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Genetic Counseling and Screening of Consanguineous Couples and Their Offspring: Recommendations of the National Society of Genetic Counselors

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The objective of this document is to provide recommendations for genetic counseling and screening for consanguineous couples (related as second cousins or closer) and their offspring with the goals of

1. *providing preconception reproductive options,*
2. *improving pregnancy outcome and identifying reproductive choices,*
3. *reducing morbidity and mortality in the 1st years of life, and*
4. *respecting psychosocial and multicultural issues.*

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The recommendations are the opinions of a multicenter working group (the Consanguinity Working Group (CWG)) with expertise in genetic counseling, medical genetics, biochemical genetics, genetic epidemiology, pediatrics, perinatology, and public health genetics, which was convened by the National Society of Genetic Counselors (NSGC). The consensus of the CWG and NSGC reviewers is that beyond a thorough medical family history with follow-up of significant findings, no additional preconception screening is recommended for consanguineous couples. Consanguineous couples should be offered similar genetic screening as suggested for any couple of their ethnic group. During pregnancy, consanguineous couples should be offered maternal–fetal serum marker screening and high-resolution fetal ultrasonography. Newborns should be screened for impaired hearing and detection of treatable inborn errors of metabolism. These recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. The professional judgment of a health care provider, familiar with the facts and circumstances of a specific case, will always supersede these recommendations.

KEY WORDS: consanguinity; genetic counseling; genetic screening; genetic testing; incest; newborn screening; tandem mass spectrometry.

> First let me start by saying that I have lived with my first cousin for six years and we are madly in love. About four years ago I became pregnant. We had never discussed having children before, mainly because of the "taboo" of us being together in the first place. I immediately went to my gynecologist and explained the situation. He was a bit stunned and said that in all his years of practice he had never come across anything like this. The only thing he told me was that our baby would be sick all the time and then suggested that I have an abortion. Me? Have an abortion? I was heartbroken. He told me that he would check into it more and call me back later. That night I got a call from his receptionist who told me that it was illegal for us to be married, but it was legal for us to have the baby. We were so confused. I went to the library and searched for information, with no luck. My cousin told his mom, who went nuts, saying that our baby would be retarded. I went ahead with the abortion. If my doctor suggested it, I thought it was the right thing to do at the time—the worst mistake of my life. About a year later I flipped on the TV and Jenny Jones was doing a show on cousin couples, saying that cousin couples only have a 3% higher chance of something being wrong with the baby than that of "normal" couples. Needless to say I cried and cried. If only I had seen this show a year sooner or my doctor would have known the facts.
>
> —Anonymous participant, on-line support group for cousin romances, August 2000

The need to disseminate recommendations for genetic counseling and screening for consanguineous unions is dramatically illustrated in the preceding quote. There is limited published information about how to advise and screen consanguineous couples, their pregnancies, and their offspring (Baird and McGillivray, 1982; Bennett *et al.*, 1999; Hall, 1978; Harper, 1998). A 1996 survey of medical geneticists and genetic counselors in the United States found wide variation in the genetic screening practices provided to consanguineous couples and their offspring, as well as disparity in risk figures quoted to these couples (Bennett *et al.*, 1999).

Consanguineous couples, their pregnancies, and their offspring are evaluated in several clinical settings (Bennett *et al.*, 1999). Couples who are cousins may seek

preconception or prenatal genetic counseling services. The child of an incestuous union may come to medical attention if the child is to be placed in foster care or adopted, or if the incestuous relationship is identified during pregnancy. The following recommendations focus on genetic screening and testing, and genetic counseling for these indications.

OVERVIEW

The terms *inbreeding* and *consanguinity* are used interchangeably to describe unions between couples who share at least one common ancestor. Inbreeding in population genetic terms refers to a departure from nonrandom "mating" in that individuals "mate" with those more similar (genetically) to them than if they "mated at random" in the population. Inbreeding is a pejorative term when applied to humans, but the *coefficent of inbreeding* (F) is a term used in population genetics.

Although marriages between close relatives are discouraged (or even illegal) in North America, in many cultures (particularly in the Middle East, Asia, and Africa) preferred marriages are between first cousins, or less commonly, between an uncle and niece or between double first cousins (Bittles, 1998; Harper, 1998). Double first cousins are the offspring of two sets of siblings, such as two brothers married to two sisters (Fig. 1 example B). In some parts of the world 20–60% of all marriages are between close biological relatives (Bittles, 1998). Reviews of Roman Catholic marriage dispensations in the United States and Canada found the prevalence of requests for cousin marriages to be between 1.3–1.5% and 0.1–0.2% respectively (De Braekeleer and Ross, 1991; Dewey *et al.*, 1965; Freire-Maia, 1968; Lebel, 1983). A study of cousin marriages in Wisconsin from 1843 to 1981 suggests a rate of consanguineous marriage of about 1 in 1300 marriages (Lebel, 1983). There are specific communities within the United States and Canada where consanguineous unions are common (Table I) (Bear *et al.*, 1988; Bittles, 1998; Brown, 1951; De Braekeleer and Ross, 1991; Drosten *et al.*, 1999; Freire-Maia, 1968; Moore, 1987; Thomas *et al.*, 1987).

