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# Genetic Counseling: Preconception, Prenatal, and Perinatal

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Clinical cognizance of the veritable explosion in the knowledge of the human genome is more vital than ever. Precise identification of genes and their pathogenic mutations has injected an urgency among care providers to become aware of the rapidly escalating opportunities parents have to avoid having offspring with serious or fatal genetic disorders. For any health or life-threatening genetic disorder, prenatal diagnosis (or even preimplantation genetic diagnosis) has become a viable option, and should be offered. Even adult-onset malignant, neurodegenerative, cardiovascular and other serious systemic disorders now feature in the indications, not only for presymptomatic or predictive diagnosis, but for prenatal diagnosis.

Given the wide scope of clinical genetics in all medical specialties, the need for clinicians to confer and refer has never been greater. The coalescence of advances in molecular genetics, fetal imaging and noninvasive prenatal screening, has culminated in the provision of new opportunities for the prevention or avoidance of genetic disorders and congenital malformations.

In context, women at risk for having progeny with abnormalities expect to be informed about their odds 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.

## **Incidence, prevalence and burden of genetic disorders and congenital malformations**

An estimated 7.9 million infants worldwide are born each year with a major congenital malformation.<sup>1</sup> Over 7,000 rare genetic disorders are known,<sup>2-7</sup> with about 1 in 12 individuals affected, aware or unaware. More than 3,412 genes with phenotype-causing mutations have been identified.<sup>4</sup> Severe intellectual disability is considered to be largely genetic in origin<sup>8,9</sup> and is estimated to occur in 0.5 percent of newborns.<sup>10</sup> 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.<sup>11</sup> In the United States in 2010, congenital malformations, deformations and chromosomal abnormalities accounted for the most infant deaths – 5,107 (20.8 percent) out of 24,586 – in any category of causation.<sup>12</sup> Many factors influence efforts to accurately determine the incidence or prevalence of congenital anomalies or genetic disorders. Box 1.1 encompasses the

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majority of known etiologic categories, discussed below, which help explain sometimes striking differences among major studies. It is almost impossible to account for all these potentially confounding factors in a study and rarely has any one study come close.

### Incidence and prevalence

Estimates of aneuploidy in oocytes and sperm reach 25 percent and 3–4 percent, respectively.<sup>13,14</sup> Not surprisingly, then, about one in 13 conceptions results in a chromosomally abnormal conceptus,<sup>15</sup> while about 50 percent of first-trimester spontaneous abortions are associated with chromosomal anomalies.<sup>16</sup> A study of blastocysts have 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.<sup>17</sup> Similar results have been reported by others.<sup>18</sup> 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. Between 5.6 and 11.5 percent of stillbirths and neonatal deaths have chromosomal defects.<sup>19</sup>

Congenital malformations with obvious structural defects are found in about 2 percent of all births.<sup>20</sup> This was the figure in Spain among 710,815 livebirths,<sup>21</sup> with 2.25 percent in Liberia,<sup>22</sup> 2.03 percent in India,<sup>23</sup> and 2.53 percent among newborn males in Norway.<sup>24</sup> 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.<sup>25</sup> 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  $\geq 50$  percent greater prevalence for seven congenital malformations (anotia or microtia, cleft lip, trisomy 18, encephalocele, limb-reduction defect).<sup>26</sup> Factors that had an impact on the incidence/prevalence of congenital malformations are discussed below.

Over 22,700 entries for genetic disorders and traits have been catalogued.<sup>4</sup> Estimates based on 1 million consecutive *livebirths* in Canada suggested a monogenic disease in 3.6 in 1,000, con-

**Table 1.1** The frequencies of genetic disorders in 1,169,873 births, 1952–1983<sup>27</sup>

| Category  | Rate per million livebirths | Total births (%)  |
|---|-----------------------------|-------------------|
| <b>A</b>  |                             |                   |
| 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 <sup>a</sup> |
| <b>B</b>  |                             |                   |
| All congenital anomalies 740–759 <sup>b</sup>                               | 52,808.2                    | 5.28              |
| Congenital anomalies with genetic etiology (included in section A)          | 26,584.2                    | 2.66              |
| <b>C</b>  |                             |                   |
| Disorders in section A plus those congenital anomalies not already included | 79,399.3                    | 7.94              |

Notes: <sup>a</sup>Sum is not exact owing to rounding. <sup>b</sup>International Classification of Disease numbers.

sisting 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).<sup>27</sup> Polygenic disorders occurred at a rate of 46.4 in 1,000 (Table 1.1).

At least 3–4 percent of all births are associated with a major congenital defect, 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.<sup>28,29</sup> If all congenital defects are considered, Baird et al.<sup>27</sup> 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.<sup>30</sup> 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.<sup>31</sup> Mitral valve prolapse affects 2–3 percent of the general population, involving more than 176 million people worldwide.<sup>32</sup> A Canadian study of 107,559 patients with congenital heart disease reported a prevalence of 8.21 per 1,000

**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                                | Maternal folic acid supplementation                      |
| Case selection, bias and ascertainment   | Maternal grandmother's age                               |
| Consanguinity  | Maternal obesity   |
| Definitions of major and minor congenital anomalies  | Maternal serum screening for chromosome abnormalities    |
| Diagnostic DNA analysis  | Maternal smoking   |
| Economic level in developed or developing world  | Maternal specific susceptibility genes                   |
| Family history   | Maternal use of medication                               |
| Frequency, inclusion and exclusion of stillbirths, fetal deaths and elective pregnancy termination | Multiple pregnancy rate                                  |
| Frequency of certain infectious diseases   | Necropsy   |
| History of recurrent spontaneous abortion  | Noninvasive prenatal screening                           |
| <i>In vitro</i> fertilization  | Parent with a congenital abnormality or genetic disorder |
| Incidence and severity of prematurity  | Paternal age   |
| Infertility  | Previous affected child                                  |
| Intracytoplasmic sperm injection   | Previous maternal immunization/vaccination               |
| Later manifestation or onset of disorder   | Season of the year                                       |
| Maternal age   | Training and expertise in examination of newborns        |
| Maternal alcohol abuse   | Use of chromosomal analysis                              |
| Maternal diabetes and gestational diabetes   | Use of chromosomal microarray                            |
| Maternal diet  | Use of whole exome sequencing                            |
| Maternal epilepsy, lupus erythematosus and other illnesses   | Use of whole genome sequencing                           |
| Maternal fever or use of hot tub in the first 6 weeks of pregnancy                                 | Use of death certificates                                |
|  | Use of registry data                                     |

livebirths, rising to an overall prevalence of 13.11 per 1,000 in adults.<sup>33</sup> 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 in the fetus are shown in Box 1.1. A metropolitan Atlanta study (1998–2005) showed an overall prevalence of 81.4 per 10,000 for congenital heart disease among 398,140 livebirths,<sup>35</sup> similar to a Belgium study of 111,225 live and stillborn infants  $\geq 26$  weeks of gestation with an incidence of 0.83 percent, chromosome abnormalities excluded.<sup>36</sup> These numbers lead to a significant genetic disease burden and have accounted for 28–40 percent of hospital admissions in North America, Canada and England.<sup>37,38</sup> Notwithstanding their frequency,

the causes of about 60 percent of congenital malformations remain obscure.<sup>39,40</sup>

The availability of prenatal diagnosis and maternal serum screening for neural tube defects (NTDs) and Down syndrome (DS) has also affected the birth frequency of these two most common congenital defects. One French study of the impact of prenatal diagnosis over a 21-year period (1979–99) in a well defined population showed a drop of 80 percent in the birth prevalence of DS.<sup>41</sup> A later report from the Paris Registry of Congenital Anomalies (2001–2005) noted a “fairly stable prevalence of DS (7.1 per 10,000 livebirths) over time.”<sup>42</sup> Multiple studies have recorded a reduction in the birth prevalence of NTDs following folic acid supplementation and/or fortification of cereal grain products with folic acid<sup>43–47</sup> (see Chapter 3).

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However, in Ireland there appears to be an increasing incidence of NTDs, almost certainly due to a lack of adherence to periconceptional folic acid supplementation.<sup>48</sup> A Scottish study aimed to assess the impact of prenatal diagnosis on the prevalence of DS from 1980 to 1996. Both births and pregnancy terminations were included. Pregnancy terminations for DS rose from 29 percent to about 60 percent.<sup>49</sup> In contrast, the prevalence of DS noted by the Dutch Paediatric Surveillance Unit in 2003 was 16 per 10,000 livebirths, exceeding earlier reports and thought to reflect an older maternal age cohort.<sup>50</sup> In the United States, a DS prevalence rate of 13 per 10,000 was found in metropolitan Atlanta (1979–2003).<sup>51</sup>

Folic acid supplementation, via tablet or food fortification, is now well known to reduce the frequency of NTDs by up to 70 percent.<sup>52,53</sup> 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.<sup>54</sup>

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.<sup>55</sup> 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 birth weight infants. The mean gestational age overall was 28 weeks and the mean birth weight was 1,007 g.<sup>56</sup> 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).<sup>57</sup> 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 key study of homozygosity in consanguineous patients with an autosomal recessive disease showed that, on average, 11 percent of their genomes were homozygous.<sup>58</sup> Each affected

individual had 20 homozygous segments exceeding 3 cM.

Incidence/prevalence rates of congenital defects are directly influenced by when and how diagnoses are made. Highlighting the importance of how early a diagnosis is made after birth, the use of echocardiography, and the stratification of severity of congenital heart defects, Hoffman and Kaplan<sup>59</sup> clarified how different studies reported the incidence of congenital heart defects varying from 4 in 1,000 to 50 in 1,000 livebirths. They reported an incidence of moderate and severe forms of congenital heart disease in about 6 in 1,000 livebirths, a figure that would rise to at least 19 in 1,000 livebirths if the potentially serious bicuspid aortic valve is included. They noted that if all forms of congenital heart disease (including tiny muscular ventricular septal defects) are considered, the incidence increases to 75 in 1,000 livebirths.

The frequency of congenital defects is also influenced by the presence or absence of such defects in at least one parent. A Norwegian Medical Birth Registry population-based cohort study of 486,207 males recorded that 12,292 (2.53 percent) had been born with a congenital defect.<sup>24</sup> 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 whites (1.44 percent) was higher than in non-Hispanic blacks (1.28 percent).<sup>60</sup> However, racial/ethnic disparities clearly exist for different types of congenital defects.<sup>61</sup>

Maternal obesity is associated with an increased risk of congenital malformations.<sup>62–71</sup> The greater the maternal body mass index (BMI), the higher the risk, especially for congenital heart defects,<sup>67,68,70</sup> with significant odds ratios between 2.06–3.5. In a population-based case-control study, excluding women with pre-existing diabetes, Watkins et al.<sup>72</sup> 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). Our own<sup>73,74</sup> and other studies,<sup>75</sup> have pointed in the direction of a prediabetic state or gestational diabetes as the

biologic mechanism accounting for the increased rate of congenital anomalies in the offspring of obese women. In this context, preconception bariatric surgery seems not to reduce the risks of congenital anomalies.<sup>69</sup> It appears that folic acid supplementation attenuates but does not eliminate the risk of spina bifida when associated with diabetes mellitus<sup>76</sup> or obesity.<sup>77</sup> In contrast, markedly underweight women reportedly have a 3.2-fold increased risk of having offspring with gastroschisis,<sup>77</sup> in all likelihood due to smoking.<sup>78</sup> 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.<sup>78</sup> 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.<sup>79</sup>

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.<sup>80</sup> A French study of 129 infants with congenital hypothyroidism noted that 15.5 percent had associated congenital anomalies.<sup>81</sup> Nine of the infants had congenital heart defects (6.9 percent).

Women with epilepsy who are taking anticonvulsant medications have an increased risk of having offspring with congenital malformations, noted in one study as 2.7-fold greater than those without epilepsy.<sup>82</sup> The possible reduction of other congenital malformations as a result of folic acid supplementation remains to be proved (see Chapter 3).

### **Congenital malformations and infant morbidity and mortality**

The leading cause of infant death in the United States in 2011 was congenital malformations, deformations and chromosomal abnormalities, accounting for 20.9 percent of all infant deaths.<sup>83</sup> Survival is clearly dependent on the severity or lethality of the congenital defect. The Centers for Disease Control and Prevention assessed mortality rates for infants born with trisomy 13 and trisomy 18. 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.<sup>84</sup> 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.<sup>85</sup> A Scottish study focused 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), neural tube defects (72 percent), respiratory system anomalies (74 percent), congenital heart disease (75 percent), nervous system anomalies (77 percent) and Down syndrome (DS) (84 percent).<sup>86</sup> The survival rate among males with congenital defects was 84 percent, compared with 97 percent in those born unaffected.<sup>24</sup> Liu et al.<sup>87</sup> examined temporal changes in fetal and infant deaths caused by congenital malformations in Canada, England, Wales, and the United States. They concluded that the major factor responsible for the accelerated decline in infant deaths was prenatal diagnosis and elective abortion of fetuses with abnormalities. Given the frequency of DS, a more detailed discussion follows.

