance.
3. Explanations should use simple language, no jargon, and be in the language of the parents (with an interpreter, if needed).
4. The details of the fetal abnormality, effect on a child (pain; disability), a progressive disorder or not, and life expectancy.
5. The use of targeted sequencing, trios, and gene panels will need explanations, including the reason and need for prior or simultaneous chromosomal microarrays.
6. The time needed to obtain a result.

7. The likely detection rate and the limitations of whole-exome sequencing (e.g. repeat expansion disorder; mosaicism).

8. The occurrence of false positives, false negatives, or error.

9. The unexpected discovery of nonpaternity or consanguinity.

10. The detection of a variant of unknown significance.⁷⁰⁹

11. A “secondary finding”^{711–714} unrelated to the original purpose of the analysis.

12. The opportunity for the parents to opt out of receiving “secondary findings”⁷¹⁵ which they should understand may have personal important health implications.

13. The choice to refuse testing.

Presymptomatic or predictive testing

Presymptomatic or predictive testing is available for a rapidly increasing number of disorders, especially neuromuscular and neurodegenerative (see Chapter 14). Huntington disease is the prototype, and predictive testing using guidelines promulgated by the World Federation of Neurology,^{716–719} the International Huntington Association, and the European Huntington Disease Network⁷¹⁹ are well established. Various programs report that a majority of patients are able to cope when it is found that they are affected,^{225–230, 720, 721} and, at least after a 1-year follow-up, potential benefit has been shown even in those found to be at increased risk.⁷²² 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.⁷²³ Prenatal diagnosis was elected by about two-thirds of those who were carriers.

Genetic counseling for Huntington disease when intermediate alleles with 27–35 CAG repeats are determined, pose significant challenges.⁷²⁴ Intermediate CAG repeats have been associated with behavioral, movement, and cognitive problems.^{725–727} The concern is the unpredictable likelihood of expansion which might account for 7 percent of new mutations.⁷²⁴ Providing counseling for those with low penetrance alleles (36–39 CAG repeats) is no less challenging. Repeats in

this range are estimated to occur randomly in the general population with a frequency of about 1 in 400.⁷²⁸ For patients with 36–39 repeats considering prenatal diagnosis, many factors will need to be addressed. These include all options discussed earlier and uncertainty, penetrance, anticipation, age of onset, and life expectancy. Experienced geneticists with an established program that includes predictive/presymptomatic testing for Huntington disease should preferably be consulted.

As others earlier,⁷²⁹ 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.⁷³⁰ 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).⁷³¹ Of the 15 who had prenatal tests, 12 had an increased risk, which led to pregnancy termination in all but one.⁷³¹

The motivations leading to the very difficult decision to have or not to have a predictive test are being recognized as extremely complex.⁷³² 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,⁷³³ highlighting earlier reports of high suicide rates⁷³⁴ 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.⁷³⁵ 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. Suicidal ideation or attempts remain a devastating reality for Huntington disease, especially given the psychopathology in those affected.^{736, 737} Depression, anxiety, and bipolar disorder are not infrequent. Suicidal behavior may be about 12 times that in the population at large, reaching an estimated 20 percent.^{738, 739} Others have written about the psychologic burden

created by knowledge of a disabling fatal disease decades before its onset.^{740–742}

Hayden⁷⁴³ 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.⁷⁴⁴ 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.⁷⁴⁵ A subgroup of tested persons were found to have long-lasting psychologic distress. An interview study of 20 who tested negative for Huntington disease revealed reactions that included obvious relief and gratitude, wishes to have (more) children, and life changes that included pursuit of a career and ending an unhappy relationship.⁷⁴⁶ Negative reactions included survivor guilt with sadness and depression or a feeling of pressure to do something extraordinary with their lives.

Homozygotes for Huntington disease are rare^{747, 748} 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,⁷⁴⁹ 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.

On the other hand, an increasing number of examples already exist (see Chapter 14) 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, especially for various cancer syndromes.⁷⁵⁰ Use of DNA linkage or mutation analysis for ADPKD^{751, 752} may lead to the diagnosis of an unsuspected associated intracranial aneurysm in 8 percent of cases (or 16 percent in those with a family history of intracranial aneurysm or subarachnoid hemorrhage⁷⁵³) and preemptive surgery, with avoidance of a life-threatening sudden cerebral hemorrhage.

It is worth noting that a subgroup of families has features similar to Marfan syndrome and that haplo-insufficiency of the *PKD1* gene influences the transforming growth factor- β (TGF β) signaling pathway.⁷⁵⁴ In a study of 141 affected individuals, 11 percent decided against bearing children on the basis of the risk.⁷⁵⁵ 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.⁷⁵⁶ Organ donation by a sibling of an individual with ADPKD, later found to be affected, has occurred more than once. Since the *PKD1* gene abuts the tuberous sclerosis (*TSC2*) gene, heterozygous deletions may lead to a contiguous gene-deletion syndrome.⁷⁵⁷

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.⁷⁵⁸ 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. In one case, an evaluation using array comparative genomic hybridization to determine the cause of intellectual disability revealed a *de novo* deletion within 3p25.3 that included the von Hippel-Lindau gene.⁷⁵⁹ For example, elective thyroidectomy is recommended for multiple endocrine neoplasia type 2B by 5 years of age in a child with this mutation, given the virtual 100 percent penetrance of this gene and the possible early appearance of cancer.⁷⁶⁰ Predictive testing, even of children at high genetic risk, poses a

host of complex issues.⁷⁶¹ 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.⁷⁶²

Identification of specific mutations in the breast/ovarian cancer susceptibility genes (*BRCA1* and *BRCA2*) has led to us providing requested prenatal diagnosis. Mothers with such mutations who have seen their own mothers and sisters die have made the difficult personal decision to terminate pregnancy.⁷⁶³ DudokdeWit et al. laid out a detailed and systematic approach to counseling and testing in these families.⁷⁶⁴ In their model approach, important themes and messages emerge:

- Each person may have a different method of coping with threatening information and treatment options.
- Predictive testing should not harm the family unit.
- Special care and attention are necessary to obtain informed consent, protect privacy and confidentiality 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.⁷⁶⁵ 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,^{766, 767} 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.⁷⁶⁸

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* (c.68 69delAG and c.5266dupC) and one in *BRCA2* (c.5946delT) that account for the majority of breast cancers in this ethnic group.^{768, 769} 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.⁷⁷⁰ Breast cancer risk by 50 years of age among mutation carriers born before 1940 was 24 percent, but 67 percent for those born after 1940.⁷⁷⁰ Lifetime ovarian cancer risks were 54 percent for *BRCA1* and 23 percent for *BRCA2* mutation carriers.⁷⁷⁰

It can easily be anticipated that, with identification of mutations for more and more serious/fatal monogenic genetic disorders (including cardiovascular, cerebrovascular, neurodegenerative, connective tissue, and renal disorders, among others), prospective parents may well choose prenatal diagnosis in an effort to avoid at least easily determinable serious or fatal 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 cancer⁷⁷¹ is also likely to be followed by thoughts of avoidance through prenatal diagnosis. This mutation has been found in 6 percent of Ashkenazi Jews.⁷⁷¹ 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.