The term incest is defined differently in biological and legal settings. The legal definition often includes unions between nonbiological relatives (e.g., between stepfather and stepdaughter, or step siblings). The prevalence of incest in the United States and Canada is difficult to establish, and is likely to be underreported because of the associated social stigma and legal consequences. Data on incest is mostly gathered from retrospective studies of child sexual abuse; approximately half of this abuse is estimated to be by family members (which may include nonbiological relatives) (Whetsell-Mitchell, 1995). Sibling–sibling contact may be the most common form of incestuous activity (Maddock and Larson, 1995). Incest perpetrators are found across all socioeconomic and ethnic backgrounds. In this report, incest is defined as a mating between biological first-degree relatives (i.e., father–daughter, mother–son, brother–sister). There is no published data on

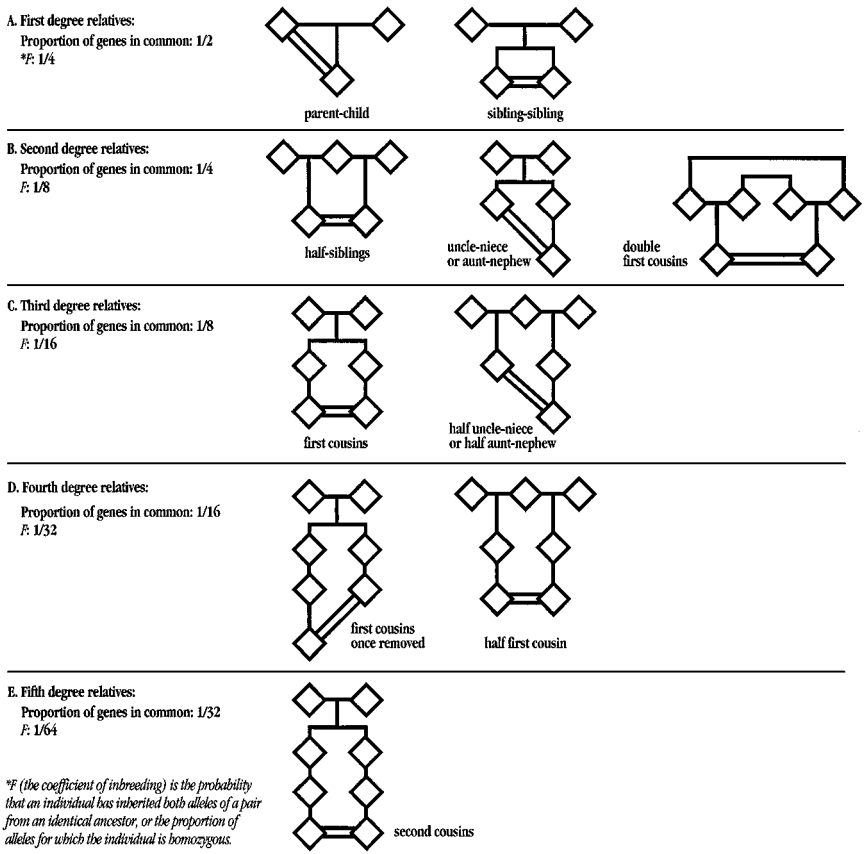

Fig. 1. Examples of consanguineous unions and their coefficients of inbreeding.

the number of offspring produced from incestuous unions between biological first-degree relatives.

The offspring of consanguineous unions may be at increased risk for genetic disorders because of the expression of autosomal recessive gene mutations inherited from a common ancestor. The closer the biological relationship between parents, the greater is the probability that their offspring will inherit identical copies of one or more detrimental recessive genes. For example, first cousins are predicted to share 12.5% (1/8) of their genes. Thus, on average, their progeny will be homozygous (or more precisely, autozygous) at 6.25% (1/16) of gene loci (i.e., they will have received identical gene copies from each parent at these sites in their genome).

Offspring of consanguineous unions may also be at increased risk for disorders of multifactorial or complex inheritance. However, well-controlled studies

Table I. Examples of Data on Consanguineous Marriage in Select Populations in the United States and Canada[a]

Location	Collection period	Study population	Sample size	Consanguinity (%)	Mean inbreeding coefficient (α)	Reference
New Brunswick Bathurst, Canada	1959	RC[b] dispensation	686	4.8	0.0010	Freire-Maia (1968)
Quebec Gaspe, Canada	1959	RC dispensation	600	6.0	0.0012	Freire-Maia (1968)
Kentucky, (Beech Creek), USA	1942	Household survey	107	18.7	0.0061	Brown (1951)
New Mexico, (Gallup), USA	1959	RC dispensation	370	1.4	0.0004	Freire-Maia (1968)
Austin, Texas, USA	1959	RC dispensation	675	1.3	0.0006	Freire-Maia (1968)
Kansas, (Mennonites), USA	1980	Pedigree analysis	194	33.0	0.0030	Moore (1987)
Boston, ("Gypsies"), USA	1980s	Pedigree analysis	21	61.9	0.0170	Thomas *et al.* (1987)
Utah (Mormon), USA	2000	Utah population database	303,675	1.2	0.0004	Jorde (2001)

[a] Adapted from Bittles (1998).
[b] RC = Roman Catholic.

evaluating the effect of consanguinity on multifactorial diseases of childhood and adulthood have not been conducted. The studies to date are not conclusive as to whether consanguinity increases the risk for multifactorial disorders (Bittles, 1998, 2001; Jaber *et al.*, 1997; Shami *et al.*, 1991; Stoltenberg *et al.*, 1997).

