Prenatal genetic testing and screening for consanguineous couples in clinical practice: is clinical practice consistent with practice guidelines?

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ABSTRACT

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A thesis presented to the Graduate Program in Genetic Counseling

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Waltham, Massachusetts

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Our study assessed the preconception and prenatal genetic counseling services offered to consanguineous couples in North America. We surveyed genetic counselors who have worked in a prenatal setting at any point between the years 2010 and 2015. We received 132 completed surveys and respondents had an average of 7.5 years of experience in a prenatal setting. Respondents in our study had counseled an average of 19 consanguineous couples since the start of their career. The mean baseline risk respondents quoted for consanguineous couples to have a child with a genetic disorder or congenital anomaly varied from 5.02% to 10.55% depending on the degree of relatedness while counselors cited a 3.57% mean baseline risk for unrelated couples. The common psychosocial concerns perceived by respondents when counseling consanguineous couples were stigma, discrimination, fear, blame and influences of cultural and religious beliefs. Fifty-four percent (N=132) of counselors reported that they refer to some guideline with the majority referring to the National Society of Genetic Counselors (NSGC) guideline for genetic counseling and screening of consanguineous couples and their offspring, published in 2002. When asked if they have recommendations for revising the NSGC guidelines, a number of respondents suggested they be revised to include information on offering new technologies such as expanded carrier screening, non-invasive prenatal testing (NIPT), chromosomal microarray and exome...
sequencing to consanguineous couples as well as strategies to discussing incidental/secondary findings with consanguineous couples. This study, although limited in size, shows that the genetic counseling practices for consanguineous couples is more consistent than observed in the previous study by Bennett et al. (1999).

Keywords: consanguinity, NSGC guidelines, genetic counseling, prenatal testing, stigma
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INTRODUCTION:

Consanguinity is becoming increasingly common in the practice of genetic counseling. There is limited literature about the preconception/prenatal genetic counseling services currently provided to consanguineous couples in North America. This study sought to learn more about genetic counseling practices for consanguineous couples and to identify some of the challenges genetic counselors faced when counseling consanguineous couples. Consanguinity is technically defined as a union between two individuals who are related as second cousins or closer (A H Bittles, 2001; Hamamy, 2012). In various communities, preferred unions may also include first cousins, first cousins once removed, double first cousins, second cousins and uncle-niece (Hamamy, 2012). Relationships between first-degree relatives (e.g. parent-child or siblings), though consanguineous, differ in both legal and cultural terms. In the context of this study, relationships between first-degree relatives are considered to be incestuous rather than consanguineous. (Benjamin M. Helm, 2013).

Consanguineous unions are common in many parts of the world. In some communities of North Africa, Middle East and West Asia, such unions can account for 20 to 50% or more of all marriages (Hamamy, 2012). In India, the prevalence of consanguinity on a national level is about 14% but the prevalence varies due to religious and regional differences. (Rafat Hussain, 2004). In North America and Europe, consanguineous unions are seen more frequently in those immigrant communities, which derive from countries where consanguinity, is more common (Teeuw et al., 2014). Common preferences for consanguineous unions are religious, economic and culturally
based (R. Hussain, 1999). Consolidation of familial property and customs like ‘dowry’ are among the reasons given to favor consanguineous unions. In patrilineal societies, consanguineous marriages may increase compatibility between families and strengthen the position of the women because they only involve rearranging family ties rather than creating ties to a new family (Darr, 2002).

The two factors that first brought the genetic implications of consanguineous marriages to medical attention were an increased migration rate of such couples to the West and the observation of increased infant mortality rates in many Middle Eastern and South Asian countries (Modell & Darr, 2002). The closer the biological relationship between parents, the higher is the chance for their progeny to receive identical copies of one or more genes. First cousin couples inherit 1/8th of their genes from one or more common ancestors and their progeny will be homozygous at 1/16 of all loci (A H Bittles & Black, 2010). The coefficient of inbreeding (F) provides a numerical estimate of the degree of inbreeding of an individual (R. Bennett et al., 2002). It is defined as the measure of the proportion of loci at which the children of a consanguineous union are expected to inherit identical gene copies from both parents (Hamamy, 2012). For a union to be consanguineous F should be 0.0156 or higher. The closer the relation the higher the value of F (Hamamy, 2012). The coefficient of inbreeding for third degree relatives (e.g. first cousin couple) is 0.0625 compared to 0.125 for unions between second-degree relatives (e.g. uncle-niece). In endogamous societies where intra-community marriages date back many centuries, unique gene pools have evolved resulting in common variants due to higher F values as compared to those in random-mating populations. As a result, the chance of founder mutations increases in an endogamous population resulting in the occurrence of specific genetic disorders in each community (Bittles, 2001).
Many studies have assessed the reproductive outcomes, infant mortality, morbidity, and adult health in communities with a high frequency of consanguineous unions. While consanguineous marriages have little effect on the incidence of dominant or X-linked disorders and an uncertain impact on multifactorial disorders, there is a higher baseline risk of occurrence of autosomal recessive disorders (Bittles & Black, 2010; Darr, 2002; Shawky, Elsayed, Zaki, Nour El-Din, & Kamal, 2013). Modell and Darr (2002) report that the prevalence of congenital and genetic disorders was 7.9% and recessive disorders were 3-3.3% in groups with a preference for consanguineous unions, while the rate of congenital and genetic disorders was 4.3% and recessive disorders were 0.28% in populations of Northern Europe where consanguinity is less common. Congenital heart defects like atrial septal defects and ventricular septal defect, autosomal recessive non-syndromic hearing loss, blindness caused by early onset retinal dystrophies and childhood glaucoma, and mild and severe intellectual disabilities were all more common in the progeny of consanguineous couples (Bittles, 2001). A large multinational study reported that infant mortality was up to 1.1% higher and the frequency of birth defects was 2-3% higher than in the general population risk (R. Bennett et al., 2002; Hamamy, 2012). The limitations of these studies are non-genetic and socio-economic confounders such as maternal age, birth interval, socioeconomic status and maternal education that are not easily accounted for (R. Bennett et al., 2002; Bittles & Black, 2010).