Expansion mutations and anticipation

In 1991 the first reports appeared of dynamic mutations resulting from the unstable expansion of trinucleotide repeats.⁷⁷² Thus far, at least 40 proven disorders with these unstable repeats have been described (see Chapter 14).⁷⁷³ All disorders described thus far are autosomal dominant or X-linked, except for Friedreich ataxia and progressive myoclonic epilepsy with myoclonic tremor,^{774–776} which are autosomal recessive and also unique in having intronic involvement.⁷⁷⁷ Typically for these disorders (except for Friedreich ataxia), the carrier will have one normal allele and a second expanded allele. The repeat expansion disorders, although diverse, share many basic features. They arise from normally existing polymorphic repeats, are unstable, changing size on

transmission, with longer repeats associated with severe and earlier onset disease, and highly variable phenotypes.⁷⁷³

These disorders (except for Friedreich ataxia and progressive myoclonic epilepsy type 1)⁷⁷⁴ 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 (rarely contraction) of the specific triplet repeat (Box 1.2). These disorders characteristically have a direct relation between the number of repeats and the severity of disease with 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 type 1, for example, with a 50 percent risk, could have an affected child with severe congenital myotonic muscular dystrophy.⁷⁷⁸ Triplet size in this disorder correlates significantly with muscular disability

as well as intellectual and gonadal dysfunction.⁷⁷⁹ These authors also noted that triplet repeat size did not correlate with the appearance of cataract, myotonia, gastrointestinal dysfunction, and cardiac abnormalities. For myotonic dystrophy type 2 there is no correlation between disease severity and tetranucleotide (CCTG) repeat length.⁷⁸⁰ Women with myotonic dystrophy type 2 have an increased risk of ovarian and endometrial cancer.^{781, 782} Somatic mosaicism with different amplification rates in various tissues may be one possible explanation for variable phenotypes. Fortunately, in very few repeat expansion disorders, including Huntington disease, do *de novo* mutations occur.⁷⁸³ Parent-of-origin effects influencing anticipation are also recognized (see fragile X syndrome discussion in Chapter 16). The offspring of fathers with Huntington disease, spinocerebellar ataxias types 2 and 7, for example, may present clinically, and on occasion even before the father has become symptomatic.⁷⁸⁴ For myotonic muscular dystrophy, paternally transmitted small expansions have

Box 1.2 Selected genetic disorders with anticipation

Disorders with anticipation

- All autosomal dominant disorders with repeat expansion mutations listed in Chapter 14 Table 14.2
- Charcot–Marie–Tooth disease type 1A
- Dyskeratosis congenita
- Familial amyloid polyneuropathy
- Hereditary nonpolyposis colorectal cancer (Lynch syndrome)

Disorders with suspected anticipation

- Ablepharon–macrostomia syndrome
- 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
- Crohn disease
- Facioscapulohumeral muscular dystrophy

- Familial adenomatous polyposis
- Familial breast cancer
- Familial chronic myeloproliferative disorders
- Familial Hodgkin lymphoma
- Familial intracranial aneurysms
- Familial pancreatic cancer
- Familial paraganglioma
- Familial Parkinson disease
- Familial primary pulmonary hypertension
- Familial rheumatoid arthritis
- Graves disease
- Hodgkin and non-Hodgkin lymphoma
- Holt–Oram syndrome
- Idiopathic pulmonary fibrosis
- Lattice corneal dystrophy type I (LCD1)
- 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

a higher risk of symptomatic offspring compared with females.⁷⁸⁵ Rarely, two triplet repeat disorders occur concurrently, as reported in a patient with both oculopharyngeal muscular dystrophy and Huntington disease.⁷⁸⁶ Anticipation does occur in Huntington disease, but not in oculopharyngeal muscular dystrophy. It is well documented that the paradoxical effects of repeat interruptions in the ATTCT expansion alleles in spinocerebellar ataxia type 10 result in a contraction in intergenerational repeat size.⁷⁸⁷ *De novo* repeat interruptions may also be associated with less somatic instability and few or no symptoms and signs in myotonic muscular dystrophy type 1.^{788, 789} Spinocerebellar ataxia type 2 has also been associated with Parkinsonism and an increased risk for amyotrophic lateral sclerosis (ALS).⁷⁹⁰ Almost all of the 59 autosomal recessive spinocerebellar ataxias⁷⁹¹ are not characterized by repeat expansions. Marked heterogeneity in the clinical features are common.

Recognition in the last decade of hexanucleotide repeat expansions in the *C9orf72* gene reveal additional challenges that have raised consideration of prenatal diagnosis, as discussed under “Accurate diagnosis.” Mutations in *C9orf72* have been reported in 40–50 percent of cases with familial amyotrophic lateral sclerosis, between 3.5 percent and 8 percent of sporadic ALS cases,^{792–795} and in 25 percent of familial frontotemporal lobar degeneration, with about 7 percent in sporadic cases.^{793, 794} The clinical spectrum includes patients with frontotemporal dementia and ALS as well as those with a corticobasal syndrome.⁷⁹⁶ The real burden and likely involvement of prenatal diagnosis is the recognition of *C9orf72* expansions noted in Western Europe as occurring in 18.52 percent of familial cases and 6.26 percent in sporadic cases of frontotemporal lobar degeneration.⁷⁹⁷ Overall frequencies of these expansions in Finland, Sweden, and Spain were much higher, being 29.33 percent, 20.73 percent, and 25.49 percent, respectively.⁷⁹⁷ A further distressing aspect of the *C9orf72* expansion is the symptomatology that extends to family members who *do not* have the expansion. In a study of 1,414 first- and second-degree relatives, a statistically significant number had an increased risk of schizophrenia (hazard ratio of 4.9), late-onset psychosis, and suicide.⁷⁹⁸ There is also evidence of anticipation.⁷⁹⁹

Preimplantation genetic testing (see Chapter 2) has been successful for many repeat expansion disorders including fragile X syndrome (see Chapter 16), Huntington disease, myotonic muscular dystrophy, and spinocerebellar ataxias types 2 and 12.^{800–802}

Imprinting and uniparental disomy

All that is genetic is not necessarily Mendelian. Developing gametes or early embryonic cells may have genes deleted or silenced, with such primal events being of a single parent origin and lifelong. Moreover, these occurrences may be a consequence of an environmental (epigenetic) factor or influence. Notwithstanding this epigenetic phenomenon, the genomic change, termed “imprinting,” is heritable with potentially serious clinical implications. Epigenetics does not alter DNA sequence, but it does alter its expression.

The expectation is that each pair of autosomes have an equal matched allele from each parent. Infrequently, a pair may be constituted by alleles from one parent, termed uniparental disomy (UPD). If those two are chromosome 7 alleles from one parent and harbor a mutation in the *CFTR* gene, and the chromosome 7 from the other parent is lost during meiosis, the offspring will have autosomal recessive cystic fibrosis.^{803, 804} Multiple different disorders are known to be a consequence of UPD and influenced by parent of origin (see Chapter 14).