The coefficient of inbreeding (F) provides a numerical estimate of the degree of inbreeding of an individual. F values are higher for unions between closer relatives, that is, the offspring of an incestuous relationship have a greater F value than do those of a first-cousin relationship. The F values for various degrees of consanguineous relationships are shown in Fig. 1. The mean inbreeding coefficient (α) can also be calculated for entire populations in which a proportion of marriages are consanguineous, and for individuals who are related through multiple loops of consanguinity (see under Populations With High Mean Coefficients of Inbreeding and under Pedigrees With Multiple Loops of Consanguinity). Populations with a high mean inbreeding coefficient do not necessarily represent a community of close cousin marriages, and in fact cousin marriage may be discouraged (Jorde, 2001).

Few studies document the actual risks to the offspring of consanguineous unions. The risks quoted for birth defects and mental retardation are often based

on studies of non-Western populations where consanguineous unions are common, and they may not be applicable to consanguineous unions in the United States and Canada (Al-Abdulkareem and Balal, 1998; Al-Awadi *et al.*, 1985; Al-Gazali *et al.*, 1997; Bittles, 1998, 2001; Bittles *et al.*, 1991; Bittles and Neel, 1994; Harper, 1998; Jaber *et al.*, 1997, 1998; Kaku and Freire-Maia, 1992; Madhaven and Narayan, 1991; Schull and Neel, 1965; Shami *et al.*, 1991; Vogel and Motulsky, 1996). Furthermore, in all such studies, the criteria for what is considered a significant medical problem in offspring are not standardized. Studies using excess mortality to measure the adverse effects of inbreeding often did not account for the effects of sociodemographic variables such as maternal age, birth interval, socioeconomic status, and maternal education, thereby exaggerating the adverse effect of consanguinity (Bittles, 1998; Kaku and Freire-Maia, 1992). The risk of adverse medical outcomes for the offspring of consanguineous unions, as compared to a baseline risk for the general population, is reviewed under Baseline Risk for the Offspring of Consanguineous Unions Compared to Those From Nonconsanguineous Unions.

PURPOSE

These recommendations are intended to assist health care professionals who provide genetic counseling and screening to consanguineous couples and their offspring. The recommendations focus on the offspring of cousin unions (related as biologic second cousins or closer), and the offspring of incestuous unions (relationships between biologic first-degree relatives). The recommendations consider genetic screening and testing that is available to practitioners in the United States and Canada, given current standards of health care prevention and genetic screening offered to the general (nonconsanguineous) population. Psychosocial and multicultural issues in genetic counseling are reviewed.

OBJECTIVES

The goals of these recommendations are to

A. Provide risk assessment and reproductive options to consanguineous couples who request genetic counseling in a preconception setting.
B. Improve pregnancy outcome and provide reproductive options when parental consanguinity is identified in a pregnancy.
C. Reduce morbidity and mortality in the first years of life for children from consanguineous unions.
D. Consider psychosocial and multicultural issues related to genetic counseling for consanguineous couples, with a focus on nonincestuous relationships.

These recommendations do not address the legal ramifications of consanguineous unions, which are unique to each state in the United States. Although

the medical and genetic consequences of biological incest are reviewed in these recommendations, the psychosocial considerations are very different from those of cousin unions. For example, there is a major attitudinal difference regarding a union involving consenting adult cousins as compared to incestuous abuse of a minor. Unions between cousins are the primary focus of this paper.

METHOD

The authoring subcommittee (Consanguinity Working Group (CWG)) consisted of experts in genetic counseling (RLB, SU, DLD, KS, EC), medical genetics (AGM, LH, CRS, EC, BM, RDS), public health genetics (DLD, KS, AGM), genetic epidemiology (AB), biochemical genetics (CRS, RDS), pediatric genetics (LH, CRS, RDS), and perinatology (EC). The CWG included non-NSGC (National Society of Genetic Counselors) members (AGM, LH, CRS, EC, BM, RDS, AB).

The MEDLINE and PubMed databases were searched (using the key words consanguinity and incest) to locate relevant English language medical papers published between 1965 and August 2000. Additional papers were identified through bibliographies of articles. Papers were reviewed with attention to genetic counseling and multicultural issues. The data was reviewed and evaluated according to the following categories outlined by the U.S. Preventive Services Task Force (1995):

I. Evidence obtained from at least one properly designed randomized controlled trial.
II-1. Evidence obtained from well-designed controlled trials without randomization.
II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3. Evidence obtained from multiple time series, with or without the intervention.
III. The opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

All supporting evidence cited in this document is Class III. No supporting literature of Categories I or II was identified.

The authoring committee sought expert review from specialists in North America. Opinions were sought from representatives of a support group for consanguineous couples (www.cousincouples.com). The recommendations were presented at the 2000 Annual Education Conferences of both the NSGC and the American Society of Human Genetics. They also were presented in September 2000 at the First International Workshop on Consanguinity, Endogamy and Cultural Diversity in Leeds, United Kingdom (www.consang.net/Leeds2000/index.htm). A draft of the document was made available on the Internet to all members of the NSGC for comment (91% of the 1867 NSGC members are registered on the NSGC listserv). The NSGC membership includes genetic counselors, physicians, nurses, attorneys, PhD genetics professionals, social workers, and students. The

NSGC Ethics Subcommittee (composed of seven genetic counselors, and an ad hoc bioethicist/clergy representative) and an attorney for the NSGC reviewed the revised document. No conflicts with the NSGC Code of Ethics were identified in the final document. The NSGC Board of Directors unanimously approved the final document in May 2001.