### **Down syndrome**

The special problems and associated defects in DS are well known, as is the increasing life expectancy. Studies from Japan,<sup>88</sup> Denmark,<sup>89</sup> England,<sup>90</sup> Australia,<sup>91</sup> and Canada<sup>92,93</sup> highlight the increased life expectancy with DS. Baird and Sadovnick<sup>92</sup> reported a large study of 1,610 individuals with DS 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 DS (Table 1.2) and for the general population.<sup>94</sup> Their estimates show that 44.4 percent and 13.6 percent of liveborn individuals with DS will survive to 60 and 68 years, respectively, compared with 86.4 percent and 78.4 percent of the general population. In another report,<sup>95</sup> these authors have analyzed the causes of death in DS, highlighting congenital defects and cardiovascular and respiratory illnesses as the most important. A UK population prevalence study noted a median life expectancy of 58 years in 2011.<sup>96</sup>

Additional studies of mortality rates in individuals with DS revealed that those up to about 35 years of age were little different from others with intellectual disability. Thereafter, however, mortality rates in DS doubled every 6.4 years, compared with 9.6



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**Table 1.2** Life expectancy with Down syndrome, between 1908–1981, to age 68 years (excerpted from<sup>92</sup>)

| Age | Total | Survival at start of age interval (%) |
|-----|-------|---------------------------------------|
| 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                                 |

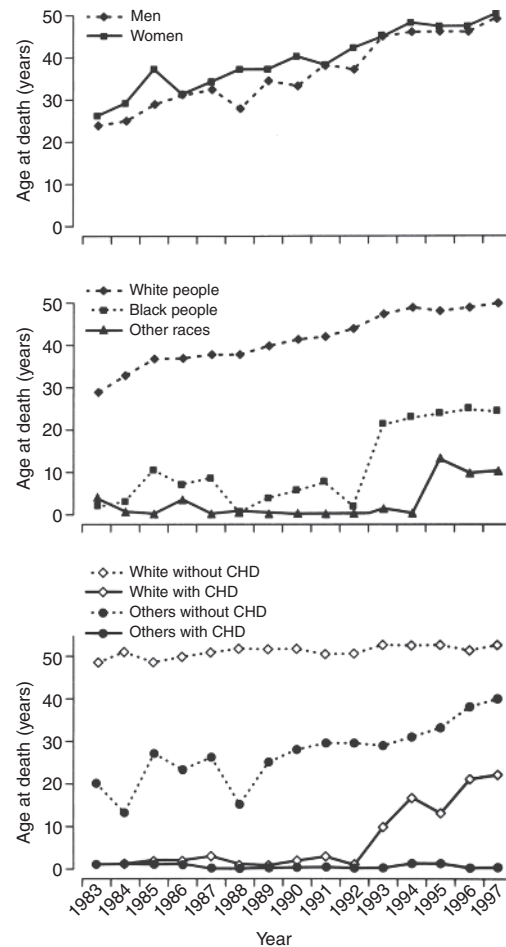
Source: Baird and Sadovnick 1989.<sup>94</sup>

years for other intellectually disabled individuals.<sup>95</sup> Life tables constructed by these authors indicated a life expectancy of 55 years for a 1-year-old patient with DS and mild/moderate developmental delay and a life expectancy of 43 years for a 1-year-old patient with DS more profoundly affected.

A study from the Centers for Disease Control and Prevention focused on the death certificates of 17,897 individuals with DS born between 1983 and 1997.<sup>97</sup> These authors reported that the median age at death for those with DS increased from 25 years in 1983 to 49 years in 1997 (Figure 1.1).

A 2009 Australian study found an overall survival figure for DS of 90 percent to at least 5 years of age.<sup>98</sup> The known comorbidity of DS<sup>98–115</sup> and earlier onset Alzheimer<sup>99</sup> disease casts a longer shadow. In DS individuals over 40 years of age, increasing neuropsychological dysfunction and loss of adaptive skills have been noted.<sup>115</sup> Between 50–70 percent of DS patients develop Alzheimer disease by 60 years of age,<sup>105</sup> and up to 84 percent of those with dementia develop seizures.<sup>102</sup> A French study between 1979 and 1999 found a sixfold decreased risk of death from urological cancer in those with DS.<sup>112</sup>

Table 1.3 reflects the common associated defects that occur in DS,<sup>98–115</sup> and the more common complications that can be anticipated, monitored, prevented, and treated.<sup>116,117</sup> A EUROCAT population-based register study between 2000 and 2010 in 12 countries analyzed 7,044 live births and fetal deaths with DS. This report<sup>116</sup> noted that 43.6 percent of *births* with DS had congenital heart disease while 15 percent had another congen-



**Figure 1.1** 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.<sup>97</sup> Reproduced with permission of Elsevier.

ital malformation. The National Society of Genetic Counselors published valuable guidelines for communicating both prenatal and postnatal diagnoses of DS.<sup>104</sup> A US population prevalence study estimated, in 2008, that there were 250,700 with DS.<sup>118</sup>

### 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

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**Table 1.3** Defects and complications associated with Down syndrome

| <i>Defect or complication</i>                    | <i>Prevalence (%)</i>               |
|--|-------------------------------------|
| <i>Neurologic</i>                                |                                     |
| Intellectual disability                          | 100                                 |
| Hypotonia  | 100                                 |
| Alzheimer disease and dementia                   | > 50                                |
| Obstructive sleep apnea                          | 30–57                               |
| Behavior problems                                | 18–38                               |
| Hearing impairment                               | 12–78                               |
| Epilepsy   | 12–46                               |
| Psychiatric disorders                            | 11–30                               |
| <i>Heart</i>                                     |                                     |
| Mitral valve prolapse                            | 57                                  |
| Congenital heart disease                         | ±50                                 |
| Aortic valve regurgitation                       | 17                                  |
| <i>Immune system</i>                             |                                     |
| Susceptibility to infection                      | 100                                 |
| Hearing impairment                               | 12–78                               |
| Juvenile rheumatoid-like arthritis               | 1.2                                 |
| <i>Gastrointestinal</i>                          |                                     |
| Congenital defects of the gastrointestinal tract | 4–10                                |
| Celiac disease                                   | 2–20                                |
| <i>Endocrine/metabolic</i>                       |                                     |
| Obesity  | 30–35                               |
| Hypothyroidism                                   | 7–50                                |
| Diabetes mellitus                                | 1.4–10.6                            |
| Hyperthyroidism                                  | 1–3                                 |
| <i>Ophthalmologic</i>                            |                                     |
| Eye disorders <sup>a</sup>                       | 80                                  |
| Cataract   | 17–29                               |
| Keratoconus                                      | 8–10                                |
| <i>Hematologic/oncologic</i>                     |                                     |
| Leukemia   | > 20-fold excess                    |
| Testicular cancer                                | Standardized incidence ratio of 4.8 |
| Transient myeloproliferative disorder            | 10                                  |
| Retroperitoneal teratoma                         | Increased                           |
| <i>Musculoskeletal</i>                           |                                     |
| Atlantoaxial instability                         | 10–30                               |
| Osteoarthritis                                   | 8–28                                |
| Atlantoaxial subluxation                         | 1–2                                 |
| <i>Dental</i>                                    |                                     |
| Orthodontic problems                             | ±all                                |
| Periodontal disease                              | ±all                                |

**Table 1.3** (Continued)

| <i>Defect or complication</i> | <i>Prevalence (%)</i> |
|-------------------------------|-----------------------|
| <i>Dermatologic</i>           |                       |
| Dermatologic disorders        | 1.9–39.2              |
| <i>Urinary tract</i>          |                       |
| Urinary tract anomalies       | 3.2                   |

Notes: <sup>a</sup>Includes strabismus, nystagmus, refractive errors, glaucoma, and lens opacities.

Data from references.<sup>98, 99–103, 105–108</sup>

high.<sup>119</sup> 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 diagnosis (see Chapter 10) does, however, provide another 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 a positive result on a noninvasive prenatal screen – see Chapter 11 – or advanced maternal age), the well informed obstetrician should be able to provide the necessary information.<sup>120, 121</sup> 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.<sup>122</sup> Neither a questionnaire in the physician's office nor limited consultation time is likely to reveal many of these disorders.

### **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 Kessler<sup>123</sup> 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 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.<sup>124</sup> This study focused on a review of 12,093 "genetic events" involving potentially avoidable cases of DS, NTDs, cystic fibrosis,  $\beta$ -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.<sup>125</sup> Other physicians, too, have been found lacking in the necessary knowledge and communication skills.<sup>126-129</sup> Given the importance of genetic considerations in all specialties, these problems can be anticipated to become more problematic, more especially in family practice.<sup>130</sup>

After the prenatal diagnosis of a serious genetic disorder, the physician should be able to inform the family fully about the anticipated burden and to detail the effects of this burden on an affected child, the family, other siblings, the family economics and marital relations, along with any other pros and cons of continuing pregnancy. The reality of early Alzheimer disease and other comorbidities in DS



and the care requirements that may devolve on the siblings should not be omitted from the discussion. Exact details should also be known about the risks of elective abortion (see Chapter 29).

### **Expertise in genetic counseling**

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

Gordis et al.<sup>131</sup> 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.<sup>132</sup> 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.<sup>133-135</sup>

### **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,<sup>136</sup> as have others.<sup>137,138</sup>

Simple language, an adequate allocation of time, and care and sensitivity are keys to successful genetic counseling. Technical jargon, used with distressing frequency,<sup>139</sup> is avoided only through conscious effort. How an issue requiring a decision is framed,<sup>140</sup> and the nature of the language used,<sup>141</sup> may influence the patient's choice.<sup>142</sup> 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)<sup>143</sup> are choices a counselor must make. Clearly, the simpler, the better and the more likely the information is understood. Patients' perceptions of risk not infrequently differ markedly from those of the counselor, a realization that should elicit no comment. An essential ingredient of the counseling process is time. The busy practitioner can hardly expect to offer genetic counseling during a brief consultation. Distress and misunderstanding are invariable sequelae of such hastily delivered counseling.

### **Knowledge of ancillary needs**

For the couple at high risk of having a child with a serious genetic disorder, prenatal diagnosis is not the sole option. Even in situations in which a particular disease is diagnosable prenatally, it is important to be certain that other avenues are explored. Prospective parents who are known, for example, to be carriers of an autosomal recessive disorder may be unaware of the possibility of sperm or ovum donation, or may be unwilling to raise the question. This option may be viewed more favorably than prenatal diagnosis and elective abortion. Physicians should be certain that their patients are familiar

with all the aforementioned important options, as well as with adoption, vasectomy, tubal ligation, treatments of the mother and/or fetus during pregnancy, and other methods of assisted reproduction (e.g. intracytoplasmic sperm injection,<sup>144</sup> epididymal sperm aspiration,<sup>145</sup> and preimplantation genetic diagnosis) (see Chapters 5 and 10).

### Empathy

Empathy embodies the ability to not only understand the perspectives and emotions of others but to communicate that understanding.<sup>146</sup> 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 anxiety<sup>147</sup> 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.<sup>148</sup>

Beyond the qualifications and factual knowledge of the counselor is the person, who is key to

successful and effective counseling. Attitude, body language, warmth, manners, dress, tone of voice and personality are facets that seriously influence the credibility and acceptance of the counseling offered. Curiously, counselors rarely realize during their counseling session that they are simultaneously being assessed. Patients assess the apparent knowledge and credibility of the counselor, seek and are encouraged by evidence of experience, and consider the information provided in light of the counselor's attitude, body language and other non-verbal characteristics. Staring at a computer screen while counseling conveys deep insensitivity.

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 psychological pain and distress the person or couple has experienced (e.g. recurrent pregnancy loss followed by multiple IVF efforts and subsequently a successful pregnancy with a fetal defect).
- Compliment the coping that has been necessary, including the stress a couple might have to endure, despite sometimes conflicting feelings.
- Recognize (and explain) psychological 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 comments<sup>123</sup> that may erode these fundamental prerequisites. Well intentioned statements are frequently perceived in a very different way.<sup>136</sup>

It is self-evident that empathy would engender greater patient satisfaction and may well be correlated with clinical competence.<sup>149</sup>

### 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.<sup>150</sup> Explanations that we all carry harmful

genes often helps. Mostly, however, encouragement to move anguish into action is important. This might also help in assuaging any blame by the husband in such cases.<sup>151</sup>

Guilt is not only the preserve of the obligate carrier. Affected parents inevitably also experience guilt on transmitting their defective genes.<sup>152,153</sup> 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.<sup>153</sup> 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<sup>154-160</sup> confirm not only survivor guilt with a new reality (a future) but also problems in relationships with close family members. Huggins et al.<sup>157</sup> 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<sup>161-163</sup> and surveyed international guidelines.<sup>164</sup>

#### Accurate diagnosis

Clinical geneticists, obstetricians or pediatricians are frequently the specialists most confronted by patients seeking guidance because of certain genetic diseases in their families. A previous child or a deceased sibling or parent may have had the disease in question. The 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 prenatal diagnosis. Now whole exome or genome sequencing and the

demonstrated potential diagnostic yield of 25-42 percent for previously undiagnosed patients with severe intellectual disability<sup>10,165,166</sup> 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 22). 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),<sup>167</sup> and many are still to be molecularly identified. Similarly, a history of epilepsy gives no clear indication of which genes are involved.<sup>168</sup> Birth of a previous child with craniosynostosis requires precise determination of the cause (where possible) before risk counseling is provided. Mutations in at least 13 genes are clearly associated with monogenic syndromic forms of craniosynostosis.<sup>169-171</sup> Moreover, a chromosomal abnormality may be the cause.

Awareness of genetic heterogeneity and of intrafamily and interfamily phenotypic variation of a specific disorder (e.g. tuberous sclerosis)<sup>172</sup> 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 due to mutations in the ADPKD1 gene has an early infancy presentation in 2-5 percent of cases.<sup>173</sup> Moreover, mutations in the ADPKD2 gene may result in polycystic kidney disease and perinatal death<sup>174</sup> and, further, should not be confused with the autosomal recessive type due to mutations in the ARPKD gene. Awareness of contiguous gene syndromes, such as tuberous sclerosis and polycystic kidney disease (TSC2-PKD1) has become increasingly 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.<sup>175</sup> 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.<sup>176</sup>

Myotonic muscular dystrophy type 1 (DM), the most common adult muscular dystrophy, with an incidence of about 1 in 8,000,<sup>177</sup> serves as the paradigm for preconception, prenatal and perinatal genetic counseling. Recognition of the pleiomorphism of this disorder will, for example, alert the physician hearing a family history of one individual with DM, another with sudden death (cardiac conduction defect), and yet another relative with cataracts. Awareness of the autosomal dominant nature of this disorder and its genetic basis due to a dynamic mutation reflected in the number of trinucleotide (CTG) repeat units, raises issues beyond the 50 percent risk of recurrence in the offspring of an affected parent. As the first disorder characterized with expanding trinucleotide repeats, the observation linking the degree of disease severity to the number of triplet repeats was not long in coming.<sup>177</sup> In addition, the differences in severity when the mutation was passed via a maternal rather than a paternal gene focused attention on the fact that congenital DM was almost always a sign of the greatest severity and originating through maternal transmission. However, at least one exception has been noted.<sup>178</sup> 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.<sup>179</sup> Rare cases also exist in which complete reversal of the mutation occurs with spontaneous correction to a normal range of triplet repeats.<sup>180–183</sup>

There are also reports of patients born with a decreased number of triplet repeats who nevertheless show no decrease in the severity of their DM.<sup>184–186</sup> It is unclear whether these cases in part reflect somatic or germline (either or both combined) mosaicism.<sup>179</sup> Somatic mosaicism is certainly well documented in DM with, for exam-

ple, larger expansions being observed in skeletal muscle than in peripheral blood.<sup>187</sup> Discussion about potential complications of pregnancy in the prospective affected mother is crucial,<sup>188</sup> and includes pregnancy loss, polyhydramnios, prolonged labor, uterine atony, postpartum hemorrhage, cardiac arrhythmias, increased sensitivity to anesthetic and relaxant agents, newborn apnea, neonatal death, arthrogyriposis and intellectual disability.