Due to the increased risk for birth defects and infant mortality in consanguineous couples, a discussion of reproductive risk is likely to be included in all preconception and prenatal genetic counseling sessions for consanguineous couples. Attitudes of people from different ethnic backgrounds towards reproductive risk and decision making regarding prenatal testing and pregnancy termination is complex (Ahmed et al., 2008; Ahmed, Green, & Hewison, 2006; Shaw,
Religion has been considered to be a critical influence with regard to prenatal testing and termination decisions (Ahmed et al., 2008). Other factors that influence parental response to risk information is their experience with caring for a child with a genetic disorder and the possibility of new therapies (Kelly, 2009; Shaw, 2011). In addition, a person’s culture influences their expectations from health care professionals. Couples, who are from a collectivistic culture, like many where consanguinity is common, are more likely to expect their health care professionals to be authoritative and directive in providing services (Weil, 2001).

In the United States, prenatal screening using maternal serum screens and ultrasound and diagnostic testing such as amniocentesis are offered to all pregnant women. Additional testing is often offered when the pregnancy is classified as high-risk based on advanced maternal age, family history, or increased risk for founder mutations based on ethnicity and degree of parental consanguinity. As a result, consanguineous couples, not otherwise considered high-risk, are increasingly being referred for prenatal genetic counseling (Port, Mountain, Nelson, & Bittles, 2005). Challenges in counseling such families include the existence of consanguinity loops, a reluctance for prenatal testing, and uncertainty about the baseline risks and/or prevalence of founder mutations for recessive genes in particular endogamous populations (Port et al., 2005).

In 1999, Bennett et al conducted a survey of genetic counselors and geneticists certified by the American Board of Medical Genetics, to determine the risk figures they provided to consanguineous couples for congenital birth defects and intellectual disabilities and to learn which genetic services they provided in preconception/prenatal and pediatric genetic counseling setting (R. L. Bennett, Hudgins, Smith, & Motulsky, 1999). They found that the risk figures provided for first cousins ranged from 0.1% to 30% and from 1% to 75% for incestuous unions. The genetic screening and testing offered ranged from screening based on ethnicity to various combinations of
carrier screening and diagnostic testing offered based on consanguinity alone. Given the variability in responses, the National Society of Genetic Counselors (NSGC) published a set of guidelines providing recommendations to assist health care professionals who provide counseling and screening to consanguineous couples and their offspring (R. Bennett et al., 2002). This guideline recommends that:

i. Genetic counselors obtain a three to four generations of family history and offer screening based on reported family history and ethnic background. There is no need to offer any genetic screening based on consanguinity alone but in endogamous populations, as unions are often within the same group, genetic screening should be offered for genetic disorders that occur with a higher frequency in that specific population.

ii. In the case of a known genetic condition, the genetic evaluation should proceed as it would for a non-consanguineous couple.

iii. For prenatal screening, genetic counselors should offer maternal-fetal serum marker at 15-18 weeks to screen for congenital conditions and a high-resolution ultrasound at 20-22 weeks of gestation. As children are at risk for autosomal recessive conditions, which include inborn errors of metabolism, they should offer newborn screening. Further, they should offer tests for hearing loss by 3 months of age as autosomal recessive prelingual hearing loss is common in the progeny of consanguineous unions.

Our study assesses the prenatal screening, genetic testing and counseling offered to consanguineous couples in the US and Canada today and determines the extent to which current clinical practice is consistent with the National Society of Genetic Counselors (NSGC) recommendations for counseling consanguineous families (R. Bennett et al., 2002). We looked at
the reproductive risk figures used by genetic counselors in clinical practice, and determined the current screening and genetic testing offered to consanguineous couples in a prenatal setting. In addition, we assessed the perceived psychosocial issues and challenges counselors face when counseling consanguineous couples. This study provides up-to-date information on the genetic counseling services offered to consanguineous families in North America and suggests updating the NSGC guidelines to include newer technologies such as universal carrier screening and strategies for discussing incidental findings on genomic microarray.
METHODS:

Study Design:

We used an anonymous online survey to collect information from genetic counselors who self-identified as having experience in counseling consanguineous couples in a prenatal or preconception setting. The invitation to participate in the research was posted on the National Society of Genetic Counselors (NSGC) website via listserve. The survey was active for three weeks from January 22 to February 12, 2015. We limited the inclusion criteria to genetic counselors who have worked in a prenatal or preconception setting in the last 5 years (i.e. 2010-2015) and who have counseled at least one consanguineous couple.

We provided the link to the online survey in the recruitment notice (Appendix A) and entry to the survey presumed participant consent. The Brandeis University Review Board approved the study (Protocol #15068).

Data Collection Tool:

We created and hosted the anonymous survey using Qualtrics, an online survey tool. The survey collected data on the clinical genetic counseling practices and perceived psychological issues faced by consanguineous couples in a preconception or prenatal setting (see Appendix B). The survey included the following sections: demographics, clinical genetic counseling practices for consanguineous couples and genetic counselor’s perception of common psychological issues faced by consanguineous couples. To explore clinical counseling practices, we included questions about-
potential issues addressed when taking a medical and family history, the baseline risk provided to consanguineous couples for having a child with a congenital anomaly or genetic disorder and prenatal screening and genetic testing offered to couples related as second cousins or closer. The survey also included open-ended questions that explored in more depth counselors’ perception of views and concerns that consanguineous couples bring to a preconception/prenatal setting, the challenges and legal issues, if any, faced by counselors when counseling consanguineous couples, and the professional guidelines used by counselors for counseling consanguineous couples. Lastly, we asked counselors if they would suggest any updates to the current NSGC guideline for counseling consanguineous couple. At the end of the survey, we offered respondents the opportunity to participate in a raffle for two $50 Amazon.com gift cards.

Data Analysis:

We analyzed the data using Statistical Package for the Social Sciences (SPSS) (version 22) software. We excluded participants who did not complete a majority of the survey questions from the data analysis. We used frequencies and descriptive analysis to summarize the results of the quantitative data collected. Univariate, bivariate and multivariate statistical techniques were used to examine the relationship between the variables of interest. We analyzed the open-ended responses using thematic network analysis (Sheets Kayla M., 2012) to identify common themes.
RESULTS:

We received a total of 169 responses. We removed 37 responses from our analysis because they were incomplete for the majority of the survey’s questions.