PRIMARY GENETIC SCREENING AND TESTING CONSIDERATIONS FOR CONSANGUINEOUS COUPLES AND THEIR OFFSPRING

Baseline Risk for the Offspring of Consanguineous Unions Compared to Those From Nonconsanguineous Unions

The probability of an adverse outcome in the offspring of a consanguineous union is not an absolute number. Rather, the estimated risk must be based upon background population risk, degree of consanguinity, and relevant family history. The chance of a significant medical problem in the offspring of a consanguineous couple can be thought of as two additive risks—the background population risk, plus the additional risk because of consanguinity. Population studies in the United States and Canada that estimate the general population risk for birth defects in the first years of life are summarized in Table II (Applegarth *et al.*, 2000; Baird *et al.*, 1988; Leppig *et al.*, 1987; Wilcox and Marks, 1999). Compiling an absolute risk for the offspring of consanguineous unions is impossible because the populations from which these risk estimates have been generated vary in their sociodemographic characteristics, the methods of subject ascertainment, and the definition of an adverse health outcome. For illustrative purposes, data from several studies that estimate the excess risks of birth defects and prereproductive mortality in the

Table II. Examples of Studies Determining Baseline Population Estimates for Birth Defects, Genetic Disorders, and Metabolic Disease in the United States and Canada

Reference	Risks quoted	Population studied
Baird *et al.* (1988)	5.3%, for disease with important genetic component by age 25 years	British Columbia, Canada
Applegarth *et al.* (2000)	0.04% (40 cases per 100,000 live births), minimum incidence of metabolic disease[a]	British Columbia, Canada (mostly Caucasian)
Wilcox and Marks (1999) (Center for Disease Control, Birth Defects Monitoring Program)	3–4%, for major birth defects in 1st year of life	USA, >17 million births from ~1200 mid-sized community hospitals
Leppig *et al.* (1987)	3.16 %, for major malformation to age 5 days	Boston, MA, USA, 4305 Caucasian births

[a] Diseases of amino acids, organic acids, urea cycle, galactosemia, lactic acidosis, glycogen storage disease, lysosomal storage diseases, peroxisomal and mitochondrial respiratory chain dysfunction.

Table III. Estimate of Risk to the Offspring of a First Cousin Union Compared to Nonconsanguineous Unions

Reference	Population studied	Risk, general population	Risk, offspring of first cousins
Jaber *et al.* (1998)	Compiled data from 9 populations (Chicago, U.S., Middle East, Norway)	2.1% major malformations	4.5% major malformations
Demirel *et al.* (1997)	1120 randomly selected women in Konya, Turkey	0.8% congenital anomaly ($n = 20/2804$)	2.5% congenital anomaly ($n = 13/543$)
Stoltenberg *et al.* (1999)	1.56 million births in Norway from 1967 to 1993	1.5% structural birth defects in first few days of life[a]	3.6% structural birth defects in first few days of life[b]
Schull and Neel (1965)	Data on 9122 pregnancies in the cities of Hiroshima and Nagasaki, Japan	Mortality in childhood: Hiroshima 6.4%, Nagasaki 7.7%	Mortality in childhood: Hiroshima 9.2%, Nagasaki 8.7%
Bittles and Neel (1994)	Compiled data from 38 populations in eastern and southern Asia, Middle East, Africa, Europe, South America	Population-specific prereproductive mortality to median 10 years: 3.1–39.5%	4.4% increased prereproductive mortality above background risk
Jorde (2001)	Compiled data on 303,675 members of the Utah Mormon population born between 1847 and 1945	13.2% prereproductive mortality (before age 16 years)	8.8% increased prereproductive mortality above background risk

[a] 3.3% if parents had child with a previous birth defect.
[b] 6.8% if parents had child with previous birth defect.

offspring of first cousin unions are reviewed in Table III (Bittles and Neel, 1994; Demirel *et al.*, 1997; Jaber *et al.*, 1998; Jorde, 2001; Schull and Neel, 1965; Stoltenberg *et al.*, 1999). In these studies, the increased risk for a significant birth defect in offspring of a first cousin union range between 1.7 and 2.8% above the risk of the general population risk. There is an estimated 4.4% risk for prereproductive mortality (to median age of 10 years) above that of the background population risk (this number includes birth defects resulting in mortality) (Bittles and Neel, 1994). This figure is derived from combined data from 38 populations in eastern and southern Asia, Africa, Europe, and South America.

Given the almost universal cross-cultural stigma, social disapproval, and legal sanctions to incestuous unions, there is a paucity of data regarding adverse medical outcomes in the offspring of incestuous unions. Published studies are fraught with significant ascertainment biases. These biases, such as lack of paternity documentation, young maternal age, possible parental disease and/or intellectual impairment, parental socioeconomic status (or lack of report of this variable), and complications of unsuccessful attempted pregnancy termination (Bittles, in press). Table IV summarizes the four most comprehensive published studies of incest (Adams and Neel, 1967; Baird and McGillivray, 1982; Carter, 1967; Seemanova,

Table IV. Abnormalities in the Offspring of First Degree Incestuous Unions

Year and origin of study	Number of participants	Years follow-up	Normal	Known autosomal recessive disorders	Congenital malformations/SIDS[a]	Nonspecific severe intellectual impairment	Mild intellectual impairment
USA (Adams and Neel, 1967)	18	0.5	7	2	4	0	5
UK (Carter, 1967)	13	4–6	5	2	1	1	4
Czechoslovakia (Seemanova, 1971)	161	1–37	78	20	21	24	18
Canada (Baird and McGillivray, 1982)	21	0.5–1.9	8	1	8	0	4
Totals	213		98 (46.0%)	25 (11.7%)	34 (16.0%)	25 (11.7%)	31 (14.6%)

[a] Adapted from Bittles (in press).
[b] SIDS – sudden infant death syndrome.