Myotonic muscular dystrophy type 2 (DM 2), in contrast to DM 1, has more prominent proximal muscle weakness compared with distal weakness of DM 1. While multisystem involvement is similar in both types, neither congenital myotonic muscular dystrophy nor anticipation occurs in DM 2.<sup>189</sup> Cardiac involvement in DM 2 also is less frequent and less severe than DM 1.<sup>190</sup> DM 2 results from a large tetranucleotide repeat (CCTG) within an intron in CNBP gene. Again in contrast to DM 1, the DM 2 repeat number may contract rather than increase over generations.<sup>189</sup>

The lack of CAG triplet expansion among individuals presenting with Huntington disease-like symptoms and a family history of neurodegenerative disease has focused attention on phenocopies of Huntington disease.<sup>191</sup> Estimates of such phenocopies range between 1 and 2.4 percent of patients manifesting Huntington disease-like signs with a family history of a neurodegenerative disorder.<sup>192</sup> Among the reported phenocopies found thus far are a familial prion disease<sup>191</sup> and a triplet expansion (CAG/CTG) in the junctophilin-3 gene on chromosome 16 in patients presenting with Huntington disease-like manifestations.<sup>193</sup>

The recognition in 2011 of a hexanucleotide repeat expansion in C9ORF72 as the cause of either or both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia<sup>194,195</sup> revealed a neurological spectrum clearly recognized previously.<sup>196</sup> Between 40–50 percent of those affected by *familial* ALS have the characteristic expansion. About 15 percent of patients with ALS also have frontotemporal dementia, while 50 percent have some cognitive and/or behavioral dysfunction.<sup>196</sup> Of those patients who present with frontotemporal lobe *degeneration*, the extreme end of the spectrum, 15 percent also have ALS. Hence, assessment of the family history in an effort to

determine sporadic from familial disorder, may well note a direct relative with involvement in this spectrum. Prenatal diagnosis has not yet been reported for ALS.

There are counseling and diagnostic challenges raised by the possibility of somatic mosaicism (see Chapter 9). Between 6–20 percent of cases are thought to be due to somatic mutation. While such a possibility should always be considered, proof that somatic mutation has occurred and a recognizable phenotype reported may not have been established. While many examples are known some disorders pose particular challenges.

For example, a reported patient with the full autosomal dominant Costello syndrome phenotype due to a HRAS gene mutation, was reported as having no detectable mutation in blood DNA, but did have the typical mutation in buccal swab samples.<sup>197</sup> The neuronal migration disorder, subcortical band heterotopia with DCX mutations, results in lissencephaly and intellectual disability in males. Mildly affected males have, however, been found to be somatic mosaics by hair-root analysis for DCX.<sup>198</sup> Somatic mutations that arise in early embryonic development may result in mosaicism confined to only a few organs or only one. For example, in some cases of hemimegalencephaly, which results in enlargement and extensive malformation of an entire cerebral hemisphere, mutations in the AKT3 gene may be present only in brain tissue, but not in peripheral blood DNA.<sup>199</sup> An assay choice in determining the presence of a deletion could be important. Somatic mosaicism in neurofibromatosis type I may involve large rearrangements that can be determined by multiplex ligation-dependent probe amplification (MLPA). However, this method has been shown to be less sensitive in detecting low-grade somatic mosaicism, compared with fluorescence *in situ* hybridization, or a mutation-specific PCR analysis.

The guiding rule to explain a clinical diagnosis as due to a single cause will not always apply. Careful attention to the clinical presentation, including the family history, will enable recognition of more than a single disorder. Two examples include personal cases of hypohidrotic ectodermal dysplasia and the Loeys–Dietz syndrome, cystic fibrosis and achromatopsia, and a reported case of concomitant spinal muscular atrophy and Rett syndrome.<sup>200</sup>

### **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,<sup>201–205</sup> as well as by the World Health Organization Expert Committee on Genetic Counseling,<sup>206</sup> and in a multinational study focused on the attitudes of genetic counselors.<sup>207,208</sup> In an analysis of nondirective genetic counseling, Kessler<sup>209</sup> 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.<sup>210,211</sup> Not unexpectedly, significant differences in counseling techniques mirror the divergent views of counselors on the goals, content and process of genetic counseling.<sup>30</sup> On the other hand, Kessler<sup>209</sup> 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.<sup>212</sup> 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.

Clarke<sup>213</sup> 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 1970<sup>214</sup> it was emphasized that the offer of prenatal diagnosis was not associated with any explicit or implicit commitment to abort. Clarke<sup>213</sup> 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,<sup>215–217</sup> and rightly so. He regarded reproductive choice as part of the “1980s consumerism model of clinical genetics.”<sup>218</sup> 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.<sup>218</sup> 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.”<sup>218</sup> Others have reported that people’s decision-making processes are more rational than they might appear to be.<sup>219</sup> Simms<sup>220</sup> 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.”<sup>221</sup>

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.<sup>222</sup> A breach of this principle, supported by some,<sup>223</sup> 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.<sup>224</sup>

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.<sup>225</sup> 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.<sup>226</sup> The optimistic counselor may unwittingly color the texture of counseling provided in contrast to the depressed counselor. Hsia<sup>227</sup> 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.<sup>228</sup>

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 (HD) 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.”<sup>229</sup> She further argued that in the interest of beneficence, directive counseling is acceptable for individuals at 50 percent risk of HD, 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 HD, the Canadian authors emphasized

the importance of preparation for receiving test results.<sup>230</sup> In a study of counseling following prenatal diagnosis of Klinefelter syndrome, Marteau et al.<sup>231</sup> found that pregnancy was almost two-and-a-half times more likely to continue when counseling was provided by a geneticist.

### Concern for the individual

Many issues should be raised by the physician or genetic counselor during counseling. 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,<sup>148</sup> and the economic and other societal implications, as well as the need for contraception. Many feel that the economic burden of a defective offspring on society should at least be mentioned as part of a comprehensive view of all issues being considered. Although this may be reasonable, the major emphasis should focus on the concern for the individual, whose priorities, needs and choices remain paramount. In the physician/counselor–patient relationship, concern for the individual should always 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.<sup>193</sup> More than 95 percent of such couples do not need to consider elective abortion. The few who are initially ambivalent almost invariably move to terminate the pregnancy after the detection of a serious fetal defect. Nevertheless, abortion may be declined after the prenatal diagnosis of disorders such as trisomy 21, anencephaly, or trisomy 13. Concern for the individual includes providing ambivalent couples with the opportunity

for reassurance or the choice to decline abortion with preparation for the consequences. Moreover, opportunities to save their offspring's life, or at least to improve the outcome, now exist in specific circumstances (e.g. for omphalocele). The availability of adoption should be emphasized.

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

### Truth in counseling

Since the time of Hippocrates, physicians have often withheld the truth from their patients and, as Katz<sup>232</sup> emphasized in *The silent world of doctor and patient*, defended the morality of this position. Sparing the patient emotional distress, removing hope, and/or diminishing the physician's personal esteem may have been some of the quintessential reasons for the lack of truth telling. While recognizing the modern change in moral sentiment, Lantos<sup>233</sup> acknowledged that truth telling has become "morally obligatory." Notwithstanding his preference that he "would not want a doctor judging the morality of my decision," he remained uncertain about the value of the "comforting lie."

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

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

with certainty the ultimate development of an individual so affected (see Chapter 5).

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

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

### **Confidentiality and trust**

Action by the physician after the diagnosis of the carrier state for an X-linked disease demands more than simply offering prenatal studies in all subsequent pregnancies. There is an obligation to convey this information to the sisters of any such carrier female. The patient may, however, expressly forbid the physician to communicate this information, even to her sisters at risk, despite the international consensus that individuals have a moral obligation to communicate genetic information to their family members.<sup>234</sup> Certain legal pitfalls involving the transmission of privileged communications and breach of medical ethics<sup>234</sup> need to be considered by the conscientious physician faced with this rare but not unheard of situation. A view reinforced by the courts posits that there is a duty to warn the relative at risk as a standard of expected care despite the absence of a physician/counselor relationship,<sup>223,235</sup> regardless of privacy laws! Prior consent to contact relatives (given frequent disaffection in families) is another option.<sup>236</sup> The need

for caution is clear when one realizes that in some states in the United States the physician may lose his or her license to practice medicine after a breach of confidentiality.

Disclosure to third parties, other than relatives, also includes employers, insurance companies, and schools. It is hoped that the confidentiality of the physician-patient relationship and the patients' right to privacy and personal autonomy remain sacrosanct. The American Medical Association has affirmed the importance of keeping genetic information confidential.<sup>237</sup> Established precedent for breaking this confidentiality relates to recognition by the physician of danger to a third party. Threats to kill a former girlfriend shared with a psychiatrist were recognized by the courts as knowledge that should have been communicated.<sup>238,239</sup> Certainly, the clinical notes and letters should reflect the geneticist's recommendation that the patient promptly contact the indicated close relatives who are at risk for a specific genetic disorder.

However, faced with an intractable patient, some guidance about disclosure is reflected in a statement issued by the American Society of Human Genetics in 1998.<sup>240</sup> 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.<sup>241</sup>

### **Timing of genetic counseling**

Today, more than ever before, counseling before conception or marriage<sup>242</sup> may provide opportunities for carrier detection, prenatal diagnosis or the presentation of other important options noted earlier. Therefore, the optimal time to initiate counseling is not during pregnancy. Counselees whose first antenatal visits occur after the second missed menstrual period miss the critical period of organogenesis and patients referred well after conception have lost almost all their options except for

selective abortion. Given the 70 percent protection afforded by periconceptional folic acid supplementation against the occurrence of an NTD<sup>52,53</sup> (see Chapter 3), 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.<sup>221,243,244</sup> 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<sup>133-135</sup> 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 session<sup>245</sup> (a recommended procedure, to summarize the essence of the counseling provided) can safely substitute for face-to-face discussions with both, allowing for questions and interchange

about the issues and an opportunity to examine the partner.

Genetic counselors should be cognizant of the complex interactive factors involved in parental reproductive decision making. Frets<sup>246</sup> 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 post-counseling support, recognition of high risk, disapproval by relatives, the presence of an affected child, and decisions not to have a (or another) child. Due diligence is necessary for the partners of genetic disease carriers who clearly experience significant psychologic distress.<sup>247</sup>

### Counselee education

Hsia et al.<sup>244</sup> emphasized that genetic counseling is an educational process in which the counselee acquires a set of facts and options. Fraser's<sup>202</sup> 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<sup>247-251</sup> 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 remarkable and rapid advances in medical genetics have introduced a “new” responsibility related to the well established requirement to disclose risk information that materially bears on a patient’s decision making.<sup>252,253</sup> Pelias<sup>253</sup> focused attention on the geneticist’s continuing obligation to recontact patients when new information develops that would prove material to them, so far as personal health and childbearing are concerned. The implications raise serious ethical, legal and policy issues.<sup>240,254,255</sup> Certainly, following genetic research and new meaningful results, an ethical duty to inform the patient has become apparent.<sup>256</sup> 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 lawsuit<sup>257</sup> 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.<sup>258</sup> 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.”<sup>253</sup>

In cases in which reasonable expectations for significant advances exist (e.g. new diagnostic tests, tests for carrier detection or prenatal diagnosis), the authors systematically recommend in their postcounseling letters, that the patient be in contact annually and/or before planned childbearing. Pelias<sup>253</sup> opined that this recommendation should be recorded in clinical notes and echoed in letters to referring physicians and patients alike. Ultimately, the responsibility to return for further counseling in the light of new advances must be vested with the patient’s primary care physician and shared with the patient. To a variable extent, the patient’s physician can be expected to remain cognizant of genetic risks family members may have and refer them for specific genetic counseling or testing when appropriate. However, given that tens of millions change their addresses annually and frequently seek

other medical care, the patients themselves, once informed of potential advances and the need to remain in contact with a clinical geneticist, take on personal and primary responsibility.

**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; some of the spinocerebellar ataxias), cardiovascular and other serious disorders including multiple endocrine neoplasia type 2B, and breast, colon and other malignancies. Published recommendations and guidelines<sup>259</sup> urge rigorous pretest and post-test genetic counseling and recommendations that testing of children younger than 18 years of age be proscribed, except in life-threatening disorders (e.g. multiple endocrine neoplasia type 2B). The inherent harm that could potentially be done by presymptomatic testing is the potential for demoralization and depression with possible suicidal consequences. Extreme caution is recommended in considering predictive testing for a disorder without curative, let alone meaningful, palliative treatment. Although for certain dominant disorders some 50 percent of individuals at risk may receive good news, the other 50 percent face, effectively, a death sentence. Given the remarkable pace of advances in human genetics, it may well be possible in the foreseeable future to develop a therapy that enhances the extant biologic mechanism already in place that delays the manifestations of later onset disease for decades after birth. No life should be ruined by severe depression or suicide only to discover later that a critical palliative remedy has emerged.