Demographics

The majority of respondents were female (76.5%, N=104) between the ages of 27-35 years. Their mean age was 34.5 years. Respondents were from all NSGC regions with a slightly higher representation from Regions II, IV and VI. We also received some responses (N=5) from other countries including Canada and United Arab Emirates.

Experience in a clinical prenatal setting

The majority of our respondents (81%, N=132) are currently employed in a prenatal genetic counseling setting and the rest have all worked in a prenatal setting within the past 5 years. Respondents have a mean of 7.5 years of experience as a genetic counselor in a prenatal setting.

Experience working with consanguineous couples

The mean number of couples respondents have counseled with any degree of consanguinity since the start of their clinical practice is 19 with a range between 1 and 125 couples (Figure 1). When asked to define consanguinity, almost half counselors (44.7%, N=132) defined it as couples related as second cousins or closer, which is the clinical definition of consanguinity. Another 21.2% of counselors defined consanguinity as ‘any couples related by blood’. Couples related as first cousins or closer and couples related as double first cousins or closer each accounted for 13.5% of
the responses. A few of the respondents defined consanguinity more broadly as couples with any degree of relationship or couples with shared ancestry (Figure 2).

When asked about the baseline risk to have a child with a congenital birth defect or a condition that manifests in the first year of life. The highest mean baseline risk was for couples related as uncle-niece, 10.55% (N=97) (Figure 3a). Counselors cited a mean baseline risk of 7.22% (N=106) (Figure 3b) for couples related as first cousins. For couples related as first cousins once removed the mean baseline risk cited was 5.02% (N=101) (Figure 3c) and the mean baseline risk for second cousins was 5.13% (N=103) (Figure 3d). The mean baseline risk cited for couples who were not related but were from the same ethnicity was 3.66% (N=107) (Figure 3e) and counselors reported a mean baseline risk of 3.57% (N=107) for unrelated couples from different ethnicities (Figure 3f).

We explored the differences in the prenatal screenings and testing being offered by counselors to both non-consanguineous and consanguineous couples. We requested they select all tests that are standard-of-care in their institution for a 25-year-old couple with a pregnancy at 15 weeks. Maternal serum screen was the test most commonly offered to a 25 year-old couple at 15 weeks of gestation (76.5%, N=132). Level II ultrasound was the second most common response (62.9%, N=132). Amniocentesis and karyotype was reported to be standard-of-care for 18.9% (N=132) of counselor’s institutions and non-invasive prenatal testing was offered as standard-of-care for all couples by 12.9% (N=132) of counselors.

When asked if there were any screens or tests that they were more likely to offer to a comparable consanguineous couple, 43% (N=88) of counselors responded that they were more likely to offer universal carrier screening to a consanguineous couple than to a non-consanguineous couple.
Three counselors specified that if they were to offer NIPT to a consanguineous couple, they would offer it through a company that provided non-SNP based testing.

**Challenges faced when counseling consanguineous couples**

In order to assess which psychological concerns genetic counselors perceived to be more prevalent when counseling consanguineous couples, we asked respondents to indicate how frequently they encountered feelings such as stigma, guilt, shame, and fear as compared to non-consanguineous couples. Forty-eight percent (N=107) of counselors said they encounter feelings of stigma more frequently when counseling consanguineous couples. Other issues encountered more frequently were fear (37.1%), concerns about discrimination (31.1%) and concerns due to cultural/religious beliefs (36.4%). Feelings of joy and excitement regarding their pregnancy were reported to be similar to those expressed by non-consanguineous couples (75%). We also asked counselors if they have ever consulted the risk management team in their institution about a consanguineous case and five (N=132) reported that they have consulted the risk management team for cases of suspected incest or rape.

In order to gain additional insight into counselor’s experiences, we asked counselors to describe their experience addressing the psychosocial issues that arose more frequently when counseling consanguineous couples. We used thematic network analysis (Sheets Kayla M., 2012) and identified three organizing themes from their responses: challenges faced due to cultural and language barriers, challenges in assessing risk and challenges related to societal concerns.
Organizing theme 1: Challenges due to cultural and language barriers

Consanguinity is common in many ethnic backgrounds and is an acceptable practice in many cultures. A number of counselors reported that when couples come from a culture that is open to consanguineous marriages there is less stigma and shame associated with such relations. However, they note that the feelings of stigma may increase with the amount of time spent in countries where consanguinity is not a common practice. Due to the stigma associated with consanguinity, some couples were unwilling to share medical information with other family members. Additional cultural challenges mentioned by respondents included: couples not speaking English, expectations for women to have healthy children and the expectations for directive advice from health care professionals.

ID 125: “Most (not all) of my consanguineous are not native to the USA and are usually from other countries. Given they were raised in a different culture, they usually don't have a lot of shame/stigma because they were raised differently.”

ID 125: “I've found that the long a couple is in the USA, the more feelings of guilt and shame there are associated with consanguinity.”

ID 132: “I have had positive experiences with couple's address stigma associated with consanguinity in the US vs. their country of birth. I have also had positive experiences discussing that most babies are born healthy. I have seen families with consanguinity and a very complicated family history, were there is significant guilt and no specific genetic testing can offer a diagnosis. Those have been some of the more difficult cases medically and psychosocially to manage.”

ID 22: “They will often be resistant to discussing carrier screening or other familial issues with relatives & prefer to keep info private.”

ID 56: “Language barriers tend to be the biggest challenge to overcome in my workplace when it comes to describing some of the more technical pregnancy-related risks and risk numbers.”

ID 8: “I've found that sometimes in cultures where consanguinity is more common, they are more likely to be a couple who wants a doctor to prescribe testing to them, rather than choose the testing that sounds right for their values and beliefs.”
Organizing theme 2: Challenges with risk assessment

Counselors faced various challenges in providing appropriate risk estimates to consanguineous couples. Consanguinity loops were a common concern among counselors making it difficult for them to provide exact risk estimates for genetic conditions. Adding to the complexity of risk assessment counseling was the fact that some consanguineous couples denied their relationship, while some had difficulty acknowledging that they were at an increased risk for having a child with a medical condition.