1971). Three of these studies were retrospective, and the controls for matched nonincestuous pregnancies were highly variable (Baird and McGillivray, 1982; Carter, 1967; Seemanova, 1971). These studies are also limited in the number of years that the incestuous progeny were followed. Although the highest risk for morbidity and mortality would be expected in the first year of life, moderate medical problems and mental retardation would not be evident until later.

By combining the four sets of data in Table IV, and selecting the cases of specific autosomal recessive disorders recorded ($n = 25$), plus major congenital malformations ($n = 34$), and nonspecific severe intellectual handicap ($n = 25$), 84 of 213 (39.4%) of the progeny of incestuous unions had died or were impaired (Bittles, in press). This analysis does not control for nongenetic variables. In the two studies for which nonconsanguineous reference groups were available, 8.0% of the control children (9 of 113) died or had a serious defect (Carter, 1967; Seemanova, 1971). Thus, the excess level of death and severe defect in the offspring of incestuous unions (a proportion of which may have been nongenetic in origin) was 31.4% (Bittles, in press).

An alternative method of analysis is to use the risks observed in first cousin unions to calculate mortality and morbidity associated with incest, based on the coefficient of inbreeding F (refer to Fig. 1). This assumes that risks for mortality and birth defects are directly scalable with F, which may not be an accurate assumption, particularly for disorders with complex inheritance. If the excess prereproductive mortality rate among first cousin offspring (who have an F value of 1/16) is 4.4%, then one would predict an excess death rate of approximately 17.6% for offspring of incestuous unions (with an F value of 1/4). Likewise if the offspring of first cousin unions are estimated to be at 1.7–2.8% risk above the background (Table III), then the predicted risk to the offspring of first-degree relatives would be at 6.8–11.2% risk above the population background for significant birth defects.

Genetic Screening and Testing for Consanguineous Couples and Their Offspring

The simplest and most comprehensive tool for providing genetic screening to consanguineous couples and their offspring is obtaining a medical family history covering 3–4 generations from the consultand(s), as reviewed under Medical Family History (Bennett, 1999). Appropriate testing can be requested based on the family history and the ethnic background, just as it would be offered in the genetic evaluation of a nonconsanguineous couple. When a known or suspected genetic condition is identified in a fetus or newborn of a consanguineous union, the genetic evaluation should proceed as it would for a nonconsanguineous union. Likewise, genetic evaluation and risk assessment for a consanguineous couple with a previous child with a known or suspected genetic condition should proceed as it would for a nonconsanguineous couple. Genetic evaluation of the offspring of a

consanguineous union would proceed with a high index of suspicion for autosomal recessive disorders in the differential diagnosis.

Endogamy refers to a society in which mating partners are preferentially chosen from within the group, usually because of a combination of geographical, cultural, and religious factors. In populations that are highly endogamous, genetic counseling and screening should be offered with consideration of the genetic disorders that occur with higher frequency in that specific population (because of founder effects and genetic drift), as well as current standards of preconception, prenatal, and newborn genetic screening for the general population in that geographic location (see under Baseline Risk for the Offspring of Consanguineous Unions Compared to Those From Nonconsanguineous Unions). For example, cystic fibrosis carrier testing might be offered to a Northern European couple who are first cousins, because cystic fibrosis is a common condition in that population (Grody *et al.*, 2001). A listing of over 1000 references to inherited disorders that have been described in specific population groups is available at www.consang.net. Note that the probability that an offspring of a consanguineous union, affected with an autosomal recessive condition is autozygous is lower if the carrier frequency (q) is high and the coefficient of inbreeding (F) is low, than it would be for an autosomal recessive disorder for which q is small (e.g., the offspring of a consanguineous union can be an autosomal recessive condition without being autozygous). Ten Kate *et al.* (1991) use the example of two children with cystic fibrosis born to a couple related through multiple loops of consanguinity where both children were compound heterozygotes and had a delta F508 mutation and another mutation. The anticipated result in a consanguineous union would be that both parents carried the same mutant allele and children would be homozygous for the same mutant allele.

Preconception Genetic Screening for Consanguineous Couples

Sometimes couples who are related as second cousins or closer request genetic counseling prior to marriage or before they conceive a pregnancy. Aside from a thorough medical family history, there is no need to offer any genetic testing on the basis of consanguinity alone. The couple may be from a population or community that has a high coefficient of inbreeding because of many common ancestors (e.g., Amish community in the United States; Hutterites from Alberta and Saskatchewan, Canada, etc.). Certain autosomal recessive disorders may be common in a specific population and carrier screening can be an option in this instance (refer to www.consang.net).

Genetic Screening for a Fetus of a Consanguineous Union

As in nonconsanguineous unions, maternal–fetal serum marker screening should be offered at 15–18 weeks gestation to screen for congenital medical

conditions including neural tube defects (American College of Obstetrics and Gynecology, August 1994). The use of first trimester maternal–fetal markers and ultrasound as an early mode of screening for some congenital anomalies and chromosome aneuploidy is promising, but this method is still investigational (Economides *et al.*, 1999). The pregnancy of a consanguineous couple should be screened for major fetal structural anomalies with the use of high-resolution fetal ultrasound at 20–22 weeks gestation (Allan, 2000; Economides *et al.*, 1999; Schwarzler *et al.*, 1999). The identification of an anomaly by fetal ultrasound or an abnormal maternal–fetal marker profile should be evaluated without special consideration to consanguinity (aside from considering autosomal recessive disorders as a possible etiology). The chance of having a child with a chromosome anomaly does not appear to be increased in consanguineous unions (Devoto *et al.*, 1985; Hamamy *et al.*, 1990).