Relatively rarely, with biparental alleles, one gene (or a cluster) on one allele may be silenced (imprinted). If it is the paternally only expressed region on chromosome 15q, the consequence would be Prader–Willi syndrome, and if it is the maternally expressed *UBE3A* gene, Angelman syndrome would be the consequence. Silencing occurs through a process of DNA methylation. The repressed allele is methylated; the functional allele is unmethylated. Various assays are available to determine methylation status.^{805, 806} Multilocus imprinting may also occur, and result in a phenotypic spectrum.⁸⁰⁷ Accurate detection of UPD can also be determined by whole-exome sequencing.⁸⁰⁸ Imprinted gene clusters are primarily found on chromosomes 6, 7, 11, 14, 15, and 20.⁸⁰⁹

Recommendations made by the ACMG⁸¹⁰ for prenatal UPD testing include the following:

- Multiple-cell pseudomosaicism or true mosaicism for trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 from amniocentesis or CVS.
- Multiple-cell pseudomosaicism or true mosaicism for trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 in CVS followed by normal karyotype in amniocentesis.
- In the context of preimplantation genetic screening (PGS), a transfer of mosaic embryos with trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 should be followed by prenatal studies including UPD testing.
- Prenatal imaging anomalies consistent with a UPD phenotype. The classic example is the pathognomonic coat-hanger sign in paternal UPD14.
- Familial or *de novo* balanced Robertsonian translocation or isochromosome involving chromosome 14 or 15 based on CVS or amniocentesis. Both familial and *de novo* translocations are associated with an increased risk for UPD.
- *De novo* small supernumerary marker chromosome with no apparent euchromatic material in the fetus.
- Non-Robertsonian translocation between an imprinted chromosome with possible 3:1 disjunction that can lead to trisomy or monosomy rescue or gamete complementation. Although every chromosome abnormality that increases the occurrence of nondisjunction in theory would increase the risk of UPD of the chromosomes involved, there are only very few cases reported.

Imprinting disorders are the results of abnormal expression of imprinted genes at seven imprinted domains on the six chromosomes noted above. These disorders are due to different molecular changes that include copy number variation (loss or gain), UPD, point mutation in the active allele, an epimutation resulting in gain or loss of DNA methylation at the imprinting control region, a microdeletion or microduplication at an imprinting control region interfering with DNA methylation, and structural chromosome rearrangements.⁸¹¹ Recurrence risks for imprinting disorders vary according to the molecular alteration. For example, copy number variations or point mutations may occur *de novo* or come from one parent, who may or may not be affected, depending upon which grandparent transmitted the mutant allele.⁸¹¹ For Angelman syndrome and

the Prader–Willi syndrome genetic alterations are almost invariably *de novo*, resulting in extremely low risks of recurrence. The expectation, however, is a point mutation in the culprit *UBE3A* gene that causes Angelman syndrome, with a recurrence rate of 50 percent when inherited from an unaffected mother. Fortunately, only about 1 percent of our genes find expression from one or other parent.⁸¹²

Multilocus imprinting disorders with maternal effect genes (including *NLRP2*, *NLRP7*, and *PADI6*) can affect oocytes and resulting offspring, who may manifest with atypical imprinting disorders.^{813, 814} Multilocus imprinting disturbance in methylation may affect growth and development. Epigenetic effects are evident in sperm, oocyte, and zygote genomes.^{815, 816} It is no surprise then, that mutations in *NLRP* genes may result in early miscarriages, hydatidiform moles, and apparent infertility.⁸¹³ Most imprinted genes express in the placenta, and loss of imprinting can affect placental weight, fetal growth, and development,^{817–821} and the regulation of placental hormones.⁸²¹

Potential imprinting disturbances at the sperm, oocyte, or zygote stages are associated with ART and preimplantation procedures. Cogent evidence exists of an increased incidence of imprinting disorders following ART.^{822–828} In the most extensive report to date, Hattori et al.⁸²² in a nationwide study in Japan, reported on 931 patients with imprinting disorders. These included 117 cases of Beckwith–Weidemann syndrome, 67 with Silver–Russell syndrome, 520 with Prader–Willi syndrome, and 227 with Angelman syndrome. Most were conceived through ART including intracytoplasmic sperm injection. They noted a 4.46- and 8.91-fold increased frequency of Beckwith–Weidemann syndrome and Silver–Russell syndrome respectively. Cortesis et al.,⁸²⁸ in a meta-analysis of 23 studies on ART and the occurrence of imprinting disorders, reported significant odds ratios of 4.7 for Angelman syndrome, 5.8 for Beckwith–Weidemann syndrome, 2.2 for Prader–Willi syndrome, and 11.3 for Silver–Russell syndrome.

Mutations in imprinted genes that occur after fertilization can result in somatic mosaicism.⁸²⁹ An interesting example is represented by discordant monozygotic twins in which only one has the disorder (Beckwith–Weidemann syndrome)^{830–832}

or Silver–Russell syndrome,^{829, 833} pointing to epigenetic disturbances in early development.⁸²⁹

About 1.7 percent of births in the United States result from ART.⁸³⁴ Although the frequency of imprinting disorders is increased, the actual risks are very low, but should be discussed.

Genotype–phenotype associations

DNA mutation analysis has slowly clarified genotype–phenotype associations requiring extensive databases and definitive phenotyping^{835, 836} (see Chapter 14). Notwithstanding this limitation, mutation analysis does provide precise prenatal diagnosis opportunities and detection of affected fetuses even 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. Allelic combinations of missense, nonsense, and compound heterozygous mutations within different genes could result in overlapping clinical phenotypes as exemplified for the Kabuki syndrome and Schinzel–Giedion syndrome.⁸³⁷ Now that clinical diagnostic criteria have been established⁸³⁸ and two genes (*KMT2D* and *KDM6A*) recognized, syndrome identification has been facilitated.⁸³⁹ Additional novel pathogenic variants continue to be discovered.⁸⁴⁰ It appears that hyperinsulinism, long halluces, large central incisors, and hypertrichosis are more common in Kabuki syndrome due to *KDM6A* mutations,^{841, 842} while the classic Kabuki facial features and renal/palatal anomalies are more commonly found with *KMT2D* mutations.^{839, 843} In the autosomal dominant Marfan syndrome (due to mutations in *FBNI*), 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.⁸⁴⁴ In Gaucher disease with one of the common Ashkenazi Jewish mutations, only about one-third of homozygotes have significant clinical disease.⁸⁴⁵ At least two-thirds have mild or late-onset disease or remain asymptomatic (see Chapter 21). Compound heterozygotes for this disorder involving mutations p.L444P and p.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.⁸⁴⁶

In cystic fibrosis, a strong correlation exists between genotype and pancreatic function but only a weak association has been noted with the respiratory phenotype⁸⁴⁷ (see Chapter 15). Although individuals who are homozygous for the common cystic fibrosis mutation ($\Delta F508$) can be anticipated to have classic cystic fibrosis, those with the less common mutation (p.R117H) are likely to have a milder disease.⁸⁴⁸ On occasion, an individual who is homozygous for the “severe” $\Delta F508$ mutation might unexpectedly exhibit a mild pancreatic-sufficient phenotype. Illustrating the complexity of genotype–phenotype associations is the instance noted by Dork et al.⁸⁴⁹ of a mildly affected $\Delta F508$ homozygote whose one chromosome 7 carried both the common $\Delta F508$ mutations and a cryptic p.R553Q mutation. Apparently, a second mutation in the same region may modify the effect of the common mutation, permitting some function of the chloride channel⁸⁵⁰ and thereby ameliorating the severity of the disease. Modifying genes in cystic fibrosis are being increasingly recognized^{851–853} (see Chapter 15).