ID 3: “….Due to the high level of consanguinity among their extended relatives (even those that 'were not related' were simply related as 3rd or 4th cousins instead of 1st or 2nd, but were still ALL RELATED), exact risk estimates even for the known single-gene disorder was not possible. I had to give my best estimate as to the couple's chances for being carriers, letting them know that what I was using would be the LOWEST risk possible, but that it could be higher than that….”

ID 51: “Provided education on autosomal recessive inheritance, talked about everyone is a "carrier" for some AR disorders, spoke about the possibility it may have been passed down from a relative in common, or may be independently inherited. Information on risk f the disorder in question and what the disorder involves, prenatal testing, risk to other family members…..”

ID 22: “they typically think that consanguinity is NOT a medical concern & many times will decline testing/screening for that indication. If there is a medical problem that we believe is based in relatedness, many times they have trouble believing it, since they have so many family members in similar relationships with healthy children.”

Further, thirty-two percent of our respondents (N=108) reported that they had identified regions of homozygosity as an incidental finding on microarray results. Some faced challenges in discussing these incidental findings with the couples or providing appropriate follow up testing based on these incidental findings.

ID 5: “On microarray I have had 3 couples with consanguineous relationships. One was a first or second degree relative. This was very difficult to explain to the patient.”
ID 68: “We discussed the increased risk for autosomal recessive disorders of genes located in that region and the need for follow-up postnatally (as the patient declined other testing).”

ID 87: “I spoke to the patient alone and showed her the test result. I then asked if there was any chance that she and the father of the baby were related. I then offered additional testing (universal carrier screening) that we offer to consanguous (sic) couples.”

**Organizing themes 3: Challenges relating to societal concerns**

As the practice of consanguinity is not common in North America, many counselors noted that consanguineous couples were more likely to face stigma and feel judged by people outside their ethnicity. As a result, some couples were reluctant to disclose their relatedness and expressed concern about how their children would be regarded by others outside their community. Adding to these issues is the fact that consanguineous marriages are illegal in many states of North America: this can create fear in the minds of a consanguineous couple and add to the taboo surrounding consanguinity.

ID 22: “I find that most preg (sic) consanguineous couples are from ethnic backgrounds where this is acceptable. They feel no shame or personal problems with it. They do have concerns about how a person outside their ethnicity will judge them for something that is not n(sic) American norm, & is seen as taboo for judeo-Christian values. Once we establish that I am not offended/judging, they typically think that consanguinity is NOT a medical concern & many times will decline testing/screening for that indication. If there is a medical problem that we believe is based in relatedness, many times they have trouble believing it, since they have so many family members in similar relationships with healthy children. They will often be resistant to discussing carrier screening or other (sic) familial issues with relatives & prefer to keep info private.

ID 22: “American black couple discovered they were 3rd cousins after they had been dating several months. They saw this as "too related" & came to ask medical questions about future family planning. Even after hearing there was no elevated medical concern, they felt (sic) the social stigma was too high and ended the romantic relationship.”

ID 39: “I had first cousins who were carrying a baby with a severe heart defect. They wished to get married, but is prohibited by state law in my state. They wanted
to leave the state to get married, then return to deliver baby and all had questions regarding te (sic) legal rights that the FOB would have in this situation (i.e. would he be able to legally consent for procedures/meds/surgeries) the baby would need.”

**Challenges arising from cases of incest and rape**

As a part of the open-ended questions, we also asked the respondents if they had ever contacted their institution’s risk management team and, if so, to describe the circumstances that lead them to request a consult with them.

Nine counselors out of the 132 respondents reported that they had worked with patients who were involved in an incestuous relationship or were sexually abused by a relative. Several of these reported that these cases were among the most challenging cases they faced from a medical, psychosocial and legal point of view.

ID 23: “My most challenging consanguineous couple was a brother and sister. The girl was 13 and she was raped by her older brother who was incarcerated at the time of our visit because of the rape. She came to the visit with her mother. Her mother had a strong faith (sic) in God that he would take care of things. She stated termination was not an option because of their faith. The young girl didn’t say much during the session. There were so many issues which made this session difficult; teen pregnancy, rape, consanguinity, (sic) young girl’s loss of autonomy…..”

ID 130: “I had on (sic) session counseling a young woman who was raped by her first cousin. It was particularly challenging because she was still working through the psychological struggles left from the rape and was not in an emotionally stable place to hear about the increased (sic) risks for her baby based on the her relation to her rapist. ….”

Genetic counselors are mandated reporters of incest and/or abuse. Counselors reported connecting with their practice manager, social worker or medical director about their role in police investigations. One counselor explained how she had to be involved in the case herself to help the patient.
ID 42: “I once had a 13 year old pregnant by the maternal uncle….The police refused to arrest him because (sic) there was no proof that the baby was his and now the patient and her 16 yo sister (sic) were out of the house so they felt that there was no danger. After the baby was born, at term, w HRHS and hypophosphatasia, the baby was very ill. I personally went to the hospital and collected a buccal swab from the dying baby for the district attorney because I didn't trust that anyone else would save blood or get it done before the baby died. He did a plea bargain and was sentenced (sic) for incest, rape and an armed robbery (sic) to 10 years in prison…. Her relatives told me that after the baby died, she was sad, but no exactly mourning. Later, the whole experience faded into a sort of distant bad dream for her. This was challenging in that I was very angry at the local police, but I did what I could to protect the other children in the neighborhood….I am glad that the girl was so young and simple that she could recover somewhat from the experience.”

Use of professional guidelines and resources

We asked counselors if they refer to any professional guidelines or resources for genetic counseling of consanguineous couples. Seventy-two (N=107) reported that they refer to guidelines, 16 said they were not aware of any such guidelines and 19 reported that they do not refer to any guidelines. The most common reference used was the NSGC guidelines published in 2002 (R. Bennett et al., 2002). Other guidelines used by counselors are the ACMG guidelines (Rehder Catherine W. et al., 2013), “Practical Genetic Counseling” (Harper, 1998) and their own institutional resources.