Genetic Screening for Offspring of Consanguineous Unions

The children of consanguineous unions are at increased risk for autosomal recessive disorders, some of which may be inborn errors of metabolism with treatment options (Applegarth *et al.*, 2000; Rashed *et al.*, 1995). In addition to standard neonatal screening, the offspring of consanguineous unions (where the parents are related as second cousins or closer) should be offered supplemental neonatal screening of filter paper blood spots by tandem mass spectrometry (MS/MS) for analysis of amino acids and acylcarnitines (American Society of Human Genetics Social Issues Committee and the American College of Medical Genetics Social, Ethical, and Legal Issues Committee, 2000; Rashed *et al.*, 1995; U.S. Department of Health and Human Services, April 13, 2001). Some states in the United States and provinces in Canada already offer MS/MS screening for all neonates. Infants with abnormal results should be offered diagnostic confirmation and referral to medical specialists with expertise in inborn errors of metabolism (U.S. Department of Health and Human Services, April 13, 2001).

Many forms of prelingual hearing loss are inherited in an autosomal recessive pattern and collectively represent one of the most common groups of recessively inherited conditions (Willems, 2000). Early identification of children with hearing impairment, accompanied by treatment and appropriate learning opportunities, is likely to improve their ability for successful communication strategies in a hearing world. Therefore, hearing screening should be offered by 3 months of age, and ideally before hospital discharge to children of consanguineous unions (related as second cousins or closer). Universal newborn hearing screening is being implemented in some U.S. states and Canadian Provinces (refer to the American Speech–Language–Hearing Association website at www.asha.org).

In the United States and Canada the standard of care is for all children to receive periodic well child checkups with their primary health care providers (Committee on Practice and Ambulatory Medicine, American Academy of Pediatrics,

2000, website, www.AAP.org). These scheduled evaluations are particularly important for the child of a consanguineous union so that potential medical problems of genetic origin can be identified at an early age, allowing appropriate interventions.

PRIMARY GENETIC COUNSELING ISSUES IN CONSANGUINITY

Assessment

Ascertain the client's primary questions and concerns and mutually develop a plan to address these concerns.

Medical Family History

A. The consanguineous relationship should be documented in the form of a pedigree (Fig. 1). Patients often confuse degrees of relationships (e.g., confuse first cousins once removed with second cousins, or confuse step-relatives as being biologically related) (Bennett, 1999; Spence and Hodge, 2000; Young, 1999).
   i. Using standardized pedigree symbols (Bennett, 1999; Bennett *et al.*, 1995) obtain a comprehensive three or more generation pedigree from the consultand or proband. Include offspring, siblings, parents, grandparents, aunts, uncles, nieces, nephews, and first cousins of the consultand or proband, as appropriate.
   ii. Consanguinity is noted on the pedigree with two parallel mating lines between the couple (Fig. 1) (Bennett, 1999; Bennett *et al.*, 1995).

B. Note in particular if any relatives have a medical history compatible with inborn errors of metabolism (Table V), or other potentially genetic disorders (Bennett, 1999).
   i. Verify potential genetic disorders with medical records, if possible. Consider referral for clinical genetic evaluation of individual(s) suspected to be affected with a genetic condition, as needed.
   ii. Provide a genetic risk assessment for carrier status and the chances of affected offspring if autosomal recessive disorders or other inherited conditions are identified (Harper, 1998; Spence and Hodge, 2000; Vogel and Motulsky, 1996; Young, 1999).
   iii. Offer genetic testing depending on test availability, as appropriate.

C. Note the ethnicity of all grandparents and offer genetic screening appropriate for any couple of that ethnic background (e.g., cystic fibrosis testing for a Caucasian couple, hemoglobinopathy and thalassemia screening for African American couples or those of Caribbean descent, thalassemia screening for couples of Eastern Mediterranean or Asian background,

Table V. Specific Patient Interview Questions to Help Identify a Family History of Inborn Errors of Metabolism

Do any of your biological relatives have a history of
- Mental retardation or developmental delay?
- Failure to thrive (e.g., poor weight gain, poor feeding, frequent vomiting)?
- Normal physical and/or mental development followed by progressive decline of physical and/or mental skills?
- Floppiness (hypotonic or low muscle tone)?
- Chronic illness, infections, or vomiting? Note any triggers to illness, particularly fasting or unusual dietary patterns
- Unusual odor, particularly when ill? Describe the odor
- Cataracts, corneal clouding, lens or retinal abnormalities, detected at or soon after birth or in childhood?
- A seizure disorder?
- Coma?
- Sudden infant death, particularly if preceded by a period of vomiting or fasting from an illness?
- Death in the first few days of life or in early childhood?

[a] Adapted from Bennett (1999).

etc.) (American College of Obstetrics and Gynecology, 2000; Grody *et al.*, 2001).

D. Maintain confidentiality of the family history with respect to the consultand(s) and extended family members.

Psychosocial History of the Consultand(s)

Attempt to build a relationship with the consultand(s) by validating feelings, empathizing, and listening. For each consultand, assess and address

A. Level of comprehension and communication.
B. Level of education, employment, and social functioning.
C. Perceived risk and perceived burden of risk. Clarify any family myths and misconceptions about risks.
D. Coping skills.
E. Family/community support structure. Discuss any stigma that the consultand(s) may perceive from family and peers.
F. Cultural beliefs about causation of birth defects and risks to offspring associated with consanguinity.