The extensive mutational heterogeneity in hemophilia A^{854–856} is related not only to variable clinical severity but also to the increased likelihood of antifactor VIII antibodies (inhibitors) developing. Miller et al.⁸⁵⁷ found about a fivefold higher risk of inhibitors developing in hemophiliac males with gene deletions compared with those without deletions. In Netherton syndrome, a severe autosomal recessive ichthyosis that affects skin, hair, and immune system, upstream mutations in the *SPINK5* gene correlate with more severe phenotypes.⁸⁵⁸

The many mutations and wide phenotypic range seen in neurofibromatosis type 1 is well known, and characterized by variable expressivity and age-dependent clinical features. This variability makes phenotype prediction difficult. Among the few thousand constitutional variants in the *NF1* gene, recurrent pathogenic missense variants at p.Met1149, p.Arg1276 or p.Lys1423 have been associated with a Noonan-like phenotype.⁸⁵⁹ Moreover, these authors also found that mutations at p.Arg1276 was associated with spinal neurofibromas, and that mutations at both p.Lys1423 and p.Arg1276 were associated with a high prevalence of cardiovascular abnormalities, including pulmonic stenosis.

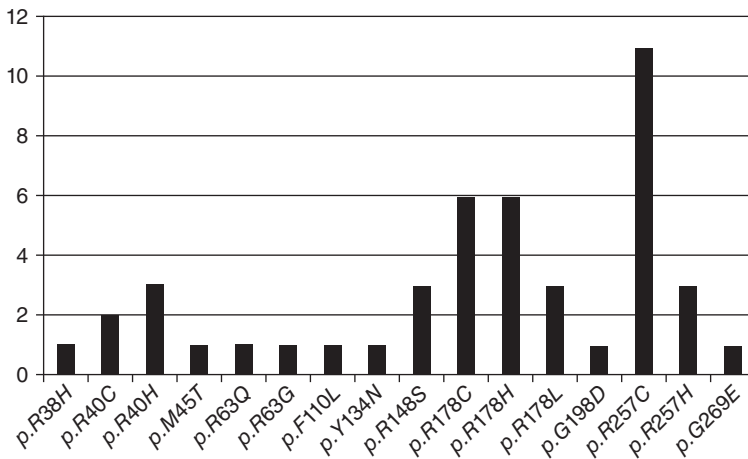


Figure 1.3 Shown are the 16 pathogenic variants reported in the *ACTG2* gene and the number of times each mutation was observed in 45 probands.⁸⁶³

Chronic intestinal pseudo-obstruction (CIPO), also known as megacystis–microcolon–intestinal–hypoperistalsis syndrome, is a severe debilitating visceral myopathy involving enteric smooth muscle.^{860–863} Mutations in the *ACTG2* gene account for about 44–50 percent of cases. We noted in a whole-exome sequencing study a mutational hotspot in the *ACTG2* gene (Figure 1.3).⁸⁶³ We subsequently determined somatic *ACTG2* mosaicism,⁸⁶⁴ further complicating genotype–phenotype determination.

Japanese authors have assembled mutation data for the *NOTCH3* gene and recognized three mutations as major contributors to the phenotype of CADASIL.⁸⁶⁵ They also recognized gender differences in symptomatology (worse in males) that included migraines, stroke, psychiatric problems, cognitive impairments, and dementia. Although CADASIL is mostly adult onset, we have provided prenatal diagnosis for a family with an affected young father, as noted earlier.

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), to check constantly updated databases where prior alterations are or are not considered pathogenic, and to perform newly available mutation analyses when applicable.

Recognition of genotype–phenotype associations remains challenging for reasons that include expressivity, penetrance, multiple causal genes, modifier alleles, compound heterozygosity, locus heterogeneity, interacting polymorphisms of small effect, and digenic inheritance. For the vast

majority of monogenic disorders, even without known epigenetic influence (such as epilepsy, microcephaly, holoprosencephaly, hydrocephalus, craniosynostosis), definitive genotype–phenotype associations remain unknown.

Somatic mosaicism

We are all somatic postzygotic mosaics, either born that way or later as a consequence of spontaneously occurring mutations during our lifetimes. Using single-cell whole-genome sequencing of B lymphocytes, Zhang et al.⁸⁶⁶ found that the number of somatic mutations increases from <500 per cell in newborns to >3,000 per cell in centenarians. These dynamic changes involving other tissues as well, are likely to be associated with cancer and aging,⁸⁶⁷ and many disorders (Table 1.8).

Somatic mosaicism has been described in almost all autosomal dominant disorders. Tissue- or organ-specific segmental mosaicism explains certain overgrowth syndromes exemplified by the *PIK3CA*-associated developmental disorders that result in focal overgrowth, brain overgrowth, or capillary malformations with overgrowth.^{868–870}

A remarkable example of focal growth due to somatic mosaicism was the hyperinsulinism noted in an infant without any signs of the Beckwith–Wiedemann syndrome. Following removal of 80 percent of the pancreas, atypical histological features with enlarged hyperchromatic nuclei in islets were observed. Methylation analysis, a chromosomal microarray, and short tandem repeat markers led to a diagnosis of mosaic segmental paternal uniparental disomy

Table 1.8 Selected examples of monogenic disorders with established somatic mosaicism with DNA confirmation.

<i>Disorder</i>	<i>Gene</i>	<i>Reference</i>
Achondrogenesis type 2	<i>COL2A1</i>	885
Aicardi–Goutières syndrome	<i>TREX1</i>	886
Alport syndrome	<i>COL4A5</i>	887
Alzheimer disease, early-onset	<i>PS1</i>	888
Androgen insensitivity	<i>AR</i>	888
Atelosteogenesis type I	<i>FLNB</i>	889
Beta-propeller protein-associated neurodegeneration	<i>WDR45</i>	890
Campomelic dysplasia	<i>SOX9</i>	888
Catecholaminergic polymorphic ventricular tachycardia	<i>RYR2</i>	891
Centronuclear myopathy	<i>DNM2</i>	892
Charcot–Marie–Tooth disease type 1E	<i>PMP22</i>	893
CHARGE syndrome	<i>CHD7</i>	888
Chronic infantile neurologic, cutaneous, articular syndrome	<i>NLRP3</i>	894, 895
Chronic intestinal pseudo-obstruction	<i>ACTG2</i>	864
Cleidocranial dysplasia	<i>RUNX2</i>	888
<i>COL2A1</i> disorders	<i>COL2A1</i>	896
Congenital central hypoventilation syndrome	<i>PHOX2B</i>	897
Congenital contractural arachnodactyly	<i>FBN2</i>	888
Congenital disorder of glycosylation	<i>SLC35A2</i>	898
Congenital lipomatous overgrowth with vascular, epidermal and skeletal anomalies	<i>PIK3CA</i>	899
Cornelia de Lange syndrome	<i>CdLS</i>	900
Costello syndrome	<i>HRAS</i>	901
Creutzfeldt–Jakob disease	<i>PRNP</i>	902
Crouzon syndrome	<i>FGFR2</i>	903
Duchenne muscular dystrophy	<i>DMD</i>	888, 904
Ectrodactyly	<i>SHFM3</i>	905
EEC (ectrodactyly, ectodermal dysplasia, and orofacial clefts)	<i>P63</i>	888
Epidermal nevus, rhabdomyosarcoma, polycystic kidneys and growth restriction	<i>KRAS</i>	906
Epidermolysis bullosa simplex	<i>KRTS 5</i>	888
Epilepsy with mental retardation in females	<i>PCDH19</i>	907, 908
Facial infiltrating lipomatosis	<i>PIK3CA</i>	909
Familial polymicrogyria	<i>TUBA1A</i>	910
Fanconi anemia	<i>FANCD2</i>	911
Fascioscapular humeral muscular dystrophy	<i>D4Z4</i>	888
Freeman–Sheldon syndrome	<i>TNNI2</i>	912
Gardner syndrome	<i>APC</i>	913
Hemi-megalocephaly	<i>PIK3CA</i>	914
Hemophilia A and B	<i>F8</i> and <i>F9</i>	888
Hereditary hemorrhagic telangiectasia associated with pulmonary arterial hypertension	<i>ACVRL1</i>	915
Hereditary nonpolyposis colon cancer (Lynch syndrome)	<i>MLH1</i>	916
Hereditary spastic paraplegia	<i>SPG4</i>	888
Hunter syndrome	<i>IDS</i>	888
Hyper-IgE syndrome	<i>STAT3</i>	917
Hypocalcemia	<i>CASR</i>	888
Infantile spinal muscular atrophy	<i>SMN1</i>	888
Intellectual disability	<i>GATAD2B</i>	918
Isolated growth hormone deficiency	<i>GH1</i>	919