At the end of the survey, we asked counselors if they think the NSCG guidelines for genetic counseling of consanguineous couples, should be updated (R. Bennett et al., 2002). Fifty-eight percent (N=132) of counselors suggested updating the guidelines to include new information on expanded carrier screening, as well as professional guidelines for offering new technologies such as NIPT, microarray and whole exome sequencing for consanguineous couples and their children. Several recommended including other newer studies that addressed risk calculations or insights into providing more sensitive counseling for consanguineous couples. Some respondents wrote:
“I would like to see these revamped to clearly define consanguinity, clearly label the risks associated with each level of relatedness, and clearly state the recommended follow-up including current-day technologies, such as expanded carrier screening.”

“Address incidental findings of consanguinity through microarray testing and guidelines for how to discuss this aspect of the test with patients.”

“New literature on the number of birth defects/ carrier rtes (sic) in countries where consanguineous marriages are more common.”

“Consideration of exome sequencing in cases in which a diagnosis of a child has not been possible through other molecular genetic testing.”

“I think multicultural sensitivity is important and should be elaborated on. I think concerns about incest should definitely receive more attention.”
DISCUSSION:

Our study surveyed genetic counselors about their experiences counseling consanguineous couples in a preconception and prenatal setting. We assessed the baseline risks provided to consanguineous couples for having a child with a congenital anomaly or genetic disorder, the screens and tests offered to consanguineous couples as well as the psychosocial concerns addressed in counseling sessions with them. Finally, we asked the respondents to list the professional guidelines they use to counsel consanguineous couples and suggest possible revisions for the NSGC guidelines (R. Bennett et al., 2002).

Assessment of current genetic counseling practices for consanguineous couples:

We received 132 completed surveys from genetic counselors who had prenatal counseling experience within the past five years and who had counseled at least one consanguineous couple in the course of their career. Many provided genetic counseling for more than one consanguineous couple and a majority had counseled 10 or more such couples. Approximately half of the respondents’ defined consanguinity according to the clinical practice guidelines as couples related as second cousins or closer. Others used broader definitions such as ‘any couple related by blood’. The mean baseline risk respondents quoted for consanguineous couples to have a child with a genetic disorder or congenital anomaly varied from 5.02% to 10.55% depending on the degree of relatedness while counselors cited a 3.57% baseline risk for unrelated couples. The mean risk cited for first cousin couples to have a child with a birth defect was 7.22% (range 3%-46%). Our results are in keeping with published guidelines stating that the risk for such couples is about 1.7% to
2.8% higher than for general population (R. Bennett et al., 2002). Several counselors commented that they generally provide a range of risk numbers (e.g. 3-5%) to couples rather than quote a single number as specified in the survey.

When asked to list the standard test(s) and screening routinely offered to all low risk couples at their institutions most reported offering maternal-serum screen and level II ultrasound with fewer than 20% offering amniocentesis and NIPT. Half of the respondents indicated that, in addition, they were more likely to offer universal carrier screening to consanguineous couples than to non-consanguineous couples. These tests screen for over one hundred recessive conditions and can identify carriers of a larger number of disorders than would be found with a targeted screening test based on ethnicity. A small number of respondents also stated that if they were to offer non-invasive prenatal testing for a consanguineous couple, they would choose a non-SNP based tests. This study, although limited in size, shows that the genetic counseling practices for consanguineous couples is more consistent than what was seen in 1999 (R. L. Bennett et al., 1999) where there was great variability in the tests that were offered to consanguineous couples. We hypothesize that this is at least partly due to the 2002 publication of NSGC guidelines for genetic counseling of consanguineous couples, a resource used by almost half our respondents.

**Challenges genetic counselors report with perceived psychological concerns:**

We explored the common psychosocial and societal concerns noted by counselors when counseling consanguineous couples. Major challenges in counseling consanguineous couples were due to cultural differences. Our study found that many prenatal genetic counselors perceive that consanguineous couples experience significant stigma and guilt in North America due to their consanguineous relationship. However, a few counselors reported that couples expressed less stigma associated with consanguinity when it was an acceptable practice in their culture.
Counselors noted that social acceptance of children of consanguineous couples was also a concern for some couples.

“There is definitely much more an assumed stigma around consanguinity. Patients often assume that we will blame them for anything that happens to their child as a result of their relatedness. It’s easiest to address this as it comes up and inform them of the (sic) risks while being careful not to place blame.”

“In my experience, consanguineous couples experience more fear and potential guilt than non-consanguineous couples. Most are very relieved to hear the risk estimations; the numbers are lower than they expected to hear.”

For couples who come from cultures where consanguinity is a common practice, counselors noted that some couples had difficulty believing that there was an increased risk for their children to have a genetic disorder or congenital anomaly. Many of these couples have seen others in their family have healthy children so they did not expect any increased risk for their offspring. Some may even deny or resist discussing their relatedness for either medical or legal reasons. This presents a significant challenge for genetic counselors and several expressed concern that by talking about the increased risk for a couple to have a child with a medical condition, they actually increased the couple’s anxiety.

“Couples seem more reluctant to disclose relatedness. I try to normalize the situation and provide them with reassurance of a likely normal outcome.”

Another significant issue faced by counselors was the difficulty of providing appropriate risk estimates when there are multiple consanguinity loops in a family. Obtaining exact risk estimates for a genetic condition identified in a pedigree when couples are related in more than one way is difficult. Other challenges mentioned are not unique to consanguineous couples and include: the challenge of balancing offering additional testing while not unduly increasing anxiety for the couple; the difficulty of counseling a couple whose native language is not English and managing
the expectations of a couple who expect health care professionals to be directive and instruct them about their health care.