Risk Assessment

A. Analyze the pedigree. Calculate the coefficient of inbreeding if multiple loops of consanguinity are present (see under Pedigrees With Multiple Loops of Consanguinity) (Spence and Hodge, 2000; Young, 1999).

B. Offer genetic testing and screening as appropriate (see under Genetic Screening and Testing for Consanguineous Couples and Their Offspring).

Psychosocial Issues

In the United States there is significant stigma associated with consanguineous relationships (Ottenheimer, 1996). Mistaken societal beliefs in the "ills of cousin unions" are deeply ingrained as noted by Dr Bell, a New England physician in 1859:

> Perhaps no opinion, upon subjects of a medical character, is more widely diffused among the public, or more tenaciously held, than that the results of the marriage of blood relations are almost uniformly unfortunate. This opinion has been so long held and so often reiterated, that by sheer force of these circumstances alone it has come to be regarded as an unquestioned and unquestionable fact.

The history of hemophilia in the royal families of Europe in the 18th and 19th centuries is often cited as an example of the detrimental effects of inbreeding, even though the inheritance of this X-linked recessive condition would have occurred regardless of the consanguineous unions in the Royal families (Ottenheimer, 1996).

A key component of genetic counseling is to ascertain the client's preconceived notion of the nature and magnitude of genetic risks to their offspring (Baker *et al.*, 1998). If the client is from a culture where consanguineous unions are uncommon, discussing how frequent consanguineous unions occur in other parts of the world can be reassuring. Providing historical examples of cousin couples may also help to "normalize" their situation (e.g., Charles Darwin and his wife Emma Wedgwood were first cousins, as were Albert Einstein and his second wife Elsa Einstein; Queen Elizabeth II and her husband Prince Philip are related as closer than third cousins, etc.).

Consanguineous couples may keep their relationship hidden because of fears of stigma, discrimination, ostracization, and even legal prosecution. Discussing such fears and the attitudes of family and friends regarding their relationship is important. If a consanguineous couple has a child with a congenital anomaly or a genetic disorder, there may be an attitude of "I told you so" among family members and acquaintances, adding to feelings of parental guilt. Providing a follow-up letter after the genetic counseling session can clarify misconceptions that may circulate among the couple's family and peers.

Shame reactions to perceived or actual external disapproval, ridicule, and scorn are also prominent in these families, particularly in the United States where consanguinity has been traditionally frowned upon. Kessler (in Resta, 2000) and Weil (2000) have written excellent reviews on the management of guilt and shame reactions in a genetic counseling setting.

Psychosocial counseling concerning incestuous unions is complex, particularly if the union involves a minor (Damon and Card, 1999; Maddock and Larson, 1995; Whetsell-Mitchell, 1995). Referral to specialized therapists and community support services is indicated if such services are not already in place.

Identification of positive carrier status may alter the person's self-concept. There may be an altered perception of genetic identity, changed relationships with the family of origin, damage to self-esteem, altered social identity, altered perception of health, and a threat to the parental role (Baker *et al.*, 1998; McConkie-Rosell and DeVellis, 2000; Weil, 2000).

Multicultural Issues

Immigrants to the United States and Canada from populations where consanguineous unions are common may have attitudes about the preference of consanguineous unions that are deeply embedded in cultural beliefs. Factors include the desirability of familiarity with the family's social and biological traits, and possible better treatment by in-laws (Alwan and Modell, 1997; Bittles, 1998, 2001; Demirel *et al.*, 1997; Hussain, 1999; Panter-Brick, 1991; Shiloh *et al.*, 1995). There may be an economic rationale for keeping goods and property within a family. Genetic counseling should explore the client's cultural belief systems while being respectful of client beliefs and cultural traditions (Panter-Brick, 1991; Shiloh *et al.*, 1995).

FOLLOW-UP

A. Arrange/facilitate additional appointments to complete the family history, risk assessment, and testing considerations as indicated. Assist in referrals for evaluation of abnormal tests or screening results (e.g., abnormal ultrasound, positive neonatal screening, etc.).
B. A letter to the consultand(s) that includes a summary of major topics discussed in the genetic counseling session is helpful (Hallowell and Murton, 1998). The consultand(s) may also choose to share the letter to educate family members and health professionals.
C. Provide the consultand/couple with names of support groups and resources (see under Patient Resources).

PATIENT RESOURCES

The Cousin Couples website (www.cousincouples.com) provides access to support services for cousins who are romantically involved. Ottenheimer (1996) provides a historical perspective on the legal and cultural views of consanguinity in the United States.

ETHICAL ISSUES AND SPECIAL CONSIDERATIONS

Genetic Testing for the Child of a Consanguineous Union Placed for Adoption

A child of an incestuous union or even a nonincestuous consanguineous union may be placed for adoption or in foster care because of legal and/or social ramifications. Earlier publications on genetic testing of children from incestuous unions suggested postponing permanent adoption until after 1 year of age, because many diseases would not manifest until that time (Baird and McGillivray, 1982; Hall, 1978; Harper, 1998). A child from a consanguineous union (incestuous or otherwise) who is placed for adoption should not receive special consideration for genetic testing beyond the recommendations for testing outlined under Genetic Screening for Offspring of Consanguineous Unions. This policy is congruent with the American Society of Human Genetics (ASHG) Social Issues Committee and American College of Medical Genetics (ACMG) Social, Ethical, and Legal Issues Committee statement on genetic testing in adoption (2000). This statement does not support genetic testing for adoption that would not be performed on a child "of a similar age for the purpose of diagnosis or of identifying appropriate prevention strategies." It further states that "genetic testing of newborns and children in the adoption process should be limited to testing for conditions that manifest themselves during childhood or for which preventive measures or therapies may be undertaken during childhood." However, prospective parents considering the adoption of a child from a consanguineous union should receive genetic counseling as to the nature and probability of the risks for adverse outcomes, particularly if the child is the product of an incestuous union.