(Continued)

Table 1.8 (Continued)

<i>Disorder</i>	<i>Gene</i>	<i>Reference</i>
Juvenile myelomonocytic leukemia	<i>NRAS</i>	920
Keratinocyte epidermal nevi	<i>RAS</i>	921
Lesch–Nyhan syndrome	<i>HPRT1</i>	888
Li–Fraumeni syndrome	<i>TP53</i>	922
Loeys–Dietz syndrome	<i>TGFBR2</i>	888
Lone atrial fibrillation	<i>Cx43</i>	923
Maffuci syndrome	<i>IDH1</i>	924
Marfan syndrome	<i>FBN1</i>	888
McCune–Albright syndrome	<i>GNAS1</i>	888
Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria	<i>IDH1</i>	925
MYH9 disorders	<i>MYH9</i>	888
Myoclonic epilepsy	<i>SCN1A</i>	888
Myofibrillar myopathy	<i>BAG3</i>	926
Myotonic dystrophy type 2	<i>ZNF9</i>	927
Nail–patella syndrome	<i>LMX1B</i>	928
Neonatal diabetes	<i>KCNJ11</i>	888
Neurofibromatosis type 1 (generalized and segmental)	<i>NF1</i>	929
Neurofibromatosis type 2	<i>NF2</i>	930
Ohtahara syndrome	<i>STXBP1</i>	931
Ollier disease	<i>IDH1</i>	924
Ornithine transcarbamylase deficiency	<i>OTC</i>	888
Osteochondromas	<i>EXT</i>	932
Osteogenesis imperfecta II	<i>COL1A1, COL1A2</i>	888
Osteopathia striata	<i>AMER1</i>	933
Otopalatodigital syndrome	<i>FLNA</i>	888
Paroxysmal nocturnal hemoglobinuria	<i>PIGA</i>	888
Phenylketonuria	<i>PAH</i>	888
Pheochromocytomas and hemihyperplasia	UPD 11p15	934
Pitt–Hopkins syndrome	<i>TCF4</i>	935
Polycythemia–paraganglioma syndrome	<i>HIF2A</i>	936
Progeria	<i>LMNA</i>	937
Proteus syndrome	<i>AKT1</i>	938
Pseudohypoparathyroidism type 1a	<i>GNAS</i>	939
Pyruvate dehydrogenase complex disorder	<i>PDHA1</i>	940
Retinitis pigmentosa	<i>RPGR</i>	941
Retinoblastoma	<i>RB1</i>	942
Rett syndrome in males	<i>MECP2</i>	943
Rett syndrome, atypical	<i>CDKL5</i>	944
Rubinstein–Taybi syndrome	<i>CREBBP</i>	945, 946
Shprintzen–Goldberg syndrome	<i>SKI</i>	947
Sotos syndrome	<i>NSD1</i>	948
Spondyloperipheral dysplasia	<i>COL2A1</i>	949
Stickler syndrome	<i>COL2A1</i>	896
Subcortical band heterotopia and pachygyria	<i>LIS1</i>	950
Testicular dysgenesis syndrome	<i>SRY</i>	951
Thanatophoric dysplasia	<i>FGFR3</i>	888
Timothy syndrome type 1	<i>CACNA1C</i>	952
Townes–Brock syndrome	<i>SALL1</i>	888
Uniparental disomies	–	953

(Continued)

Table 1.8 (Continued)

<i>Disorder</i>	<i>Gene</i>	<i>Reference</i>
Von Hippel–Lindau	<i>VHL</i>	888
Wiskott–Aldrich syndrome	<i>WASP</i>	954
X-linked anhidrotic ectodermal dysplasia with immunodeficiency	<i>NEMO</i>	955
X-linked chronic granulomatous disease	<i>CYBB</i>	956
X-linked craniofrontonasal syndrome	<i>EFNB1</i>	957
X-linked creatine deficiency	<i>SLC6A8</i>	958
X-linked Danon disease	<i>LAMP2</i>	959
X-linked dilated cardiomyopathy	<i>DMD</i>	960
X-linked dyskeratosis congenita	<i>DKC1</i>	888
X-linked focal dermal hypoplasia	<i>PORCN</i>	961, 962
X-linked hypophosphatemia	<i>PHEX</i>	888
X-linked incontinentia pigmenti	<i>NEMO</i>	963
X-linked Menkes disease	<i>ATP7A</i>	964
X-linked mental retardation	<i>ARX</i>	888
X-linked osteopathia striata with cranial sclerosis and developmental delay	<i>WTX</i>	965
X-linked periventricular nodular heterotopia	<i>FLNA</i>	966
X-linked protoporphyria	<i>XLDPP</i>	967
X-linked subcortical band heterotopia	<i>DCX</i>	968

11p15.5-p15.1 in pancreatic tissue, but not in the infant's blood.⁸⁷¹

Brain somatic mutations occurring during cortical development may result in sporadic intractable epilepsy.⁸⁷² One study focused on the parents of children with Dravet syndrome due to *SCN1A* mutations.⁸⁷³ *SCN1A* mosaicism was found in 5.2 percent (30 out of 575) of families with affected children. Discovery of an oncogene (e.g. *RB1*) for retinoblastoma occurring in the absence of a family history, will inevitably lead to examination of the parents to determine recurrence risk. An analysis using targeted deep sequencing of the parents of 124 offspring with bilateral retinoblastoma revealed only one parent with somatic mosaicism for the deleterious *RB1* mutation, a 0.4 percent risk of recurrence.⁸⁷⁴

Over 700 genes are linked to neurodevelopmental disorders, some with epilepsy. Discovery of a putative *de novo* mutation now invariably leads to genomic evaluation of both parents in a search for somatic mosaicism. Disorders in this category include intellectual disability, epileptic encephalopathies, cerebral cortical malformations, and autism spectrum disorders.^{875, 876}

In a study of 10,362 consecutive patients, over 1 in 200 were shown to have somatic mosaicism.⁸⁷⁷ In that study, mosaicism was detected for aneuploidy, ring or marker chromosomes, microdeletion/duplication copy number variations, exonic copy number variations, and unbalanced translocations. Examples include hypomelanosis of Ito, other syndromes with patchy pigmentary abnormalities of skin associated with intellectual disability, and some patients with asymmetric growth restriction.^{878, 879} Gonadal mosaicism (see Chapter 14) should be distinguished from somatic cell mosaicism in which there is also gonadal involvement. In such cases, the patient with somatic cell mosaicism is likely to have some signs, although possibly subtle, of the disorder in question, while those with gonadal mosaicism are not expected to show any signs of the disorder. Current methodologies for clinical and prenatal diagnosis invariably list detection of very low degrees of mosaicism in a caveat that accompanies the reports. Additional examples of somatic and gonadal mosaicism include autosomal dominant osteogenesis imperfecta,^{880, 881} Huntington disease,⁸⁸² and spinocerebellar ataxia type 2.⁸⁸³ Lessons from these and the other examples quoted

for gonadal mosaicism indicate a special need for caution in genetic counseling for disorders that appear to be sporadic (see Chapter 14).