“In many of my consanguineous patients, they are more 'related' than they think because of compound consanguinity. Basically, yes they are 'first cousins' or 'second cousins' but their grandparents were also cousins, and their parents were cousins, etc. Pedigree (sic) can become somewhat collapsed when everyone is consanguinous (sic)”

The most difficult issue raised by respondents was when they had cases of incest or rape, many of which involved a minor, and they needed to consult their institution’s risk management team. As per law, counselors need to report any suspected abuse to their supervisors and legal teams. Several respondents indicated that they had also connected with their medical director, practice manager or social worker to find ways to support their patient. While cases of rape or incest involving a minor is not common in genetic counseling, it presents significant psychological concerns such as teen pregnancy, loss of autonomy, anxiety, drug and alcohol abuse, panic attacks, phobias and suicidal thoughts (Turell, 2000). In such cases, genetic counselors’ roles may not limited to genetic risk assessment, but they may be called upon to provide additional support to their patients and perhaps, involve law enforcement.

“I worked with a team who saw a patient whose fetus had a high percentage of loss of heterozygosity. The percentage suggested a first-degree relationship between the parents, but the mother denied any relationship except (sic) with her partner who was not related. She was an adult, so we did not feel that we could do much more than provide information. We worried that she may have been a victim of long-term abuse. In another case, I was asked by police authorities for guidance (sic) regarding prenatal paternity testing. Ultimately, this testing was not pursued, but after delivery (sic) the father of the baby was also found to be the father of the baby's mother. This incestuous relationship lasted an additional 3 to 5 months due to the lack of testing, despite concerns voiced by multiple parties.”
Importance of professional guidelines:

After the study by Bennett et al (R. L. Bennett et al., 1999) identified inconsistencies in the practice of genetic counseling for consanguineous couples, the NSGC published a guideline for genetic counseling of consanguineous couple in a preconception/prenatal setting (R. Bennett et al., 2002). This NSGC guideline is the resource most commonly used by our respondents for counseling consanguineous couples and our data suggests that the use of the guideline is at least partially responsible for a greater consensus in practice of genetic counseling for consanguineous couples. However, since the publication of the NSGC guidelines in 2002, there have been many advances in molecular and genomic technologies and changes in the clinical practice of prenatal genetic counseling. A significant number of counselors suggested updating the NSGC guidelines to include information and recommendations on the use of new technologies and their implications for counseling consanguineous couples.

Although, NSGC guidelines states that there is no need to offer any genetic testing based on consanguinity alone (R. Bennett et al., 2002), our study found that counselors were more likely to offer universal carrier screening to consanguineous couples than to non-consanguineous couples in order to identify carriers for recessive conditions that would not be identified with an ethnicity based screen alone.

Another suggestion for updating the guidelines concerns the use of genomic microarrays that are now offered for abnormal ultrasound findings and for the genetic evaluation of children with intellectual disability and/or multiple congenital anomalies. In addition to copy-number changes, these microarray platforms can also identify long stretches of homozygosiy (Rehder Catherine W. et al., 2013). When observed in one single chromosome, it can be indicative of uniparental disomy. However, when they are distributed throughout the genome, they more likely represent regions
that are identical by descent (IBD), and are indicative of consanguineous relations between the parents (Rehder Catherine W. et al., 2013). As the parental relationship becomes closer, the proportion of autozygous genomic region will increase. In addition to revealing consanguinity, inheriting long stretches of homozygosity can increase the likelihood of inheriting two copies of a deleterious genes thereby increasing the possibility of an autosomal recessive disorder. The American College of Medical Genetics and Genomics recently published a set of guidelines for documenting and reporting such incidental microarray findings. Since it is common to identify small stretches of homozygosity in normal populations, most laboratories limit their reporting of likely IBD’s to segments >2-5Mb (Rehder Catherine W. et al., 2013). Regardless of the finding, speculation of specific relationships in written reports is discouraged (Rehder Catherine W. et al., 2013) but these incidental findings of homozygosity are often addressed in genetic counseling sessions and can present significant challenge for counselors when discussing the findings with their patients.

“We brought up the possibility that they could be related (as they had denied the possibility prior to testing), and the couple came clean that there was some distant relationship between them. The test suggested closer relationship than they admitted, bu (sic) I just counseled on the risks of ROH without pushing for more on the relationship.”

“I raised the question of the possibility of shared ancestry between the MOB and FOB. MOB was the only one present. Although consanguinity was initially denied, when the possibility was raised--she revealed that there was a chance that the FOB was a second cousin.”

If the NSGC guidelines are to be updated, however, the challenge will be to make certain that all testing guidelines are evidence-based and to clearly delineate the difference between incestuous situations compared to more distant consanguinity (such as first cousin unions).
**Limitations:**

The major limitation of this study is the small sample size. We surveyed prenatal genetic counselors and our response rate was representative of about 1% of all the prenatal genetic counselors associated with the NSGC (NSGC Professional Status Survey, 2014). However, we were not able to assess whether our respondents were representative of all prenatal genetic counselors in terms of age, years of experience or geographical region. This is a retroactive study of genetic counselors’ experience with consanguineous couples and thus has its limitations. The genetic counselors are recalling the information presented and this was not corroborated with medical records or with interviews of the couples who received genetic counseling. Our respondents varied enormously in their experience counseling consanguineous couples and this could have contributed to the variability in responses. Another limitation is that our survey did not allow respondents to provide a range of numbers for the baseline risks they quoted so the numbers provided may not be reflective of the exact risk estimate they cite. Finally, not all respondents completed the survey and, as a result, 37 of the 169 surveys started had to be excluded from our analysis.