Clearly, there are extraordinarily difficult circumstances related to planned 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.<sup>260</sup> Physicians also need to reorient their practices so that women of childbearing age understand that to optimize the chance of having a healthy child,<sup>247</sup> prenatal care is best initiated before conception and not after the second missed menstrual period, as is still anachronistically practiced so widely.

The discovery or realization of nonpaternity at the time of prenatal diagnosis is fraught with potentially serious personal, medical, social, and legal problems. The counseling provider has to be extremely adept in managing these cases. Warning about the potential discovery of nonpaternity as part of informed consent prior to testing<sup>261,262</sup> may lead a pregnant woman to decline an indicated chorionic villus sample (CVS) or amniocentesis. Nondisclosure is ill advised when nonpaternity is discovered. In the effort to do no harm, we have requested a counseling session with the prospective mother alone. Her decision, taken in confidence, would govern further action. If, however, testing of the misattributed partner has genetic implications, nondisclosure becomes legally untenable.

### **Duty to warn**

Physicians and counselors traditionally owe no duty to individuals with whom they have never met or entered into any treatment relationship. However, following the decision of the California Supreme Court (in *Tarasoff v. Regents of the University of California*),<sup>192</sup> 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.<sup>263,264</sup> A salutary lesson is provided in the study of 43 families with at least one sudden unexplained death.<sup>265</sup> Identification of the genetic cardiac disorder (e.g. long QT syndrome) was made in 40 percent of the families who harbored 151 presymptomatic carriers! The loss of chance 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.<sup>266</sup> From the judicial opinions in these cases<sup>267</sup> 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.<sup>268</sup>

### Preconception genetic counseling

It is an anachronism that preconception genetic counseling in the 21st century, despite being recognized as important, is not widely practiced.<sup>269,270</sup> 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.”<sup>120,121,271</sup> This activity includes a review of medical records, photographs (e.g. previous stillbirths) and pertinent autopsy reports, radiographs, brain scans, and chromosome or other special laboratory reports. Physical examination and necessary special tests also focus on acquired and genetic disorders that could, during pregnancy, threaten maternal and/or fetal welfare. Previously undiagnosed/undetected disorders may be determined for the first time at this visit and may be important for planned child-bearing and the selection of future prenatal diagnostic tests. There is a need to insist that the male partner attend the preconception visit (or absolutely the first prenatal visit), providing an opportunity to detect at least obvious genetic disorders and solidify information possibly provided earlier about his family history. The senior author recalls, over many years during prenatal diagnosis counseling for other issues, diagnosing various disorders in male partners who were wholly unaware of their conditions, including osteogenesis imperfecta, Treacher–Collins syndrome, tuberous sclerosis, neurofibromatosis, Charcot–Marie–Tooth (type 1A) disease, limb girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, blepharophimosis, mitral valve prolapse, the XYY male, and spinocerebellar ataxia.

The first preconception visit also serves to instruct about the need for folic acid supplementation for the avoidance of NTDs 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, 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 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. In some countries, largely for economic reasons, older ages have been used as an indication for prenatal study. Advances in fetal imaging and low risks of fetal loss following amniocentesis (0.1–0.4 percent) or CVS (0.2–0.4 percent)<sup>272,273</sup> (see Chapter 2) have led to a policy change. The maternal age guideline, while still an important marker for increased risk communication, is no longer sacrosanct. The advent of noninvasive prenatal screening has further assisted in enabling younger women to benefit from early prenatal diagnosis (see Chapter 11).

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.<sup>274</sup> 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.

#### 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 diagnosis 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.<sup>275</sup> Such delay has become problematic given that the NF-1 gene and genes for many other monogenic disorders are routinely sequenced for a precise diagnosis.

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,<sup>276</sup> requiring serial ultrasounds during the pregnancy.

Given the heterogeneous nature of genetic disease, being alert to alternative mechanisms of causation will on occasion be rewarding. For example, during a consultation with a patient who had previously delivered a child with cystic fibrosis (CF), preparatory discussions about establishing the specific mutation from each parent could reveal that the father is not a carrier of the mutated CF gene. Although nonpaternity is more likely, a judicious approach would also include consideration of uniparental disomy.<sup>277</sup> 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<sup>278</sup> and Angelman syndrome.<sup>279,280</sup> About 25 percent of cases of Prader–Willi syndrome are caused by maternal uniparental disomy.<sup>281</sup> Involvement of chromosomes 7, 11, 14 and 15 have been notable.<sup>282</sup> Uniparental disomy is caused primarily by meiotic nondisjunction events and followed by trisomy or

monosomy “rescue.”<sup>283</sup> Most cases described have been associated with advanced maternal age and have been detected primarily in the process of prenatal genetic studies.<sup>283–285</sup>

Recognition of the molecular basis of a disorder from which a previous child died may provide a couple with an opportunity for prenatal diagnosis in a subsequent planned pregnancy. A caveat would be the availability of analyzable tissue from the deceased child. In the recent past this was mostly not done but with the escalation of new discoveries in genetics, tissues are now being frozen for potential future DNA analysis. The establishment of the molecular basis of recognized syndromes, previously undetectable prenatally, now provides new opportunities for couples seeking prenatal diagnosis. Examples abound 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.<sup>286</sup>

Heterogeneity and pleiotropism also require consideration in the context of a previous child's disorder and anticipation of future prenatal diagnosis. For example, a previous child with tuberous sclerosis or a fetus with cardiac rhabdomyomas would prompt molecular analysis of the TSC1 and 2 genes for more precise future prenatal diagnosis.<sup>287</sup>

### 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 now considered. The long-established prenatal diagnosis for both presymptomatic and symptomatic neurodegenerative disorders continue to be expanded to include disorders such as amyotrophic lateral sclerosis and even frontotemporal dementia, by analysis of the C9orf72

gene.<sup>196</sup> In all of these adult-onset disorders, thoughts and discussion 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.<sup>288</sup> Mutation analysis in a subsequent pregnancy assured an unaffected fetus.<sup>289</sup>

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.<sup>287</sup> Discovery of fetal cardiac rhabdomyoma led to sequencing of both the *TSC1* and *TSC2* genes in the fetus and diagnosis in one of the asymptomatic parents. Parental decisions are neither simple nor predictable. In a UK study<sup>290</sup> of 644 deaf individuals and 143 with hearing impairment, 2 percent opined that they would prefer to have deaf children and would consider an elective abortion if the fetus was found to be hearing!

Certain genetic disorders may (i) threaten maternal health in pregnancy, (ii) threaten fetal health and survival, or (iii) be aggravated by pregnancy.

### Genetic disorders that threaten maternal health

Advances in medical care have resulted in more women affected by genetic disorders surviving to childbearing age and becoming pregnant. There are several genetic disorders affecting the mother that can be aggravated and worsened during pregnancy. Awareness of these disorders facilitates better preconception anticipatory guidance and expectant management during pregnancy. Metabolic disorders that may worsen include ornithine transcarbamylase deficiency, homocystinuria, acute intermittent porphyria, and lysinuric protein intolerance. Hyperammonemia during pregnancy/delivery or postpartum coma may be the presenting signs of a female heterozygote

with ornithine transcarbamylase deficiency.<sup>291</sup> Thrombophlebitis and other thromboembolic events have been reported during pregnancy and operative delivery in women with homocystinuria.<sup>292</sup> Ehlers–Danlos syndrome IV and Loeys–Dietz syndrome may have associated aortic/vascular rupture, tissue friability and wound dehiscence during pregnancy and delivery.<sup>293–295,296</sup> In a study of 565 deliveries by women with Ehlers–Danlos syndrome IV, pregnancy-related deaths occurred in 30 (5.3 percent).<sup>296</sup> Life-threatening complications were noted in 14.5 percent of deliveries and included arterial dissection/rupture (9.2 percent), uterine rupture (2.6 percent), and surgical complications (2.6 percent). In a study of 12 women with Loeys–Dietz syndrome with 21 pregnancies, six had one of these major complications.<sup>297</sup> Management recommendations and guidelines for cardiovascular care and surgery for the Loeys–Dietz syndrome are well established.<sup>298</sup> Diagnostic gene-panel sequencing for many connective tissue disorders is available.

Sophisticated and multidisciplinary care and counseling are necessary for women with Marfan syndrome. These guidelines include the following.<sup>34,293,299–308</sup>

#### 1. Preconception:

- A clinical diagnosis should be confirmed by analysis of the *FBN1* gene.
- Women with Marfan syndrome who are planning to have children should be encouraged to do so in their early 20s, given that the mean age of aortic dissection is 32 years.<sup>309</sup>
- The 50 percent risk of having an affected child should be communicated.
- The availability of prenatal diagnosis and preimplantation genetic diagnosis should be discussed.
- Women should be counseled about the significant likelihood of aortic dissection if the aortic root dimension exceeds 4 cm, as well as the potential for other complications.
- Women should be appraised of the need for surveillance for themselves and the fetus by ultrasound or MRI.
- Women should be advised that an increase in the size of the aortic root between 4 and 4.5 cm would lead to serious consideration for elective aortic replacement surgery.

- Lifestyle recommendations should include restriction of physical activity, including isometric exercises, avoidance of contact sports and lifting any weights.
  - Counseling should include the recommendation to test all first degree relatives for the recognized FBN1 mutation.
2. Pregnancy care:
- All appropriate information that would have been reviewed in the preconception period should be discussed if counseling was shortly after pregnancy was established.
  - Echocardiographic surveillance is recommended at intervals of 4–6 weeks throughout pregnancy.
  - Close blood pressure monitoring is so important that some recommend daily measurements.<sup>305</sup>
  - Beta blockers are invariably recommended but increase the incidence of intrauterine growth restriction, preterm delivery and possible fetal bradycardia. (A study of 608 children and young adults with Marfan syndrome, in a short 3-year followup, revealed no significant difference in the rate of aortic-root dilatation between those who took losartan or a beta blocker).<sup>310</sup>
  - Symptoms or signs of an arrhythmia may require further observation with a Holter or even Telemetry.
  - Should prenatal cardiac decompensation become evident, steroids for fetal lung maturity should be provided.
3. Labor and delivery:
- Planned delivery should occur in hospitals with available cardiac surgery and neonatal intensive care unit facilities.
  - Vaginal delivery with epidural anesthesia is recommended for women with stable aortic measurements < 4 cm.
  - Elective cesarean section with epidural anesthesia is recommended for women with changes in aortic root dimensions during pregnancy and for those with measurements exceeding 4 cm. Caution should be exercised in using epidural anesthesia because of the often associated dural ectasia and/or the presence of scoliosis.
  - During labor and delivery the left lateral position is recommended.
- Beta-adrenergic agents such as terbutaline should be avoided.
  - Prophylactic antibiotics should be used because of the likely associated presence of mitral valve prolapse.
4. Postpartum:
- Women should be advised about the continuing risk of aortic dissection in the postpartum period with attention to all matters covered in previous counseling.
  - Continuing surveillance is recommended up to 6 months.
  - Medical therapy to diminish the rate of aortic dilatation should be used. Current recommendations suggest greatest therapeutic efficacy by combining a beta blocker with losartan to reduce the rate of aortic root dilatation.<sup>310–312</sup>
- In a Netherlands study of 63 affected women with Marfan syndrome who had 142 pregnancies, an obstetric or neonatal complication was noted in 40 percent.<sup>313</sup> Awareness and anticipatory management for women with Marfan syndrome is necessary given the 7–31 percent risks of obstetric and neonatal complications that include cervical incompetence, intrauterine growth restriction, preterm delivery, adverse fetal outcome and postpartum hemorrhage.<sup>301,302,306,313</sup> The risk of aortic dissection in pregnancy in patients exists even with an aortic root diameter of < 4 cm.<sup>306</sup> An even greater risk is likely if there has been a rapid rate of aortic growth. Women with short stature and Marfan syndrome appear to have an increased risk of aortic dissection and hence elective surgery would need earlier consideration. The first degree relatives of an affected woman with a thoracic aortic aneurysm have up to 30 percent likelihood of having or developing an aneurysm.<sup>308</sup>
- First-trimester spontaneous abortion and gastrointestinal bleeding during pregnancy have been described in women with pseudoxanthoma elasticum.<sup>314</sup> Worsening of the mother's pulmonary status is seen with cystic fibrosis.<sup>315</sup> In addition to the well known neurologic consequences of neurofibromatosis type I (NF1), there is a well recognized effect on the vascular system with consequences of not only earlier onset of cardiovascular disease but also an increased cardiac mortality.<sup>316</sup> The vascular complications include renal artery stenosis, Moya Moya syndrome, cerebral



aneurysms, and stenotic or ectopic cerebral vessels which may predispose to stroke or cerebral hemorrhage.<sup>316</sup> In a study of 1,553 pregnant women with NF1, a significant increase in prenatal and peripartum complications were noted and included gestational hypertension, preeclampsia, intrauterine growth restriction, cerebrovascular disease and preterm labor.<sup>316</sup> An increase in the size and number of neurofibromata during pregnancy in women with NF1 may occur (in 60 percent of 105 cases in one study<sup>317</sup>) and has resulted in both cosmetic changes as well as significant morbidity (paraplegia with rapid growth of intraspinal tumors).<sup>318</sup> Symptoms and signs of myotonic muscular dystrophy may worsen during pregnancy and be associated with life-threatening events for both the fetus and the mother.<sup>319-322</sup> One study showed that 12 percent of the offspring of affected women were stillborn or died as neonates, 9 percent survived although severely affected, and 29 percent were affected later.<sup>323</sup> Awareness of the obstetric related risks facilitates optimal pregnancy care but does require in-depth preconception discussion. Hypertension may be a problem for the pregnant patient with autosomal dominant polycystic kidney disease. Hematologic disorders may complicate pregnancy by altering normal physiology.