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 gonadal mosaicism would likely yield risks considerably lower than these figures, such as 4–8 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 11 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 ten women with mosaic trisomy 18.⁸⁸⁴

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 or counselor 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, distress, doubt, anger, and denial surface rapidly. The compassionate physician or counselor 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. The language used should be clear and without jargon. Attention to a patient's cultural background and possible need for an interpreter is important. This is a communication not to be rushed but characterized by sensitivity and

empathy. Informing a couple with bad news about the fetus by telephone or email is unacceptable. Arrangements for a follow-up visit and support where needed is advisable. Ptacek and Eberhardt⁹⁶⁹ and others,⁹⁷⁰ 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 during pregnancy or about their infants.⁹⁷¹

Almost all couples would have reached this juncture through maternal serum screening, non-invasive prenatal testing, an ultrasound or MRI 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. More recently, prenatal diagnosis using whole-exome sequencing⁹⁷² has led to the diagnosis of unexpected genetic disorders, and in the process introduced ethical issues and challenging quandaries.^{973, 974} Commonly, an anxious patient insists on a prenatal study. Physicians are advised not to dissuade patients from prenatal diagnosis but rather to inform them about the risks of fetal loss balanced against the risk of fetal abnormality, distinctly different from recommendations for accepted indications. Given the low risks, prenatal diagnosis can be offered to all couples (see Chapter 9).

Recognition of a fetal abnormality by imaging, molecular, or cytogenetic study may reveal, for the first time, the genetic disorder in an affected asymptomatic parent. Robyr et al.⁹⁷⁵ described 20 such parents with disorders including spinal muscular atrophy, DiGeorge syndrome, osteogenesis imperfecta, arthrogryposis, and Noonan-like syndrome.

Frequently, second-trimester ultrasound studies reveal fetal abnormalities of uncertain etiology with a subsequent normal karyotype. A chromosomal microarray may enable a precise diagnosis in 6–8.1 percent^{976, 977} (see Chapter 13). In a 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 intellectual disability despite no definitive diagnosis. The child was born with holoprosencephaly with marked psychomotor delay. Diagnostic uncertainty must be shared with parents at risk. Uncertainty should not and cannot be suppressed for the patient's sake. Expressing uncertainty does not imply ignorance or incompetence. An honest accounting of the problems at hand, the offer of a second opinion, and an empathetic approach all go a long way in averting a catastrophic outcome and aggravating litigation. Moreover, responsibility shared is anxiety halved.

Decision making

The presence of both parents for the consultation concerning possible elective abortion for a fetal anomaly 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 50 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 or counselor must have thoroughly checked all the logistics and potential pitfalls before initiating this consultation. Errors have indeed occurred in the past.^{184, 185}

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 Chapters 9, 11, and 14), 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 11) or a microdeletion or microduplication (see Chapter 13) are key examples. VOUS, especially in a gene known to harbor pathogenic mutations, is unnerving. Where a VOUS is uninterpretable, decision making reverts to the fetal anomaly seen or biochemical abnormality observed. The sensitive counselor should offer a second opinion to anxious parents facing an uncertain prenatal diagnosis. The "complete 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, there are powerful disparate attitudes to abortion between the spouses as discussed earlier. 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 then 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. These appointments must not be rushed. It is important that the many variables influencing parental decisions about pregnancy termination be recognized.^{978, 979} 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. Personal experience with loss or bereavement is likely to influence the emotional guidance provided.⁹⁸⁰ Certainly there is a wealth of literature suggesting inadequate preparation for those who ultimately care for individuals facing bereavement or death.^{980, 981} An in-depth understanding of the disability that the affected child and parents could anticipate is of obvious importance. The principles and prerequisites for counseling discussed earlier apply fully in these circumstances and the fact that this is a parental decision, not a medical "recommendation," should not need reiteration.

Anticipatory counseling in these consultations has been characterized by in-depth discussions of two areas: first, all medical and scientific aspects of the prenatal diagnosis made (and discussed earlier), and second, recognition and vocalization of emotional responses and reference to experiences (preferably published) of other couples in like circumstances when it was helpful. These sessions have then included explorations concerning guilt, a possible feeling of stigma (because of abortion), anger, upset, family pressures, and how other couples have coped. All of this anticipatory counseling should be tintured with support and hope when possible.

It is important that the many variables influencing parental decisions about pregnancy termination when faced with a serious disability and/or life-threatening or limiting disorder or anomaly be recognized and understood.^{979, 982-985} Parents will automatically bring their moral and religious beliefs to bear on their decision making. So too will their experience of disability and what they had seen in families with affected children. A mother's age, prior periods of infertility, previous

miscarriages, a history of an elective abortion or fetal abnormality, all factor into their decisions. Fortunately, not common is the painful quandary of uncertainty concerning severity of the prenatally diagnosed genetic disorder. One example is the mildly affected mother with a 22q11.2 deletion informed about a conotruncal cardiac anomaly in her fetus and uncertain future intellectual disability, the risk for which approximates 30 percent, further compounded by up to 30 percent risk of developing schizophrenia in young adulthood, and autism/autism-spectrum disorders in about 20 percent.⁹⁸⁶⁻⁹⁹¹

Longing for and imagining becoming a parent anew or again may also have been bolstered by unexpected bonding that occurred when the mother saw fetal features and/or movements on obstetric ultrasound. A frequent expressed concern is the effect a disabled child would have on the family's other child or children. Worse still, would that child have the burden of caring for the affected sibling after the death of the parents. Would some stigma attach and eventually have an effect on a potential marriage mate for their child or children. Would they have to devote so much time and energy to the needs of a disabled child that it would result in relative neglect of their other children. To what degree, if any, would there be pain or suffering (including psychological) for the affected child.

Perhaps not surprising is the influence of their own parents and their belief in the couple's ability to parent a child with a serious disability. Economic issues also loom large, depending upon the pressures and circumstances of their lives. On occasion, there is an unwillingness to continue pregnancy when a partner has suffered from the same later onset disorder. Marital ambiguity about the abortion decision can dominate the process and destroy a relationship. Any argument should be relegated to the couple's home, with a request to return when a decision has been made.

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.⁹⁹² showed the long-range effects. 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.⁹⁹³ Marital discord in these circumstances has been noted previously.^{993,994} 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, irritability, and subsequent guilt and indifference (Table 1.9).⁹⁹² Women with secondary infertility and those younger than 21 years of age (or immature women) had the most prolonged emotional, physical, and social difficulties.⁹⁹² After a loss of a child, with or without an anomaly, between 10 and 25 percent of distressed parents have disturbed emotional stability and adverse mental and physical health effects.⁹⁹⁵ Anticipated

grief experienced by mothers, especially those faced with a third-trimester diagnosis of a lethal fetal abnormality, requires psychological help with preparedness. Empathy and sensitivity are critical at these intensely painful times and mature counseling and nonjudgmental support are vital to help parents cope.