**Future research:**

Genetic counseling is a growing profession. As the availability of genetic counseling services increase, more couples will seek genetic counseling in a preconception setting. At the same time, the United States population is becoming increasingly diverse in terms of ethnicity and cultural practices and the genetic counseling profession is continually being challenged to learn about and adapt its services and practice guidelines for patients coming from varied backgrounds. This study focuses on counseling consanguineous couples in North America but we foresee a need for studies focused on other populations as well. There is also limited literature on psychosocial issues faced
by consanguineous couples. We recommend that studies should explore more about the psychological and societal aspects of consanguinity in the United States. Further, we need to more studies to “hear” the voices of consanguineous families themselves to learn more directly about their genetic counseling needs.
CONCLUSIONS:

Our study identified the preconception and prenatal genetic counseling practices for consanguineous couples by surveying over a 100 genetic counselors who are members of the National Society of Genetic Counselors. We found that there was greater consensus in the practice of genetic counseling for consanguineous couples when compared to the previous study by Bennett et al (R. L. Bennett et al., 1999). The baseline risk numbers provided by counselors was similar to numbers quoted by the NSGC guideline (R. Bennett et al., 2002). With the emergence of new technologies, counselors are now more likely to offer universal carrier screening, non-invasive prenatal testing and microarray to consanguineous couples, which were not available in 2002. Incidental findings of possible consanguinity can be challenging to discuss with couples. The genetic counselors surveyed perceive that most couples face some stigma due to their relationship. Our study also found that legal ramifications in cases of incest and rape are significant challenges for counselors. We identified that the NSGC guidelines was used as the primary reference for counseling consanguineous couples. Many counselors suggested new specific recommendations for offering universal carrier screening and other genetic tests. In addition, counselors requested recommendations to discuss incidental findings of possible consanguinity on genomic microarray. Genetic counselors will benefit from updating the NSGC recommendations for genetic counseling of consanguineous couples in a preconception and prenatal setting using evidence based guidelines and input from the communities and couples affected by such guidelines.
Figure 1: Number of couples seen with any degree of consanguinity in their career (Mean=19, SD=22.35, N=132)
Figure 2: Definitions of consanguinity (N=132)
Baseline risk figures provided by respondents for couples with varying degrees of relatedness

*Figure 3a: Baseline risk for couples related as uncle-niece to have a child with a congenital birth defect or a condition that manifest in the first year of life. (Mean=10.55, SD=6.07, N=97)*
Figure 3b: Baseline risk for couples related as first cousins to have a child with a congenital birth defect or a condition that manifest in the first year of life. (Mean=7.22, SD=4.21, N=106)
Figure 3c: Baseline risk for couples related as first cousins once removed to have a child with a congenital birth defect or a condition that manifest in the first year of life. (Mean=5.02, SD=1.80, N=101)
Figure 3d: Baseline risk for couples related as second cousins to have a child with a congenital birth defect or a condition that manifest in the first year of life. (Mean=5.13, SD=3.52, N=103)
Figure 3e: Baseline risk for couples who are not related and from same ethnicity to have a child with a congenital birth defect or a condition that manifest in the first year of life. (Mean=3.66, SD=2.06, N=107)
Figure 3f: Baseline risk for couples who are not related and from different ethnicities to have a child with congenital birth defect or a condition that manifest in the first year of life. (Mean=3.57, SD=2.08, N=107)
REFERENCES


APPENDIX A: RECRUITMENT NOTICE

Dear NSGC Member,

Have you ever counseled a consanguineous couple in a prenatal/preconception setting? If so, we invite you to take part in a research study that assesses the current genetic screening and testing being offered to consanguineous couples. The study also assess the common psychosocial concerns that emerge during genetic counseling of consanguineous couples.

This research study is being carried out for my Masters thesis at Brandeis University's Genetic Counseling Program.

You are eligible to participate in this study if:

1. You are currently working or have worked as a prenatal genetic counselor within the last five years.
2. You have counseled at least one consanguineous couple within the last five years.

Study participation involves an anonymous online survey that will take approximately 20 minutes to complete. If you would like to participate in this study and share your experiences with counseling consanguineous couples, then please click on the following link, which will be active until February 12, 2015.

https://brandeis.qualtrics.com/SE/?SID=SV_2u91KdfWeckKkpn

Upon completion of the survey, you will be able to participate in a raffle to win one of two $50 Amazon gift cards.

Thank you very much for your consideration and participation. Please feel free to contact me at nkreddy@brandeis.edu with any questions or concerns. You could also contact Judith E. Tsipis, the Principal Investigator of this study, at tsipis@brandeis.edu. If you have any questions for the Institutional Review Board, please contact Brandeis University's IRB at irb@brandeis.edu or (781) 736-8133.

Sincerely,

Neeraja K Reddy, B.Tech
Genetic Counseling Student
Brandeis University
APPENDIX B: SURVEY

Thank you for participating in this study. Your participation in this study is voluntary and you may exit the survey at any time. The survey is confidential and no identifying information will be collected. The study has been reviewed and approved by the Institutional Review Board of Brandeis University of Waltham, MA. All information will remain confidential. By clicking next, you have acknowledged that you have read the above information and that you consent to participating in this study.

Upon completion of the survey, you may participate in a raffle to win one of two $50 gift cards to Amazon.com. If you choose to participate in the raffle, you will be asked to share your e-mail address. Participation in the raffle is voluntary and your e-mail will not be linked to your answers.

I. Clinical genetic counseling practice for consanguineous couples

1. Do you currently work as a genetic counselor in a clinical prenatal setting?
   a. Yes
   b. No

   *(If yes, skip to question 3. If no, go to question 2)*

2. Have you worked as a prenatal genetic counselor in the last five years? *(If yes, go to question 3. If no, exit the survey.)*
   a. Yes
   b. No
Thank you for your interest, but this survey is to be completed by genetic counselors who have worked previously or are currently working in a clinical prenatal setting.

3. How many years of experience do you have as a genetic counselor in clinical prenatal setting since your graduation?
   __________ years ____________ months

4. Since you first began your practice in a clinical prenatal setting, approximately, how many couples have you counseled in with any degree of consanguinity?
   Number of couples ______________________________

(If the answer is zero for Question 4, exit the survey)

5. How do you define consanguinity?
   a. Couples related as first cousins or closer
   b. Couples related as second cousins or closer
   c. Couples related double first cousin or closer
   d. Individuals related as first-degree relatives
   e. Other ______________________________