Carriers of hemophilia A are best cared for by a high-risk perinatal obstetric group. Prenatal sex determination (whether or not prenatal diagnosis by mutation analysis is chosen) is important for the management of labor and delivery, with special reference to the possible need for cesarean section. In addition, vacuum-assisted delivery with an affected male could result in a massive cephalohematoma requiring blood transfusion.<sup>324</sup> Moreover, a high incidence of primary and secondary postpartum hemorrhage in carriers of hemophilia A (22 percent) and hemophilia B (11 percent)<sup>324</sup> should further inform anticipatory care.

### **Maternal genetic disorders that may threaten fetal health and survival**

Among the more common examples in this category are diabetes, sickle cell disease, epilepsy,<sup>325</sup> and lupus erythematosus. Fetal loss, stillbirth, and malformations are the primary concerns. Lupus is associated with a significant frequency of congeni-

tal heart block in seropositive mothers,<sup>326</sup> who also have increased risks of postpartum hemorrhage, small gestational-age babies and an increased likelihood of cesarean section.<sup>327</sup> There are also concerns in the offspring of these mothers about subsequent impaired neurodevelopment.<sup>328</sup> Methods available to detect heart block in the fetus, which develops between 18 and 24 weeks of gestation, include fetal Doppler echocardiography, fetal kinecardiography, and transabdominal fetal cardiography.<sup>329</sup> Thus far no specific therapy has reached a standard of care.<sup>330</sup> In a Brazilian study, 32 (78 percent) of 41 fetuses with normal cardiac anatomy and seropositive mothers received no treatment, with live-birth and 1-year survival rates of 97 percent and 93 percent, respectively.<sup>331</sup> As many as 60 percent of mothers of offspring with congenital heart block have lupus or other connective tissue disorders. Maternal myotonic muscular dystrophy, which may be presymptomatic, is a key example in which both the life and health of the mother and fetus/child may be threatened.<sup>332,333</sup> In addition to the earlier discussion, serious-to-fatal fetal/neonatal complications can be anticipated.<sup>332,333</sup> Rigorous guidelines have been published for both presymptomatic and prenatal testing for both myotonic dystrophy 1 and 2.<sup>334</sup>

Untreated maternal phenylketonuria (PKU) represents a potentially unmitigated disaster for the fetus and child (see Chapter 23). Besides pregnancy loss, there is a 90 percent likelihood of intellectual disability, cardiac or other defects in the offspring of mothers who undertake pregnancy without being on strict preconception dietary therapy.<sup>335</sup> Caution needs to be exercised in counseling women with PKU, especially if adherence to diet has been an issue. Comprehension and decision making may be less than adequate given the increased realization of residual behavioral and intellectual deficits.<sup>336</sup> Similar cautions are obvious for other disorders (e.g. fragile X syndrome; see Chapter 7) where similar limitations may be evident and complicate informed consent and decision making generally.

### **Genetic disorders that pregnancy may aggravate**

Women who are severely affected by CF may jeopardize their survival by becoming pregnant and should be advised accordingly. Those with mild

to moderate disease are likely to have a successful pregnancy. A French study in which the outcome was known for 75 patients noted a prematurity rate of 18 percent and one maternal death during pregnancy.<sup>337</sup> Later, some 12 deaths were recorded after pregnancy, with three in the year following the pregnancy. Four affected children were diagnosed after birth. Similar maternal mortality figures were noted by others.<sup>338</sup> Clearly, partners should be tested for their CF carrier status before the initiation of pregnancy in a woman with CF (see Chapter 17). A Norwegian study of pregnancy with CF noted preterm delivery in 24 percent of cases and the development of gestational diabetes in four of 23 patients.<sup>339</sup> Similar observations were made in a Swedish study, except that these authors noted an overall mortality rate of 19 percent among 48 patients.<sup>340</sup> If pregnancy is pursued regardless of counseling, special care and attention will be necessary and hospitalization is commonly needed at some time during the third trimester. Clear guidelines are available for prenatal and preimplantation diagnosis of CF<sup>341</sup> (see Chapter 17). Noninvasive prenatal detection of CF has been achieved in a French study of seven cases.<sup>342</sup> Women with sickle-cell disease are recognized as being at high risk during pregnancy and should be counseled accordingly, including the issues of increased fetal mortality and morbidity.<sup>343,344</sup> In some women, epilepsy is aggravated by pregnancy and could threaten the life of both mother and fetus. Given the potential teratogenic risks of anticonvulsants (in the 7–10 percent range),<sup>345</sup> and neurodevelopmental impairment, change to the least teratogenic medication should be achieved in the preconception period, and should be done under the direct guidance of a neurologist.

Prospective mothers with insulin-dependent diabetes mellitus (IDDM) could find their disorder harder to control during pregnancy. Diabetes should be well controlled before pregnancy. The better the control, the lower the risk of having a child with congenital defects.<sup>346,347</sup> 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.<sup>348</sup> 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).<sup>349</sup> An important Stockholm study of 1,089 stillbirths usefully separated causes in preterm and term/post-term births.<sup>350</sup> Overall congenital malformations and/or chromosomal abnormalities were noted in 10.3 percent. Infection and IUGR/placental insufficiency accounted for over 44 percent of cases in about equal proportion.

Muscle weakness may increase in about half of pregnant women with limb-girdle muscular dystrophy, leading to the need for assistance after delivery.<sup>347,351</sup> In women with congenital myopathies, including central core disease and cytoplasmic body myopathy, cesarean sections may be needed more frequently and some deterioration in pregnancy and weakness after delivery may be experienced.<sup>352</sup> Anesthetic risks may be increased in women with central core disease in whom malignant hyperthermia may be a complication.<sup>353</sup>

## A history of infertility

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.<sup>354</sup> 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 4 and 8). 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.<sup>355</sup> 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 diagnosis.

Examples of disorders characteristically associated with recurrent pregnancy loss or infertility, include premature ovarian failure in fragile

X syndrome carriers (see Chapter 7), and the X-linked disorders, steroid sulfatase deficiency,<sup>356</sup> and incontinentia pigmenti.<sup>357</sup> Thrombophilia as a significant cause remains uncertain.<sup>358,359</sup> In about 8 percent of women experiencing recurrent abortion a mutation in the SYCP3 gene,<sup>360</sup> (which encodes an essential component of the synaptonemal complex, key to the interaction between homologous chromosomes) was noted.

Although the investigation to determine the cause of male or female infertility can be extensive, three observations are pertinent here. First, we recognized that congenital bilateral absence of the vas deferens (CBAVD),<sup>361</sup> which occurs in 1–2 percent of infertile males, is primarily a genital form of CF. Men with CBAVD should have CF gene analysis (expanded panel, sequencing, poly T variant analysis, deletion analysis, until both mutations are recognized). A meta-analysis concluded that among CBAVD patients, 78 percent had one recognizable CFTR mutation whereas 46 percent were noted to have two mutations.<sup>362</sup> The mutation detection rate is likely to exceed 92 percent including large gene rearrangements.<sup>363</sup> Of interest is the observation of Traystman et al.<sup>364</sup> that CF carriers may be at higher risk for infertility than the population at large.

Some patients with CBAVD (21 percent in one study<sup>365</sup>) also have renal malformations. These patients may have a normal sweat test and thus far no recognizable mutations in the CF gene.<sup>365,366</sup> Renal ultrasound studies are recommended in all patients with CBAVD who have normal results on a sweat chloride test and no identified CFTR gene mutations.

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,<sup>367,368</sup> with pregnancy induced by *in vitro* fertilization. Precise prenatal and/or preimplantation diagnosis can be achieved only if specific mutations have been recognized.

Second, Y chromosome microdeletions occur in 10–20 percent of men with “idiopathic” azoospermia or severe oligospermia.<sup>369,370</sup> Genes, including *DAZ* (“deleted in azoospermia”), *YRRM* (Y chromosome RNA recognition motif)<sup>370,371</sup> and others may be deleted singly or together in the region of Yq11.23.<sup>372</sup> Couples must be informed that male

offspring of men with these interstitial deletions in the Y chromosome will have the same structural chromosome defect. The female partner of the male undergoing intracytoplasmic sperm injection (ICSI) needs explanations about procedures and medications for her that are not risk free. Patients should realize that ICSI followed by *in vitro* fertilization is likely to achieve pregnancy rates between 20 and 24 percent,<sup>373</sup> a success rate not very different from the approximately 30 percent rate in a single cycle after natural intercourse at the time of ovulation.<sup>373</sup> Pregnancy follow-up data from cases culled from 35 different programs reported in a European survey<sup>374</sup> and a major American study of 578 newborns showed no increased occurrence of congenital malformations.<sup>144</sup> However, a statistically significant increase in sex chromosome defects has been observed<sup>375</sup> (see Chapter 5). Prenatal diagnosis is recommended in all pregnancies following ICSI.

Third, even “balanced” reciprocal translocations in males may be associated with the arrest of spermatogenesis and resultant azoospermia.<sup>376</sup> 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.<sup>377</sup> This study revealed a genetic abnormality in 36/150 (24 percent) of men with oligospermia or azoospermia.

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.<sup>378</sup>

### Parental carrier of a genetic disorder

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

Physicians should be alerted to the possibility of chromosomal rearrangements or gene mutations that one or the other partner might carry relative to a history of previous recurrent spontaneous abortions, infertility or previous offspring with a chromosomal or single gene defect or a positive family

history. Referral for genetic counseling in these circumstances is appropriate given complex questions relative to risk, prognosis in a future pregnancy and potential pitfalls/reservations concerning prenatal diagnosis (see Chapter 4).

Determination of single gene mutations in carriers may be prompted by the patient's ethnic group, a family history of a specific genetic disorder or a previously affected offspring. In virtually all ethnic groups, particular recessive disorders occur more frequently than in the population at large<sup>379</sup> (Table 1.4). Many carrier tests have become available for these various ethnic groups. Carrier testing for cystic fibrosis (especially Caucasians), Tay–Sachs, Canavan, and other diseases<sup>380</sup> (Ashkenazi Jews), sickle cell disease (blacks),  $\alpha$ -thalassemia (Asians) and  $\beta$ -thalassemia (peoples of Mediterranean descent), is regarded as standard, and indicated simply on the basis of ethnicity. Carrier tests performed simultaneously for a wide range of monogenic disorders have become available<sup>381</sup> raising counseling, logistic and ethical issues. Unfortunately initial commercial testing by next generation sequencing of hundreds of different monogenic disorders yielded a high proportion of incorrect “disease mutation” calls.<sup>382</sup> About 10 percent of the annotated disease mutations were incorrect and about 75 percent of errors occurred in mutation identification due to faulty interpretation or analysis. Faulty data analysis, exaggerated clinical claims, fraudulent data, misleading test results, and poor clinical performance signaled a need for major improvements.

Individuals of French Canadian ancestry living in New England were reported to have a maximum frequency of heterozygosity for Tay–Sachs disease or Sandhoff disease of 1 in 42.<sup>383</sup> Enzymatic analysis of hexosaminidase was confirmed by mutation analysis with exclusion of benign pseudodeficiency mutations. In contrast to these findings, which could reflect ascertainment bias, are the prior salutary observations of Palomaki et al.<sup>384</sup> These authors recorded no cases of Tay–Sachs disease in 41,000 births to couples who were *both* of French Canadian ancestry. Further studies are necessary before formal recommendations can be made for carrier testing in this ethnic group.

Notwithstanding the screening guidelines for CF in Caucasians, a family history of CF is a direct indi-

cation for mutation analysis.<sup>385</sup> Moreover, given the ability to detect over 90 percent of CF carriers by routine testing of the most common mutations (see Chapter 17), all women should be offered these analyses at the preconception visit.<sup>386</sup> Unfortunately, even after DNA mutation analysis, couples may not be aware of the limitations of these results. In one study, over half of those having CF carrier tests were unaware of their residual risk after having received a negative test result,<sup>387</sup> while in another report only 62 percent correctly understood their results 6 months after testing.<sup>388</sup>

Among the many items to be considered during the preconception visit are the potential physical features indicative of sex-linked disorders that may manifest in female carriers (Table 1.5). With or without a family history of the disorder in question, referral to a clinical geneticist would be appropriate for final evaluation of possible implications. Failure to recognize obvious features in a manifesting female may well result in a missed opportunity for prenatal genetic studies and an outcome characterized by a seriously affected male (or occasionally female) offspring. Of crucial additional importance in considering manifesting female carriers of sex-linked disorders is the realization that carrier females for Duchenne and Becker muscular dystrophy have preclinical or clinically evident myocardial involvement in 45–84 percent of cases.<sup>403,439</sup> A study of 197 females aged 5–60 years who were carriers of either Duchenne or Becker muscular dystrophy revealed progressive dilated cardiomyopathy, myocardial hypertrophy, and/or dysrhythmias. The American Academy of Pediatrics recommended that female carriers be informed of their risks, have a full cardiac evaluation in late adolescence or early adulthood and be re-evaluated at least every 5 years.<sup>440</sup> Unfortunately, a majority of carriers have not been informed of their risks or had cardiac evaluations.<sup>441</sup> Dilemmas may also occasionally arise in counseling, for example, the limited comprehension of a female with fragile X syndrome and mild intellectual disability, with the partner similarly limited.<sup>442</sup> The involvement of close relatives is key to the counseling needs in this type of situation.