Grief counseling becomes part of the consultation after elective termination, in which full recognition of bereavement is necessary (see Chapter 33). Compassion fatigue, characterized as feeling overwhelmed by experiencing patients' suffering,⁹⁹⁶ mainly in cancer genetic counseling, is not likely to be an issue in prenatal genetic counseling. The psychology of mourning has been thoroughly explored⁹⁹⁷⁻⁹⁹⁹ (see Chapter 33). Worden emphasized how important it is for a bereaved individual to complete each of four stages in the mourning process.⁹⁹⁸

Table 1.9 The frequency of emotions and somatic symptoms of 84 women and 68 men: overall and 24 months after terminating a pregnancy for fetal abnormality.

	Overall		24 months after termination	
	Women (%)	Men (%)	Women (%)	Men (%)
Feeling				
Sadness	95	85	60	47
Depression	79	47	12	6
Anger	78	33	27	7
Fear	77	37	46	17
Guilt	68	22	33	7
Failure	61	26	24	14
Shame	40	9	18	4
Vulnerability	35	0	18	0
Relief	30	32	16	16
Isolation	27	20	11	6
Numbness	23	0	0	0
Panic spells	20	0	5	0
Withdrawal	0	32	0	13
Left out	0	12	0	0
Somatic symptom				
Crying	82	50	22	5
Irritable	67	38	19	3
No concentration	57	41	7	1
Listlessness	56	17	2	0
Sleeplessness	47	19	2	1
Tiredness	42	21	6	3
Loss of appetite	31	10	0	0
Nightmares	24	7	5	0
Palpitations	17	-	6	0
Headaches	9	8	2	0

Source: White-van Mourik et al. 1992.⁹⁹² Rproduced with permission of John Wiley and Sons.

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 appropriate, is well recognized.^{1000, 1001} These authors have also called attention to the complex tasks of mourning for a woman who is faced with one abnormal twin when pregnancy reduction or birth might occur.

Notwithstanding anticipated loss and grief, Seller et al.,¹⁰⁰¹ reflecting our own experience, emphasized that many couples recover from the trauma of fetal loss “surprisingly quickly.” Insinuation of this reality is helpful to couples in consultations both before and after elective termination. Moreover, couples’ orientation toward the grieving process achieves an important balance when they gain sufficient insight into the long-term emotional, 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 appropriate when diagnosis of a disorder is possible. Carrier detection tests, however, need careful consideration 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.^{1002–1005} Fanos¹⁰⁰² emphasized that testing adolescents “may alter the achievement of developmental tasks, including seeking freedom from parental figures, establishment of personal identity, 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 developing an

emotional distance, recognized as the vulnerable child syndrome.¹⁰⁰⁶ Other aspects, including interference with the normal development of a child’s self-concept, introduce issues of survivor guilt or increase levels of anxiety already initiated by family illnesses or loss.¹⁰⁰⁶ Predictive testing of children for later manifesting neurodegenerative or other disorders would rarely be recommended, 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 prerequisites for genetic counseling discussed earlier apply equally in all these circumstances.¹⁰⁰⁷ Special attention should be focused on assuaging aspects of guilt and shame (see Chapter 33). Difficult as it may be for some physicians,^{1008, 1009} 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.¹⁸⁴

The rate of stillbirth in the United States in 2013 was 5.96/1,000 livebirths, occurring in 1 in 160 deliveries,¹⁰¹⁰ with about 23,600 cases ≥ 20 weeks of gestation. For twin pregnancies, the rate is about 2.5 times higher. Chromosomal abnormalities occur in 6–13 percent of stillbirths,^{1011–1013} but is greater than 20 percent in those with malformations. The risk of recurrence following unexplained stillbirth is between 2.5 and 4.18 percent.¹⁰¹⁰ In comparison, stillbirth rates in 2010–2016 in Pakistan were 56.9/1,000 births, 25.3/1,000 in India, 21.3/1,000 in Zambia and Kenya, and 19.9/1,000 in Guatemala.¹⁰¹⁴ Using whole-exome sequencing in 246 stillbirths, 15 (6.1 percent) had a molecular diagnosis in one report.¹⁰¹⁵ The genetic cause of most stillbirths remains unknown. Women with a history of stillbirth have an increased risk of

long-term chronic kidney disease and end-stage renal disease.¹⁰¹⁶

Despite anger, grief, and the gamut of expected emotions, the attending physician (not an inexperienced 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 tissue, and by subsequent DNA studies (see Chapter 10) including whole-exome sequencing (see Chapter 14). In circumstances in which parents steadfastly withhold permission for autopsy, radiographs, MRI, computed tomography, and needle liver biopsy for DNA could provide important information when a precise diagnosis has yet to be made.^{1017–1019} In most stillbirths, the cause(s) is not determined. In the long QT syndrome, which has rarely been diagnosed *in utero*,¹⁰²⁰ and which we have diagnosed in the first month of life,¹⁰²¹ affected mothers have an increased risk of fetal death, not only due to an arrhythmia, but also to putative placental or myometrial dysfunction.¹⁰²² Moreover, stillbirth at ≥ 23 weeks of gestation in these mothers is associated with an increased risk of severe maternal morbidity, especially among those with comorbidities.¹⁰²³ MRI could provide a useful acceptable alternative when fetal anomalies are expected.¹⁰¹⁷ 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 1.3) to secure a definitive diagnosis, thereby laying the foundation for providing accurate recurrence risks and future precise prenatal diagnosis. In the emotional chaos that invariably follows stillbirth, necessary actions may be forgotten. An action checklist (Box 1.4) serves to orient the process. 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 intellectual disability).

Psychologic support is important for couples who have lost an offspring from any cause – a situation compounded by fetal or congenital

abnormality.^{1024, 1025} 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 reduction¹⁰²⁶ (see Chapter 32), 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.¹⁰²⁷ Considerable psychologic skill must be marshaled by physicians if meaningful care and support are to be provided.¹⁰²⁸

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.¹⁰²⁹ 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.

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, will 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

Box 1.3 Elements of a stillbirth evaluation

Key components		Details	Comments
Patient history	Family history	• Recurrent spontaneous abortions • Stillbirths • Monogenic disorder(s) • Congenital malformations or syndromes • Chromosomal disorders • Ethnicity • Consanguinity • Neurodevelopmental delay	
	Maternal history:	• Previous venous thromboembolism • Diabetes mellitus • Chronic hypertension • Thrombophilia • Systemic lupus erythematosus • Autoimmune disease • Epilepsy • Severe anemia • Heart disease • Tobacco, alcohol, drug or medication use	
	Obstetric history:	• Recurrent miscarriages • Previous child with congenital malformation, syndrome or genetic disorder • Previous child with intrauterine growth restriction • Previous gestational hypertension or preeclampsia • Previous gestational diabetes mellitus • Previous placental abruption • Previous fetal demise	
	Current pregnancy:	• Maternal age • Paternal age • Gestational age at stillbirth • Medical conditions complicating pregnancy • Cholestasis • Pregnancy weight gain and body mass index • Complications of multifetal gestation, such as twin–twin transfusion syndrome, twin reversed arterial perfusion syndrome, and discordant growth • Placental abruption • Abdominal trauma • Preterm labor or rupture of membranes • Gestational age at onset of prenatal care • Intrauterine growth restriction • Abnormalities seen on an ultrasound image • Infections or chorioamnionitis	