6. The table below provides a list of potential issues that you might want to address when taking a medical and family history in a preconception/ prenatal setting. For each of the four couples described at the top of each column, please choose the issues that you would definitely address. Please check all that apply for each couple.
<table>
<thead>
<tr>
<th>Possible issues to address</th>
<th>Couple A</th>
<th>Couple B</th>
<th>Couple C</th>
<th>Couple D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First cousin couple</td>
<td>Second cousin couple</td>
<td>Non-consanguineous couple from the same ancestry</td>
<td>Non-consanguineous couple from different ancestry</td>
</tr>
<tr>
<td>Family history of three-generations or more that includes all cousins, siblings, parents, and other relations as appropriate.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>History of any of the following:</strong></td>
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<tr>
<td>Intellectual disabilities</td>
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<tr>
<td>Failure to thrive</td>
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<td></td>
<td></td>
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<tr>
<td>Sudden death of infants</td>
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<td></td>
<td></td>
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<tr>
<td>Normal development followed by regression</td>
<td></td>
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<tr>
<td><strong>History of any of the following:</strong></td>
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<tr>
<td>Chronic illness</td>
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<tr>
<td>Infections</td>
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<td></td>
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<td></td>
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<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unusual odor</td>
<td></td>
<td></td>
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<tr>
<td>Cataracts</td>
<td></td>
<td></td>
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<tr>
<td>Corneal clouding</td>
<td></td>
<td></td>
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<tr>
<td>History of multiple miscarriages</td>
<td></td>
<td></td>
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<tr>
<td>History of seizure disorder or staring spells</td>
<td></td>
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<tr>
<td>History of cancer less than the age of 50</td>
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<td></td>
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<tr>
<td>History of congenital anomalies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of schizophrenia, depression, anxiety or mood related disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments (Optional): ___________________________
7. What is the baseline risk (%) you would provide for each of the following couples to have a child with a congenital birth defect or a condition that manifests within the first year of life? Note: Please assume the couple is 25-years-old and has no significant family history that would change their baseline risk.
   a. Couples not related to each other and from different ethnicities
   b. Couple not related to each other but from the same ethnicity
   c. Couple related as first cousins
   d. Couple related as second cousins
   e. Couple related as uncle-niece
   f. Couple related as first cousin once removed
   g. Would you modify any of the above risks for the consanguineous couples based on their ethnicity? Yes or no. If yes, Please explain.

8. 1. Which of the following screens or tests is standard-of-care in your institution for a 25-year-old couple with a pregnancy at 15 weeks gestation? (Choose all that apply)
   a. Universal carrier screening, (if chosen) please specify which panel you would use
   b. Maternal serum screen
   c. Level II ultrasound
   d. Amniocentesis and karyotype
   e. Microarray
   f. Non-invasive prenatal testing
   g. Cord blood banking
11.2 For a 25-year-old couple with a pregnancy at 15 weeks gestation with no known significant family history or complications, which of the following screens or tests would you be more likely to offer to a couple related as first cousins than to a non-consanguineous couple. (Choose all that apply)

ONLY OPTIONS THAT ARE NOT CHOSEN IN THE PREVIOUS QUESTION SHOULD BE PRESENTED.

a. Universal carrier screening
b. Maternal serum screen
c. Level II ultrasound
d. Amniocentesis and karyotype
e. Microarray
f. Non-invasive prenatal testing
g. Cord blood banking

9. Are there any tests that you would not offer a consanguineous couple when compared to a non-consanguineous couple?
   a. Yes
   b. No

If yes, please list which one(s). ______________________________

10. Have you ever identified locus homozygosity as an incidental finding on genetic test results for issues unrelated to consanguinity?
   a. Yes
b. No

If yes, how did you discuss this incidental finding in the counseling session?

II. **Psychological issues faced by consanguineous couples**

11. The table below lists a number of feelings or concerns that may arise during a couple’s prenatal/preconception genetic counseling. Please indicate how frequently you encounter these feelings or concerns when counseling consanguineous compared to non-consanguineous couple.

<table>
<thead>
<tr>
<th>Couple’s feelings or concerns</th>
<th>Much more frequently</th>
<th>More Frequently</th>
<th>About as frequently</th>
<th>Not as frequently</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stigma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discrimination</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Guilt</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Shame</td>
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<td></td>
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<td></td>
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<tr>
<td>Fear</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Resistance</td>
<td></td>
<td></td>
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<tr>
<td>Cultural/religious concerns</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Blame</td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td></td>
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</tr>
</tbody>
</table>

*If they choose the option, much more frequently for any of the above choices then go to question 12.*

12. Please describe your experience of addressing the psychosocial issue(s) that arises much more frequently when counseling consanguineous couples.
13. Have you ever consulted with the risk management team in your institution or consulted your institution’s general counsel regarding legal issues on behalf of a consanguineous couple?
   
   a. Yes
   
   b. No

   If yes, please describe the circumstance(s) that caused you to request the consult.

14. If you had a particularly challenging session with a consanguineous couple, what made it challenging and how did you deal with this?

15. Have you known any consanguineous couples in a social setting (outside your clinical practice)? If so, how has it affected your counseling, if at all?

16. Do you refer to any professional guidelines or resources for genetic counseling and screening of consanguineous couples and their offspring?

   a. Yes
   
   b. No
   
   c. I am not aware of any such guidelines

   *If the answer to the above question is option b or c, skip question 18.*
17. If yes, could you please share these professional guidelines or resources you have used for counseling consanguineous couples in the space provided.

_________________________________________________________

18. The NSGC published guidelines for genetic counseling and screening of consanguineous couples and their offspring published in 2002 (Bennetst et al., 2002)? Given that there have been many advances in molecular and genomic technologies since then, is there anything you would recommend adding to the guidelines?

*Link to the guidelines will be provided.*

_________________________________________________________

III. Demographics

19. How do you identify your gender?

   a. Male
   
   b. Female
   
   c. Other _____________

20. How old are you?

   ____________ years

21. In which NSGC region are you currently practicing?

   a. Region 1: CT, MA, ME, NH, RI, VT, Maritime Provinces
   
   b. Region 2: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec
c. Region 3: AL, FL, GA, KY, LA, MS, NC, SC, TN

d. Region 4: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, WI, Ontario

e. Region 5: AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan

f. Region 6: AK, CA, HI, ID, NV, OR, WA, British Columbia

g. Canada

h. Other (Please specify)

Thank you for completing this survey. If you have any questions or comments regarding this research, please contact me at nkreddy@brandeis.edu

If you wish to participate in the raffle, you have the option to enter your email to win one of two $50 gift cards to Amazon.com.