Women who are known carriers of hemophilia A or B have an increased risk of primary postpartum hemorrhage with 23 percent having that

## 28 Genetic Disorders and the Fetus

**Table 1.4** Common genetic disorders in various ethnic groups

| <i>Ethnic group</i>                    | <i>Genetic disorder</i>   |
|--|---|
| Africans (blacks)                      | Sickle cell disease and other disorders of hemoglobin<br>$\alpha$ - and $\beta$ -thalassemia<br>Glucose-6-phosphate dehydrogenase deficiency<br>Benign familial leukopenia<br>High blood pressure (in females)  |
| Afrikaners (white South Africans)      | Variegate porphyria<br>Fanconi anemia   |
| American Indians (of British Columbia) | Cleft lip or palate (or both)   |
| Amish/Mennonites                       | Ellis–Van Creveld syndrome<br>Pyruvate kinase deficiency<br>Hemophilia B  |
| Armenians                              | Familial Mediterranean fever  |
| Ashkenazi Jews                         | A- $\beta$ -lipoproteinemia<br>Bloom syndrome<br>Breast cancer<br>Canavan disease<br>Colon cancer<br>Congenital adrenal hyperplasia<br>Dysferlinopathy (limb girdle muscular dystrophy 2B)<br>Dystonia musculorum deformans<br>Factor XI (PTA) deficiency<br>Familial dysautonomia<br>Familial hyperinsulinism<br>Fanconi anemia (type C)<br>Galactosemia<br>Gaucher disease (adult form)<br>Iminoglycinuria<br>Joubert syndrome<br>Maple syrup urine disease<br>Meckel syndrome<br>Niemann–Pick disease<br>Pentosuria<br>Tay–Sachs disease |
| Chinese                                | Thalassemia ( $\alpha$ )<br>Glucose-6-phosphate dehydrogenase deficiency (Chinese type)<br>Adult lactase deficiency   |
| Eskimos                                | E1 pseudocholinesterase deficiency<br>Congenital adrenal hyperplasia  |
| Finns                                  | Aspartylglucosaminuria<br>Congenital nephrosis  |
| French Canadians                       | Neural tube defects<br>Tay–Sachs disease  |
| Irish                                  | Neural tube defects<br>Phenylketonuria<br>Schizophrenia   |
| Italians (northern)                    | Fucosidosis   |
| Japanese and Koreans                   | Acatalsia<br>Dyschromatosis universalis hereditaria<br>Oguchi disease   |



Table 1.4 (Continued)

| <i>Ethnic group</i>   | <i>Genetic disorder</i>   |
|---|---|
| Maori (Polynesians)   | Clubfoot  |
| Mediterranean peoples (Italians, Greeks, Sephardic Jews, Armenians, Turks, Spaniards, Cypriots) | Familial Mediterranean fever<br>Glucose-6-phosphate dehydrogenase deficiency (Mediterranean type) |
| Norwegians  | Glycogen storage disease (type III)<br>Thalassemia (mainly $\beta$ )<br>Cholestasis-lymphedema    |
| Yugoslavs (of the Istrian Peninsula)  | Phenylketonuria<br>Schizophrenia  |

Source: Modified from Milunsky 2001.<sup>379</sup>

experience in their first delivery.<sup>443</sup> Over 50 percent of hemophilia carriers in a Netherlands study chose prenatal diagnosis.<sup>444</sup> Preimplantation genetic diagnosis remains an option.<sup>445</sup> Noninvasive diagnosis of hemophilia, although challenging, has been demonstrated.<sup>446</sup>

### A family history of a genetic disorder

The explicit naming of a specific genetic disorder when the family history is being discussed facilitates evaluation and any possible testing. Difficulties are introduced when neither family nor previous physicians have recognized a genetic disorder within the family. Such a disorder may 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.<sup>447,448</sup> 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 cancers of the uterus, ovary, stomach, small bowel, or ureter. 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.<sup>323</sup> 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),<sup>450</sup> 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.<sup>451</sup> 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<sup>265</sup> should lead to a routine electrocardiogram at the first preconception visit and possibly mutation analysis of at least 13 long QT syndrome genes. 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.<sup>177</sup>

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.<sup>452–454</sup>

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

| <i>Selected disorders</i>                             | <i>Key feature(s) that may occur</i>   | <i>Selected references</i> |
|---|--|----------------------------|
| Achromatopsia   | Decreased visual acuity and myopia   | 389                        |
| Adrenoleukodystrophy                                  | Neurologic and adrenal dysfunction   | 390, 391                   |
| $\alpha$ -thalassemia/mental retardation              | Rare hemoglobin H inclusions in red blood cells  | 392                        |
| Alport syndrome                                       | Microscopic hematuria and hearing impairment   | 393                        |
| Ameliogenesis imperfecta, hypomaturation type         | Mottled enamel vertically arranged   | 394                        |
| Arthrogyposis multiplex congenita                     | Club foot, contractures, hyperkyphosis   | 395                        |
| Borjeson–Forssman–Lehmann syndrome                    | Tapered fingers, short, widely spaced, flexed toes, mild mental retardation  | 396                        |
| Choroideremia <sup>a</sup>                            | Chorioretinal dystrophy  | 397                        |
| Chronic granulomatous disease                         | Cutaneous and mucocutaneous lesions  | 398, 399                   |
| Cleft palate  | Bifid uvula  | 400                        |
| Conductive deafness with stapes fixation              | Mild hearing loss  | 401                        |
| Congenital cataracts <sup>b</sup>                     | Posterior suture cataracts   | 402                        |
| Duchenne muscular dystrophy                           | Pseudohypertrophy, weakness, cardiomyopathy/conduction defects   | 403–405                    |
| Dyskeratosis congenita                                | Retinal pigmentation   | 406                        |
| Emery–Dreifuss muscular dystrophy                     | Cardiomyopathy/conduction defects  | 407                        |
| Fabry disease   | Angiokeratomas, corneal dystrophy, “burning” hands and feet, rhabdomyolysis  | 408, 409                   |
| FG syndrome   | Anterior displaced anus, facial dysmorphism  | 410                        |
| Fragile X syndrome                                    | Mild-to-moderate intellectual disability, behavioral aberrations, schizoaffective disorder, premature ovarian failure  | 411–413                    |
| G6PD deficiency                                       | Hemolytic crises, neonatal hyperbilirubinemia  | 414                        |
| Hemophilia A and B                                    | Bleeding tendency  | 415                        |
| Hypohydrotic ectodermal dysplasia                     | Sparse hair, decreased sweating  | 416                        |
| Lowe syndrome   | Lenticular cataracts   | 417                        |
| Menkes disease  | Patchy kinky hair, hypopigmentation  | 418, 419                   |
| Myopia  | Mild myopia  | 420                        |
| Nance–Horan syndrome <sup>b</sup>                     | Posterior Y-sutural cataracts and dental anomalies   | 421                        |
| Norrie disease  | Retinal malformations  | 422                        |
| Ocular albinism type 1                                | Retinal/fundal pigmentary changes  | 423                        |
| Oligodontia   | Hypodontia   | 424                        |
| Ornithine transcarbamylase deficiency                 | Hyperammonemia, psychiatric/neurologic manifestations  | 425, 426                   |
| Retinoschisis   | Peripheral retinal changes   | 427                        |
| Retinitis pigmentosa                                  | Night blindness, concentric reduction of visual field, pigmentary fundal degeneration, extinction of electroretinogram | 428                        |
| Sideroblastic anemia                                  | Minor red cell abnormalities without anemia  | 429                        |
| Simpson–Golabi–Behmel syndrome                        | Extra lumbar/thoracic vertebrae, accessory nipples, facial dysmorphism   | 430                        |
| Split-hand/split-foot anomaly                         | Mild split-hand/split-foot anomaly   | 431                        |
| Spondyloepiphyseal dysplasia, late onset              | Arthritis  | 432                        |
| Ulnar hypoplasia with lobster-claw deficiency of feet | Slight hypoplasia of ulnar side of hand and mild syndactyly of toes  | 433                        |
| Wiskott–Aldrich syndrome <sup>a</sup>                 | Abnormal platelets and lymphocytes   | 434, 435                   |
| X-linked mental retardation                           | Short stature, hypertelorism   | 436, 437                   |
| X-linked retinitis pigmentosa                         | Retinal changes  | 438                        |

Notes: <sup>a</sup>Uncertain. <sup>b</sup>May be same disorder.

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.<sup>455</sup> Moreover, unexpected segregation of a maternal pre-mutation may have unpredicted consequences, including reversion of the triplet repeat number to the normal range.<sup>456</sup> Genetic counseling may be valuable, more especially because the phenomena 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. Genome sequencing for intellectual disability is steadily becoming a reality, enabling the recognition of gene mutations even after SNP microarray and exome analyses.<sup>10</sup>

### Consanguinity

Consanguineous couples face increased risks of having children with autosomal recessive disorders; the closer the relationship, the higher the risks. A study in the United Arab Emirates of 2,200 women  $\geq 15$  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.<sup>457,458</sup> 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.<sup>458,459</sup> A Jordanian study also noted significantly higher rates of infant mortality, stillbirths, and congenital malformations among the offspring of consanguineous couples.<sup>460</sup> A Norwegian study of first-cousin Pakistani parents yielded a relative risk for birth defects of about twofold.<sup>461</sup> In that study, 28 percent of all birth defects were attributed to consanguinity. An observational study of 5,776 Indian newborns noted a prevalence of 11.4 per 1,000 births with a consanguinity rate of 44.74 percent.<sup>462</sup>

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.<sup>250</sup>

### 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 livebirths<sup>463</sup> in the United States but in certain regions and countries rates reach as high as 10 percent.<sup>464–466</sup> There is a limited list of known and proven human drug teratogens.<sup>40,467</sup> Maternal use of specific teratogenic medications, such as isotretinoin, may be missed, unless the physician expressly inquires about them.

Preconception advice to avoid heat exposure in early pregnancy is now appropriate. Our observations showed a 2.9 relative risk for having a child with a NTD in mothers who used a hot tub during the first six weeks of pregnancy.<sup>468</sup>

A report from the Spanish Collaborative Study of Congenital Malformations noted a 2.8-fold increased risk of DS in the offspring of women  $\geq 35$  years of age and who were taking oral contraceptives when they became pregnant.<sup>469</sup>

### 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:

- 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  $\alpha$ -fetoprotein screening for neural tube defects;
- prenatal diagnosis (CVS, amniocentesis, cordocentesis, ultrasound, MRI);
- preimplantation genetic diagnosis;
- fetal treatment for selected disorders;
- folic acid supplementation in periconceptual period (see Chapter 3);
- selective abortion.

### **Genetic counseling as a prelude to prenatal diagnosis**

Prospective parents should understand their specific indication for prenatal tests and the limitations of such studies. Frequently, one or both members of a couple fail to appreciate how focused the prenatal diagnostic study will be. Either or both may have the idea that all causes of 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, facioscapulothoracic 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 4). 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, either SNP microarrays, biochemical assays, or 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 advent of the chromosomal microarray (see Chapter 8). DNA analysis of cultured amniocytes may yield an uninterpretable microdeletion/duplication which then requires parental studies in an effort to determine significance.

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

### **Informed consent**

The introduction of chromosomal microarrays for prenatal diagnosis has made informed consent even more important given the frequent inexplicable

results, challenges of interpretation, or determination of significance. The studies enable detection of an extra 15 percent of significant chromosomal abnormalities over routine karyotyping, deletion/duplication analyses or fluorescence in situ hybridization (FISH).<sup>470,471</sup> All exome sequencing and the discovery of variations of unknown significance<sup>472</sup> provide powerful imperatives for pretest discussion and consent. Focus on the transmission of all results or only actionable results requires the most careful discussion while exome or whole genome sequencing for prenatal diagnosis is very close. The American College of Medical Genetics and Genomics has issued a list of 56 (now 58) monogenic disorders for which communication of results is regarded as medically and ethically appropriate.<sup>473</sup> Similar issues can be anticipated from analyses of circulating fetal DNA from noninvasive screening.

Patients should also be told that prenatal diagnosis is not error free. Although the accuracy rate for prenatal diagnostic studies exceeds 99 percent, it is not 100 percent. Errors have occurred in all of the following ways and most, at least in the United States, have been followed by frequently successful lawsuits<sup>133-135,474-477</sup> (see Chapter 32):

- failure to offer prenatal diagnosis;
- failure to provide accurate information regarding risks of occurrence or recurrence;
- failure to explain significantly abnormal results, with catastrophic consequences;
- failure to provide timely results of prenatal diagnosis, resulting in the birth of a child with a chromosome abnormality;
- failure to communicate the recommendation from the laboratory to perform a second amniocentesis in view of failed cell culture, resulting in the birth of a child with a detectable genetic defect;
- failure to determine the correct fetal sex or genetic disorder, due to maternal cell contamination;
- failure to diagnose a defect because of a sample or slide mix up;
- failure to order indicated tests (e.g. karyotype of prospective mother when her sister or sibling's child had DS, chromosome type unknown and which in fact was due to an unbalanced translocation);
- failure to analyze the fetal karyotype correctly;
- failure to recognize significant chromosomal mosaicism;

- incorrect interpretation (or erroneous reinterpretation) of a biochemical or DNA assay;
- failure to run appropriate controls for a biochemical assay;
- failure to order the correct test;
- failure to send or direct a sample for specific testing to a known laboratory;
- failure to communicate critical laboratory results to the physician and depending upon a fax or voice-mail transmission;
- incubator failure or infection of cell cultures, resulting in failure of cell growth, no time for a repeat study and subsequent birth with a chromosomal (or detectable) anomaly;
- failure to offer maternal serum screening or to correctly interpret and act on results;
- failure to understand a laboratory report coupled with failure to clarify the results by contacting the laboratory;
- failure to detect obvious fetal defects on ultrasound;
- failure to recommend preconception folic acid supplementation (see Chapter 12) with subsequent birth of a child with a neural tube defect;
- failure to offer indicated carrier detection tests (ethnicity; family history);
- failure to deliver a blood sample to the laboratory in a timely manner, with the subsequent birth of a child with spina bifida and hydrocephalus;
- failure to advise change or discontinuance of a teratogenic medication (e.g. valproic acid), resulting in the birth of a child with spina bifida;
- delay/failure in making a timely diagnosis of a serious genetic disorder in a previous child, thereby depriving parents of risk data and of the options for prenatal diagnosis (among others) in a subsequent pregnancy, resulting in the birth of another affected child;
- failure to warn that noninvasive maternal serum screening is not a diagnostic test.

From a previous worldwide survey of prenatal diagnosis,<sup>475</sup> and two formal amniocentesis studies,<sup>478,479</sup> an error rate between 0.1 and 0.6 percent seems likely. After communication of all the necessary information concerning amniocentesis and prenatal genetic studies pertinent to the couple and especially tailored to their particular situation, an informed consent form should be signed and witnessed. Consent forms used for minor surgery should suffice for CVS and amniocentesis.