Box 1.3 Continued

Key components	Details	Comments
Fetal autopsy	If patient declines, external evaluation by a trained perinatal pathologist. Other options include photographs, X-ray imaging, ultrasonography, magnetic resonance imaging, and sampling of tissues, such as blood or skin. Freeze tissue for future DNA study If macerated tissue, request permission for needle biopsy of liver for DNA study	Provides important information in approximately 30% of cases
Placental examination	Includes evaluation for signs of viral or bacterial infection. Discuss available tests with pathologist	Provides additional information in 30% of cases. Infection is more common in preterm stillbirth (19 vs. 2% at term)
Fetal karyotype/microarray	Amniocentesis before delivery provides the greatest yield. Umbilical cord proximal to placenta if amniocentesis declined Whole-exome or whole-genome sequencing/from frozen tissue or needle biopsy	Abnormalities found in approximately 8% of cases
Maternal evaluation at time of demise	- Fetal–maternal hemorrhage screen: Kleihauer–Betke test or flow cytometry for fetal cells in maternal circulation - Syphilis - Lupus anticoagulant - Anticardiolipin antibodies β_2 glycoprotein antibodies	Routine testing for inherited thrombophilias is not recommended. Consider in cases with a personal or family history of thromboembolic disease
In selected cases	Indirect Coombs Glucose screening (oral glucose tolerance test, hemoglobin A_{1C}) Toxicology screen	If not performed previously in pregnancy In the large-for-gestational-age baby In cases of placental abruption or when drug use is suspected

Source: Modified from American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine.¹⁰¹⁰

guilt¹⁰³⁰ 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 (see Box 1.4 checklist) include ensuring that the child be given a name and, in the case of the death of an abnormal 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.^{1000, 1001, 1031} 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,¹⁰³² a lock of hair, the baby's name band

Box 1.4 Action checklist following stillbirth

DATE OF BIRTH _____		NURSE IN CHARGE _____	
ATTENDING PHYSICIAN _____		PHONE# _____	
NAME OF CLERGY _____		PHONE# _____	

☐ FAMILY PRIVACY SECURED	☐ CARD ON DOOR	☐ PHYSICIAN CALLED	☐ FAMILY MET WITH PHYSICIAN
---	---------------------------------------	---	--

PARENTAL OPTIONS	PARENTAL DECISIONS	COMMENTS
Infant viewing	Yes ☐ No ☐	Name: _____
Infant holding	Yes ☐ No ☐	
Naming of infant	Yes ☐ No ☐	
Photographs	Yes ☐ No ☐	
Autopsy permission (signature)	Yes ☐ No ☐	
Genetic studies	Yes ☐ No ☐ N/A ☐	
Burial	Yes ☐ No ☐	
Cremation	Yes ☐ No ☐	
Family members allowed to visit/hold	Yes ☐ No ☐	
Religious rites	Yes ☐ No ☐	
Lock of baby's hair	Yes ☐ ☐	No
Tissue for DNA Study obtained and frozen	Yes ☐ ☐	No

BABY: Weight _____ Length _____	
Bathed ☐	Dressed ☐ Footprints ☐ Photos ☐ Parents viewed ☐
Death certificate ☐	
MRI of brain ☐	
(if autopsy decline)	

HOSPITAL DISCHARGE: Memory envelop given (baby items)	Yes ☐ No ☐
Grief packed with references given	Yes ☐ No ☐
Grief counseling referral	Yes ☐ No ☐ Declined
Genetic counseling referral	Yes ☐ No ☐
Follow up consultation (and to discuss autopsy results)	Yes ☐ No ☐

Nurse Completing Form: Name _____ Signature _____ Date _____

or clothing.^{1027, 1028} 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.¹⁰³³ 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.¹⁰³⁴ Follow-up contact after pregnancy has ended includes calls, condolences cards,

and recommendation for further bereavement counseling. This appointment will also enable further discussion about causation, future risks, and options, as well as coping strategies. Parents confirm that anxiety blocks the assimilation and comprehension of facts and recommendations. Vocalizing the realization is helpful while repeating information provided previously. 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.¹⁰³⁵ Similarly, parents should be fully informed about the consequences of having a “replacement child” very soon after their loss.^{1036, 1037} 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. 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

Genetic counseling is a communication process that aims to achieve as complete an understanding by the counselee(s) as possible, thereby enabling nondirective rational decision making. Studies examining the efficacy of genetic counseling in various settings and using different modalities (e.g. telephone versus in-person) and self-efficacy of genetic counselors and students continue.^{1038–1041} Anxiety, distress, uncertainty, guilt, decisional conflict, and a deficient knowledge of science, together with difficulty in understanding a balance of risks, influence the ultimate efficacy of genetic counseling. 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 this be construed as a failure in genetic counseling? Would continued pregnancy with an anencephalic fetus after genetic counseling be considered a failure of genetic counseling?

Clarke et al.¹⁰⁴² considered three prime facets that could possibly evaluate the efficacy of genetic counseling: (i) recall of risk figures and other relevant information by the counselee(s); (ii) the effect on reproductive planning; and (iii) 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. A questionnaire study from the Netherlands questioned 1,479 counselees about their experience of genetic counseling. Questionnaires were administered before and after counseling and for the third time after results were disclosed.¹⁰⁴³ They noted improvement in the level of empowerment, personal control, and anxiety after the whole process.

Evaluation of the efficacy of genetic counseling should not only include the degree of knowledge acquired (including the retention of the counselee(s) with regard to the indicated probabilities), the rationality of decision making (especially concerning further reproduction), but also the potential personal influences outlined in the Netherlands' study. Frequent contraceptive failures in high-risk families highlight the need for very explicit counseling. A further measure of efficacy is the frequency and accuracy of a proband's communication of important risk information to close relatives. It appears that communication of test results may be selective, with male relatives and parents less likely to be informed.¹⁰⁴⁴

Important points made by Emery et al.¹⁰⁴⁵ 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 studies¹⁰⁴⁵⁻¹⁰⁴⁸ document the failure of comprehension by the counselee(s). Such failures are increasingly likely with genome sequencing resulting in secondary findings and revelations of unknown significance.¹⁰⁴⁸ The reports do not reflect objective measures of the skill or adequacy of genetic counseling and the real value of a summary letter to the patient of the information provided after the counseling visit. Sorenson et al.¹⁰⁴⁹ 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 Down syndrome child, Swerts¹⁰⁵⁰ 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.

In considering the effectiveness of genetic counseling, Sorenson et al.¹⁰⁴⁹ 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 socio-medical concerns and questions was markedly worse, however. And, reproductively, 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 Kessler¹⁰⁵¹ concluded that published studies on reproductive outcome after genetic counseling revealed no major impact of counseling. Moreover, decisions made before counseling largely determined reproduction after counseling.

A study of patients' expectations of genetic counseling revealed that the majority had their

expectations fulfilled, especially with perceived personal control.¹⁰⁵² When patients' expectations for reassurance and advice were met, they were subsequently less concerned and had less anxiety when compared with such expectations that were not fulfilled, similar to the Netherlands report.¹⁰⁴³

The limited efficacy of genetic counseling revealed in the study by Sorenson et al.¹⁰⁴⁹ reflects the consequences of multiple factors, not the least of which were a poor lay understanding of science.¹⁰³⁶ 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 (one translated into nine languages) over 50 years.^{184, 331, 335, 337, 338, 1053} In addition to public education and its concomitant effect of educating physicians generally, formal specialist certification in the United States, Canada, the United Kingdom, and elsewhere, acceptance of clinical genetics as a specialty, and degree programs for genetic counselors certified by the National Board of Genetic Counselors, has undoubtedly improved the efficacy of genetic counseling. There remains, however, a pressing need to better educate practicing physicians about the "new genetics"^{184, 185, 199, 1054, 1055} in this, the golden era of human genetics.

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