Confirming Parentage When Incest is Suspected

Given the potential legal consequences when incest is suspected, parentage should be confirmed and not assumed by history alone. Genetic counselors may assist in facilitating the arrangement of DNA parentage studies and disclosure of test results. Refer to www.genetests.org for a partial listing of laboratories that perform parentage testing.

Populations With High Mean Coefficients of Inbreeding

A couple may be related because they are members of a community isolate that has many of its genes in common. A population that is geographically and/or culturally isolated, or derived from a small founder population, may have clusters of rare autosomal recessive disorders. The mean coefficient of inbreeding (α) value is available for many of these population groups (Bittles, 1998; Bittles and Neel,

1994; Brown, 1951; Freire-Maia, 1968; Moore, 1987; Thomas *et al.*, 1987). In some genetic isolates, the mean coefficient of inbreeding may approach the level of first cousins ($F = 0.0625$). Examples of the mean coefficient of inbreeding for select populations in North America are shown in Table I.

Pedigrees With Multiple Loops of Consanguinity

A couple may be related through more than one common ancestor, creating multiple "loops" of consanguinity in a pedigree. Discussion of the mathematical principles needed to calculate the coefficient of inbreeding can be found in several excellent sources (Harper, 1998; Spence and Hodge, 2000; Vogel and Motulsky, 1996; Young, 1999). Determining the F value is particularly important if a known genetic condition or multifactorial disorder (such as cleft palate or a congenital heart defect) is identified through pedigree analysis and medical record confirmation. Multiple loops of consanguinity will affect genetic risk assessment and possibly alter strategies for genetic testing and/or screening in the family.

Legal Ramifications of Consanguineous Unions

Thirty states in the United States have laws against cousin marriages. The prohibitions against cousin marriages are not based on empirical biological research or genetic theory (Ottenheimer, 1996). Some laws do not distinguish biological kin from married kin (e.g., prohibiting a stepfather from marrying a stepdaughter). Because each state has its own unique laws against consanguineous unions, genetic counselors and other health professionals should have general knowledge about the laws in their own state and neighboring states in their service area. Cousin marriages are permitted throughout Western Europe. In the United States information about a state's law regarding consanguineous unions can be obtained from the state genetics coordinator. Contact information for the state genetics coordinators can be found at www.stategeneticscoordinators.org.

SUMMARY

Romantic relationships between cousins are not infrequent in the United States and Canada, and these unions are preferred marriages in many parts of the world. The offspring of first cousin unions are estimated to have about a 1.7–2.8% increased risk for congenital defects above the population background risk (Table III). There is an approximately 4.4% increased risk for prereproductive mortality above the population background risk, some of which include major congenital defects. The risk for an adverse health outcome is greatest in the 1st year of life. The risk of an adverse health outcome in the pregnancy from an incestuous union is difficult to quantify because of ascertainment bias in all published studies.

The risk for adverse medical outcome in the offspring of incestuous unions is probably in the range of 7–31% above population background, the risk being greatest in the 1st year of life (Table IV).

There is a great deal of stigma associated with cousin unions in the United States and Canada that has little biological basis. Health providers should provide supportive counseling to these families and respect cultural belief systems. The psychosocial issues for genetic counseling in the case of a cousin union are very different from those for an incestuous union.

The most useful tool for genetic screening for consanguineous couples and their offspring is a thorough medical family history. Genetic counselors are uniquely trained to provide such comprehensive medical family history screening. Genetic testing on the basis of ethnicity should be offered to consanguineous couples, as it would be to nonrelated couples. High-resolution ultrasound should be offered at 20–22 weeks with maternal-serum marker screening at 15–18 weeks. For newborns that result from unions of second cousins or closer, supplemental neonatal screening by tandem mass spectrometry by age 1 week should be offered in addition to the standard neonatal screening tests, with the goal of identifying potentially treatable inborn errors of metabolism. Likewise, hearing screening should be offered by age 3 months to identify hearing loss and to implement subsequent language intervention. Care should be taken to assure that the offspring of consanguineous couples have standard pediatric follow-up care as outlined for all children (www.AAP.org).

These recommendations for genetic counseling and screening for consanguineous couples and their offspring are based on consensus opinion by an expert committee with outside review.

DISCLAIMER

Genetic counseling recommendations of the National Society of Genetic Counselors (NSGC) are to assist practitioners in making decisions about appropriate management of genetic concerns. Each practice recommendation focuses on a clinical or practice issue and is based on a review and analysis of the professional literature. The information and recommendations reflect scientific and clinical knowledge current as of the publication date and are subject to change as advances in diagnostic techniques, treatments, and psychosocial understanding emerge. In addition, variations in practice, taking into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant alternative approaches, treatments, or procedures to the recommendations outlined in this document. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. Genetic counseling recommendations do not displace a health care provider's best medical judgment.

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