However, each physician should have a specific form covering all key eventualities.<sup>475</sup>

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

### Carrier detection

Before any effort to make a prenatal diagnosis of an autosomal recessive or sex-linked biochemical disorder, the carrier state should be documented (see above). For autosomal recessive disorders, particular attention should be paid to the parents' ethnic origin (see Table 1.4). A previous birth of an affected child with an autosomal recessive disorder might alert the physician to consanguinity. DNA mutation analysis facilitates carrier detection for a host of disorders not previously detectable prenatally (see Chapter 9). Recognition of compound heterozygosity in a couple will influence discussions about prognosis and should also initiate tracking of carriers through the respective families.

There are at least 1,139 autosomal recessive disorders for which a next-generation sequencing carrier screen has been devised for 448 associated with severe childhood diseases.<sup>381</sup> Targeted and therefore incomplete analyses have focused on 437 genes.<sup>381</sup> This important approach has yet to achieve adequate or sufficient coverage and would currently provide potentially misleading results inevitably leaving patients with the thought that they are not carriers of a specific disorder. Further refinement of this approach may well provide a major preconception opportunity for extensive carrier detection for disorders that lead to severe childhood recessive diseases. Commercial direct-to-consumer genetic testing services have evoked considerable controversy.<sup>480</sup> Much can be learned

from specific legislation in France, Germany, Portugal, and Switzerland, that genetic tests can be initiated only by a physician after the provision of sufficient information concerning the nature, meaning, and consequences of the test and only after consent has been obtained.<sup>382</sup> In the Netherlands, the Minister of Health has licensing authority.<sup>382</sup> Thus far Belgium and the United Kingdom allow direct-to-consumer genetic tests, while in the United States there is evidence of increasing control.

### Presymptomatic or predictive testing

Presymptomatic or predictive testing is available for a rapidly increasing number of disorders, especially neuromuscular and neurodegenerative (see Chapter 9). Huntington disease is the prototype and predictive testing using guidelines promulgated by the World Federation of Neurology,<sup>259,481,482</sup> the International Huntington Association, and the European Huntington Disease Network<sup>483</sup> are well established. Various programs report that a majority of patients are able to cope when it is found that they are affected,<sup>154–159,484,485</sup> and, at least after a 1-year follow up, potential benefit has been shown even in those found to be at increased risk.<sup>486</sup> 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.<sup>487</sup> Prenatal diagnosis was elected by about two-thirds of those who were carriers.

As others earlier,<sup>488</sup> 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.<sup>489</sup> 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).<sup>191</sup> Of the 15 who had prenatal tests, 12 had an increased risk, which led to pregnancy termination in all but one.<sup>191</sup>

The motivations leading to the very difficult decision to have or not to have a predictive test

are being recognized as extremely complex.<sup>490</sup> 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,<sup>491</sup> highlighting earlier reports of high suicide rates<sup>492</sup> 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.<sup>493</sup> In their worldwide questionnaire study sent to predictive testing centers, the authors noted that 44 individuals (0.97 percent) among 4,527 tested had five suicides, 21 suicide attempts, and 18 hospitalizations for psychiatric reasons. All those who committed suicide had signs of Huntington disease, while 11 (52.4 percent) of the 21 individuals who attempted suicide were symptomatic. Others have written about the psychologic burden created by knowledge of a disabling fatal disease decades before its onset.<sup>494–496</sup>

Hayden<sup>497</sup> 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.<sup>498</sup> 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.<sup>499</sup> A subgroup of tested persons were found to have long-lasting psychologic distress.

On the other hand, an increasing number of examples already exist (see Chapter 9) 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.<sup>500</sup> Use of DNA linkage or mutation analysis for ADPKD<sup>450,501</sup> 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 hemorrhage<sup>502</sup>) and pre-emptive 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 haploinsufficiency of the PKD1 gene influences the TGF-beta signaling pathway.<sup>503</sup> In a study of 141 affected individuals, 11 percent decided against bearing children on the basis of the risk.<sup>504</sup> 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.<sup>505</sup> 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.<sup>506</sup>

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.<sup>507</sup> 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 CGH to determine the cause of intellectual disability revealed a *de novo* deletion within 3p25.3 that included the von Hippel-Lindau gene.<sup>508</sup> For example, elective thyroidectomy is recommended for multiple endocrine neoplasia type 2B by 5 years of age in the child with this mutation, given the virtual 100 percent penetrance of this gene and the possible early appearance of cancer.<sup>509</sup> Predictive testing even of children at high genetic risk poses a host of complex issues.<sup>510</sup> 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.<sup>511</sup>

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.<sup>512</sup> These cases pose challenging ethical, moral and legal questions, but both prenatal and preimplantation genetic diagnosis are now well accepted in the Western world.<sup>483,513,514</sup> Certainly rigorous recommendations and guidelines are in place for the prenatal and the preimplantation diagnosis for Huntington disease,<sup>483</sup> which would apply equally to other neurodegenerative disorders.

Homozygotes for Huntington disease are rare<sup>515,516</sup> 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,<sup>517</sup> 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.

Following 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.<sup>518</sup> DudokdeWit et al. laid out a detailed and systematic approach to counsel-

ing and testing in these families.<sup>519</sup> 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.<sup>520</sup> 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,<sup>521,522</sup> 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.<sup>523</sup>

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.<sup>523,524</sup> 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.<sup>525</sup> 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.<sup>525</sup> Lifetime ovarian cancer risks were 54 percent for BRCA1 and 23 percent for BRCA2 mutation carriers.<sup>525</sup>

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 cancer<sup>526</sup> is also likely to be followed by thoughts of avoidance through prenatal diagnosis. This mutation has been found in 6 percent of Ashkenazi Jews.<sup>526</sup> 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.<sup>527</sup> Thus far, at least 17 proven disorders with these unstable repeats have been described (see Chapter 9). All disorders described thus far are autosomal dominant or X-linked, except for Friedreich ataxia, which is autosomal recessive and also unique in having intronic involvement.<sup>528</sup> Typically for these disorders (except for Friedreich ataxia), the carrier will have one normal allele and a second expanded allele.

These disorders (except for Friedreich ataxia) are also generally characterized by progressively earlier manifestations and/or more severe expression with succeeding generations. This genetic mechanism, called anticipation, is associated with further expansion of the specific triplet repeat but there are also disorders with anticipation and no apparent dynamic mutations (see Chapter 9). Indeed, these disorders characteristically have a direct relation between the number of repeats and the severity of disease and an inverse relation between the number of repeats and age of onset. These aspects of anticipation weigh heavily in preconception counseling when it becomes clear that the relatively mild-to-moderate status of a mother with myotonic muscular dystrophy, for example, is likely to result in an affected child with severe congenital myotonic muscular dystrophy.<sup>175</sup> Triplet size in this disorder

correlates significantly with muscular disability as well as intellectual and gonadal dysfunction.<sup>529</sup> These authors also noted that triplet repeat size did not correlate with the appearance of cataract, myotonia, gastrointestinal dysfunction and cardiac abnormalities. They hypothesized that somatic mosaicism with different amplification rates in various tissues may be one possible explanation for the variable phenotypes in spinocerebellar ataxia type 10. It is well documented, however, that the paradoxical effects of repeat interruptions in the ATTCT expansion alleles result in a contraction in intergenerational repeat size.<sup>530</sup> Spinocerebellar ataxia type 2 has also been associated with Parkinsonism and an increased risk for amyotrophic lateral sclerosis (ALS).<sup>531</sup>

Recent recognition of hexanucleotide repeat expansions in the C9orf72 gene reveal additional challenges that inevitably will raise consideration of prenatal diagnosis, as discussed under accurate diagnosis. Mutations in C9orf72 have been reported in about 40–50 percent of cases with familial amyotrophic lateral sclerosis and between 3.5 percent and 8 percent of sporadic ALS cases<sup>196,532–534</sup> and in 25 percent of familial frontotemporal lobar degeneration with about 7 percent in sporadic cases.<sup>532,533</sup> The clinical spectrum includes patients with frontotemporal dementia and ALS as well as those with a corticobasal syndrome.<sup>535</sup> 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.<sup>536</sup> 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.<sup>536</sup>

### Imprinting

The phenomenon of parent-of-origin difference in the expression of specific genes introduces genomic imprinting into the genetic counseling considerations. Some genes are genetically marked before fertilization so that they are transcriptionally silent at one of the parental loci in the offspring.<sup>537</sup> A number of disorders have been recognized in which genomic imprinting is especially important (see Chapter 9).<sup>538</sup> In addition, parent-of-origin

affects anticipation in triplet repeat expansions such as in Huntington disease. Paternal transmission of the gene is associated with earlier and more severe manifestations than would be the case after maternal transmission. Families at risk may not realize that Huntington disease may manifest in childhood, not only in the teens but as early as 18 months of age.<sup>512,539</sup>

### Genotype–phenotype associations

DNA mutation analysis has clarified few genotype–phenotype associations but extensive databases will help<sup>540,541</sup> (see Chapter 9). Notwithstanding this limitation, mutation analysis does provide precise prenatal diagnosis opportunities and detection of affected fetuses with compound heterozygosity. Simple logic might have concluded that genotype at a single locus might predict phenotype. For monogenic disorders this is frequently not the case. 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.<sup>542</sup> In the autosomal dominant Marfan syndrome (due to mutations in *FBN1*), 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.<sup>543</sup> In Gaucher disease with one of the common Ashkenazi Jewish mutations, only about one-third of homozygotes have significant clinical disease.<sup>544</sup> At least two-thirds have mild or late-onset disease or remain asymptomatic (see Chapter 24). Compound heterozygotes for this disorder involving mutations L444P and N370S have included a patient with mild disease first diagnosed at 73 years of age, while another requiring enzyme replacement therapy was diagnosed at the age of 4 years.<sup>545</sup>

In CF, a strong correlation exists between genotype and pancreatic function but only a weak association has been noted with the respiratory phenotype<sup>546</sup> (see Chapter 17). Although individuals who are homozygous for the common CF mutation ( $\Delta F508$ ) can be anticipated to have classic CF, those with the less common mutation (R117H) are likely to have a milder disease.<sup>547</sup> 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.<sup>548</sup> of a mildly affected  $\Delta F508$  homozygote whose one chromosome 7 carried both the common  $\Delta F508$  mutations and a cryptic R553Q mutation. Apparently, a second mutation in the same region may modify the effect of the common mutation, permitting some function of the chloride channel<sup>549</sup> and thereby ameliorating the severity of the disease. Modifying genes in CF are being increasingly recognized.<sup>550–552</sup>

The extensive mutational heterogeneity in hemophilia A<sup>553</sup> is related not only to variable clinical severity but also to the increased likelihood of antifactor VIII antibodies (inhibitors) developing. Miller et al.<sup>554</sup> found about a fivefold higher risk of inhibitors developing in hemophiliac males with gene deletions compared with those without deletions. Recognition of genotype–phenotype associations remain challenging for reasons that include expressivity, penetrance, multiple causal genes, modifier alleles, compound heterozygosity, locus heterogeneity, interacting polymorphisms of small effect, and digenic inheritance.

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 do newly available mutation analyses when applicable.

### Mosaicism

Mosaicism is a common phenomenon. The normal process of X-inactivation and tissue differentiation results in functional mosaicism in females. Mosaicism might occur in somatic or germline cells (see Chapter 9). Its recognition is important, because a disorder may not be due to a new dominant mutation, a single nucleotide variant, or copy-number variant<sup>555</sup> despite healthy parents. Erroneous counseling could follow, with the provision of risks very much lower than would be the case if gonadal mosaicism existed. After the birth to healthy parents of a child with achondroplastic dwarfism, random risks of one in 10,000 might be given for recurrence. However, gonadal mosaicism



has been described after the birth of a second affected child.<sup>556</sup> Similarly, the birth of a male with Duchenne muscular dystrophy (DMD), no family history, and no detectable mutation on DNA analysis of maternal peripheral leukocytes might lead to counseling based on spontaneous mutation rates. Once again, gonadal mosaicism is now well recognized in mothers of apparently sporadic sons with DMD and the risk of recurrence in such cases approximates 4–8 percent.<sup>557</sup> Gonadal mosaicism has also been documented for other disorders (see Chapter 9), and undoubtedly occurs in some others yet to be discovered.

Somatic cell mosaicism with mutations has been recognized in many different disorders (see Chapter 9). In a study of 10,362 consecutive patients over 1 in 200 were shown to have somatic mosaicism.<sup>558</sup> 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.<sup>559,560</sup> Gonadal mosaicism 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. However, very low levels of mosaicism have been detected with highly sensitive assays for copy-number variants in otherwise healthy parents.<sup>555</sup> Current methodologies for clinical diagnosis invariably list detection of very low degrees of mosaicism in a caveat that accompanies the reports. Nevertheless, while accounting for the existence of a very low degree of mosaicism for a copy-number variant, there is every good reason to assume that single mutations also exist in a parental mosaic state. Examples of somatic and gonadal mosaicism include autosomal dominant osteogenesis imperfecta,<sup>561,562</sup> Huntington disease,<sup>563</sup> and spinocerebellar ataxia type 2.<sup>564</sup> 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.

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 4 but note can be taken here of a possibly rare (and mostly undetected) autosomal trisomy. A history of subfertility with mostly mild dysmorphic features and normal intelligence has been reported in at least 10 women with mosaic trisomy 18.<sup>565</sup>

### 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, 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. Ptacek and Eberhardt,<sup>566</sup> in reviewing the literature, noted consensus recommendations in breaking bad news that included the foregoing and sitting close enough for eye contact without physical barriers. Identifying a support person, if the partner cannot/will not attend the consultation,

is important and knowledge of available resources is valuable. All of the above points are preferences that have been vocalized by parents receiving bad news about their infants.<sup>567</sup>

Almost all couples would have reached this juncture through maternal serum screening, noninvasive prenatal screening, an ultrasound study, or amniocentesis/CVS for maternal age, for established known carriers, because of a previously affected child, being an affected parent, or having a family history of a specified disorder. 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.

Recognition of a fetal abnormality by imaging, molecular or cytogenetic study may reveal, for the first time, the genetic disorder in an asymptomatic parent. Robyr et al.<sup>568</sup> 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 to 8.1 percent.<sup>569,570</sup> 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.

### 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 45 years of experience in this very subject.

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

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

The question concerning a repeat prenatal study is invariable, at least if not stated then certainly in the mind of the parents. There are occasions when a repeat test might be appropriate, especially if there is a failure to reconcile cytogenetic or molecular results with expected high-resolution ultrasound observations. Maternal cell contamination (see Chapters 4 and 9), 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 4) or a microdeletion or microduplication are key examples (see Chapter 8). 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. 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. It is important that the many variables influencing parental decisions about pregnancy termination be recognized.<sup>571</sup> 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.<sup>572</sup> Certainly there is a wealth of literature suggesting inadequate preparation for those who ultimately care for individuals facing bereavement or death.<sup>572</sup> An in-depth understanding of the disability that the affected child and parents could anticipate is of obvious importance. However, concern has been expressed about the inadequacy of disability training in the genetic counseling context.<sup>573</sup> Ample time (with follow-up visits) is critical. The principles and prerequisites for counseling discussed earlier apply fully in these circumstances and the fact that this

is a parental decision, not a 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, and how other couples have coped. All of this anticipatory counseling should be tinted with support and hope when possible. Many couples have expressed their appreciation of this approach and indicated the benefits of having had these discussions before elective termination.

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.<sup>574</sup> 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.<sup>575</sup> Marital discord in these circumstances has been noted previously.<sup>575,576</sup> 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 consequent guilt and indifference (Table 1.6).<sup>574</sup> Women with secondary infertility, and those younger than 21 years of age (or immature women), had the most prolonged emotional, physical, and social difficulties.<sup>574</sup>

Grief counseling becomes part of the consultation after elective termination, in which full recognition of bereavement is necessary (see Chapter 31). Compassion fatigue, characterized as feeling overwhelmed by experiencing patients’ suffering,<sup>577</sup> mainly in cancer genetic counseling, is not likely to be an issue in prenatal genetic counseling. The psychology of mourning has been

## 42 Genetic Disorders and the Fetus

**Table 1.6** The frequency of emotions and somatic symptoms of 84 women and 68 men: overall and 24 months after terminating a pregnancy for fetal abnormality

|                        | Women (%) | Men (%) | Women after 24 months (%) | Men after 24 months (%) |
|------------------------|-----------|---------|---------------------------|-------------------------|
| <i>Feeling</i>         |           |         |                           |                         |
| 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                       |
| <i>Somatic symptom</i> |           |         |                           |                         |
| 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.<sup>574</sup>

thoroughly explored<sup>578–580</sup> (see Chapter 31). Worden emphasized how important it is for a bereaved individual to complete each of four stages in the mourning process:<sup>579</sup>

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.<sup>581,582</sup> 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.,<sup>582</sup> 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.<sup>583–586</sup> Fanos<sup>583</sup> 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.<sup>587</sup> 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.<sup>587</sup> 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.<sup>588</sup> Special attention should be focused on assuaging aspects of guilt and shame. Difficult as it may be for some physicians,<sup>589,590</sup> close rapport, patient visitation, and sincerity are necessary at these times, even when faced with commonly experienced anger. A misstep by the physician in these circumstances in failing to continue (it is to be hoped) the rapport already established during pregnancy care provides the spark that fuels litigation in relevant cases.

Despite anger, grief, and the gamut of expected emotions, the attending physician (not an 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, or by subsequent DNA studies (see Chapters 3 and 9). In circumstances in which parents steadfastly withhold permission for autopsy, radiographs, magnetic resonance imaging, computed tomography and needle liver biopsy could provide DNA and important information when a precise diagnosis has yet to be made.<sup>591,592,593</sup> Magnetic resonance imaging could provide a useful acceptable alternative when fetal anomalies are expected.<sup>591</sup> The autopsy is the last opportunity parents will have to determine causation, which may ultimately be critical in their future child-bearing plans and also for their previous children. A formal protocol for evaluating the cause of stillbirth or perinatal death is important (Box 1.2) 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 1.3) 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, spinal muscular atrophy).

Psychologic support is important for couples who have lost an offspring from any cause – a situation compounded by fetal or congenital abnormality.<sup>594</sup> The birth (or prenatal detection) of twins discordant for a chromosomal disorder is not rare, given the increased frequency of multiple pregnancy associated with advanced maternal age and the use of assisted reproductive techniques. Pregnancy reduction (see Chapter 29) 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.<sup>595</sup> Considerable psychologic skill must be marshaled by



**Box 1.2 Protocol for evaluating the cause of stillbirth or perinatal death**

1. Review genetic, medical and obstetric history.
2. Determine possible consanguinity.
3. Gently and persistently recommend that parents permit a complete autopsy.
4. Obtain photographs, including full face and profile, whole body and, when applicable, detailed pictures of any specific abnormality (e.g. of digits).
5. Obtain full-body skeletal radiographs.
6. Consider full-body magnetic resonance imaging,<sup>397</sup> if autopsy is not permitted, but disclose limitations.<sup>593</sup>
7. Carefully document any dysmorphic features.
8. Consider a needle liver biopsy for DNA.
9. Obtain heparinized cord or fetal blood sample for chromosomal or DNA analysis.
10. Obtain fetal serum for infectious disease studies (e.g. parvovirus, cytomegalovirus, toxoplasmosis).
11. Obtain fetal tissue sample (sterile fascia best) for cell culture aimed at chromosome analysis or biochemical or DNA studies. Freeze some tissue without preservative for future DNA studies.
12. Obtain parental blood samples for chromosome or DNA analysis, when indicated.
13. Communicate final autopsy results and conclusions of special analyses.
14. Provide follow-up counseling, including a summary letter.

physicians if meaningful care and support are to be provided.<sup>596</sup>

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.<sup>597</sup> 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 guilt<sup>598</sup> 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 1.3 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.<sup>581,582,599</sup> 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

**Box 1.3 Action checklist following stillbirth**

|  |   |  |   |
|--|---|--|---|
| DATE OF BIRTH _____  |   | NURSE IN CHARGE _____                                    |   |
| ATTENDING PHYSICIAN _____                                    |   | PHONE # _____  |   |
| NAME OF CLERGY _____   |   | PHONE # _____  |   |
| <input type="checkbox"/> FAMILY PRIVACY SECURED              | <input type="checkbox"/> CARD ON DOOR   | <input type="checkbox"/> PHYSICIAN CALLED                | <input type="checkbox"/> FAMILY MET WITH PHYSICIAN                      |
| <b>PARENTAL OPTIONS</b>                                      | <b>PARENTAL DECISIONS</b>   | <b>COMMENTS</b>  |   |
| Infant viewing   | Yes <input type="checkbox"/> No <input type="checkbox"/>                              | Name: _____  |   |
| Infant holding   | Yes <input type="checkbox"/> No <input type="checkbox"/>                              |  |   |
| Naming of infant   | Yes <input type="checkbox"/> No <input type="checkbox"/>                              |  |   |
| Photographs  | Yes <input type="checkbox"/> No <input type="checkbox"/>                              |  |   |
| Autopsy permission (signature)                               | Yes <input type="checkbox"/> No <input type="checkbox"/>                              |  |   |
| Genetic studies  | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |  |   |
| Burial   | Yes <input type="checkbox"/> No <input type="checkbox"/>                              |  |   |
| Cremation  | Yes <input type="checkbox"/> No <input type="checkbox"/>                              |  |   |
| Family members allowed to visit/hold                         | Yes <input type="checkbox"/> No <input type="checkbox"/>                              |  |   |
| Religious rites  | Yes <input type="checkbox"/> No <input type="checkbox"/>                              |  |   |
| Lock of baby's hair  | Yes <input type="checkbox"/> No <input type="checkbox"/>                              | No   |   |
| Tissue for DNA study obtained and frozen                     | Yes <input type="checkbox"/> No <input type="checkbox"/>                              | No   |   |
| <b>BABY:</b>   | Weight _____  | Length _____   |   |
| Bathed <input type="checkbox"/>                              | Dressed <input type="checkbox"/>  | Footprints <input type="checkbox"/>                      | Photos <input type="checkbox"/> Parents viewed <input type="checkbox"/> |
| Death certificate <input type="checkbox"/>                   |   |  |   |
| MRI of brain <input type="checkbox"/>                        |   |  |   |
| (if autopsy decline)   |   |  |   |
| <b>HOSPITAL DISCHARGE:</b>                                   | Memory envelop given (baby items)   | Yes <input type="checkbox"/> No <input type="checkbox"/> |   |
|  | Grief packet with references given  | Yes <input type="checkbox"/> No <input type="checkbox"/> |   |
|  | Grief counseling referral   | Yes <input type="checkbox"/> No <input type="checkbox"/> | Declined <input type="checkbox"/>                                       |
|  | Genetic counseling referral   | Yes <input type="checkbox"/> No <input type="checkbox"/> |   |
|  | Follow up consultation (and to discuss autopsy results)                               | Yes <input type="checkbox"/> No <input type="checkbox"/> |   |
| Nurse Completing Form: Name _____ Signature _____ Date _____ |   |  |   |

held. Important mementos that parents should be offered are photographs,<sup>600</sup> a lock of hair, the baby's name band or clothing.<sup>595,596</sup> 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.<sup>601</sup> Photos may also be helpful in providing comfort for other children and for grandpar-

ents. 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.<sup>602</sup> 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.<sup>603</sup> Similarly, parents should be fully informed about the consequences of having a “replacement child” very soon after their loss.<sup>604,605</sup> 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**

The essential goal of the communication process in genetic counseling is to achieve as complete an understanding by the counselee(s) as possible, thereby enabling the most rational decision making. Parental decisions to have additional affected progeny should not be viewed as a failure of genetic counseling. Although the physician’s goal is the prevention of genetic disease, the orientation of the prospective parents may be quite different. A fully

informed couple, both of whom had achondroplasia, requested prenatal diagnosis with the expressed goal of aborting a normal unaffected fetus so as to be able to raise a child like themselves. Would anyone construe this as a failure in genetic counseling?

Clarke et al.<sup>606</sup> 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.

Evaluation of the efficacy of genetic counseling<sup>28,244</sup> should therefore concentrate on the degree of knowledge acquired (including the retention of the counselee(s) with regard to the indicated probabilities) and the rationality of decision making (especially concerning further reproduction). Frequent contraceptive failures in high-risk families highlight the need for very explicit counseling. 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.<sup>607</sup>

Important points made by Emery et al.<sup>608</sup> in their prospective study of 200 counselors included the demonstrated need for follow up after counseling,

especially when it is suspected that the comprehension of the counselee(s) is not good. This seemed particularly important in chromosomal and X-linked recessive disorders. They noted that the proportion deterred from having children increased with time and that more than one-third of their patients opted for sterilization within 2 years of counseling.

A number of studies<sup>608-610</sup> 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.<sup>473</sup> 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.<sup>611</sup> prospectively studied 2,220 counsees 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 counsees but also on the counselors and the clinics in which genetic counseling was provided. They, too, documented that 53 percent of counsees did not comprehend their risks later, while 40 percent of the counsees given a specific diagnosis did not appear to know it after their counseling. They thoroughly explored the multiple and complex issues that potentially contributed to the obvious educational failure that they (and others) have observed. In another study of parents with a DS child, Swerts<sup>612</sup> noted that of those who had genetic counseling, 45 percent recalled recurrence risks accurately, 21 percent were incorrect and 34 percent did not remember their risks.

The expected postcounseling letter to the referring physician with a copy (or a separate letter) to the patient plays a vital role in securing comprehension of risks and issues. Printed materials, especially covering risks, test limitations, psychological and social aspects, enrich the counseling benefits.<sup>136</sup>

Genetic counseling can be considered successful when counsees, shown to be well informed, make careful, rational decisions regardless of whether their physicians consider their position to be ill advised. Clearly, counsees and counselors may differ in their perception of the consultation and the degree of satisfaction.<sup>613</sup> Notwithstanding the

obvious benefits of counseling, reproductive uncertainty is often not eliminated because it is related to factors beyond the scope of counseling.<sup>614</sup>

In considering the effectiveness of genetic counseling, Sorenson et al.<sup>611</sup> summarized the essence of their conclusion.

In many respects, an overall assessment of the effectiveness of counseling, at least the counseling we assessed in this study, is confronted with the problem of whether the glass is half full or half empty. That is, about half of the clients who could have learned their risk did but about half did not. And, over half of the clients who could have learned their diagnosis did but the remainder did not. In a similar vein, clients report that just over half of their genetic medical questions and concerns were discussed but about half were not. The picture for sociomedical concerns and questions was markedly worse, however. And, 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 Kessler<sup>615</sup> concluded that published studies on reproductive outcome after genetic counseling reveal no major impact of counseling. Moreover, decisions made before counseling largely determined reproduction after counseling.

A study of patients' expectations of genetic counseling revealed that the majority had their expectations fulfilled, especially with perceived personal control.<sup>616</sup> When patients' expectations for reassurance and advice were met, they were subsequently less concerned and had less anxiety compared with when such expectations were not fulfilled.

The limited efficacy of genetic counseling revealed in the study by Sorenson et al.<sup>611</sup> reflects the consequences of multiple factors, not the least of which are poor lay understanding of science and a previous lack or inadequacy of formal training of counselors in clinical genetics,<sup>617</sup> which is no longer the case for genetic counselors in most developed countries. Efficacy, of course, is not solely related to counselee satisfaction. Efforts to educate the public about the importance of genetics

in their personal lives have been made by one of us in a series of books (translated into nine languages) over 38 years.<sup>243,247,249,250,379</sup> In addition to public education and its concomitant effect of educating physicians generally, formal specialist certification in the United States, Canada, and the United Kingdom, acceptance of clinical genetics as a specialty, and degree programs for genetic counselors certified by the National Board of Genetic Counselors, will undoubtedly improve the efficacy of genetic counseling.

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