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Expanded Carrier Screening and the Willingness of Reproductive Healthcare Providers to Use Gamete Donors Who Are Carriers for Known Recessive Conditions

THESIS

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By

Emily Nicole Marsh

Thesis Committee:
Clinical Professor Manuel Porto, MD, Chair
HS Clinical Professor Kathryn Steinhaus French, MS, LCGC
HS Assistant Clinical Professor Meredith Jones, MS, LCGC
Adjunct Professor Kathryn Osann, PhD, MPH

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ABSTRACT OF THE THESIS

Expanded Carrier Screening and the Willingness of Reproductive Healthcare Providers to Use Gamete Donors Who Are Carriers for Known Recessive Conditions

By

Emily Marsh

Master of Science in Genetic Counseling

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Professor Manuel Porto, MD, Chair

Recent technological advances have made it possible to screen gamete donors for up to hundreds of conditions simultaneously. This inevitably will increase the number of donors who screen positive for being carriers of one or more recessive condition(s). This increase in donors who are found to be carriers has prompted the discussion among clinicians on how best to proceed with counseling and follow-up testing.

The purpose of this study was to gain insight on the willingness of providers to use gametes from carrier donors and, if they were willing, what type of follow-up testing would be most appropriate for the intended biological parent. This study also examined what types of carrier screening practices clinics currently have in place, and what resources clinicians would find most beneficial to both them and their patients.

Surveys were distributed to physicians, genetic counselors, nurses, and other medical professionals working in reproductive medicine. One hundred ninety-two participants began the survey, one hundred thirty-three completed with survey. The majority of all groups agreed a carrier donor need not be dismissed solely due to being a carrier of one or more recessive condition(s), but disagreed on the best way to

proceed when using a carrier donor. The results also show a distribution of current screening practices among clinics.

Given these results, there exists the need for standardization and regulation of carrier screening among gamete donors beyond the current limited Society recommendations.

1. INTRODUCTION

1.1 *Gamete Donation: Definition and Historical Background*

1.1.1 *Defining Gamete Donation*

Gamete donation is giving sperm, eggs, and/or embryos to another person/couple so that another person/couple may have a child (ASRM, 2014). Individuals and/or couples can choose to have either a sperm donor, an ovum donor or an embryo help aid them in conceiving a child. The process of choosing either an egg or a sperm donor followed by collecting the gametes, or choosing a previously conceived embryo, then transferring the fertilized embryo into the woman who will be carrying the child is a long and often-times expensive process.

1.1.2 *Historical Background and Prevalence*

There are multiple reasons why an individual or couple may choose to use either an egg or a sperm donor, or both, to help conceive a child. Infertility in either the male partner or the female partner leads some couples to turn to gamete donors. Of those couples choosing gamete donation due to infertility, 13% is due to a tubal factor, 15% is due to ovulatory dysfunction, 32% due to diminished ovarian reserve, 9% due to endometriosis, 6% due to uterine factor, 33% due to male factor, 16% due to other factors, 13% due to an unknown factor, 12% were due to female factors only, and 17% were due to female and male factors, (CDC, 2014). Some causes of male infertility include: cystic fibrosis, trauma, testicular failure, infection, treatment involving chemotherapy or radiation, among others. Generally, women over 40 who are struggling to become pregnant use donor eggs much more frequently than their younger counterparts. The number increases dramatically at age 40, and by age 48, 86% of all

artificial reproductive technology (ART) cycles were conceived using ovum donors (CDC, 2014). In addition to increasing the likelihood of conceiving, using a younger ovum donor also decreases the risk for aneuploidies in the fetus. For example, a women age 45 has a 1 in 22 mid-trimester risk to have a fetus with Down syndrome and a 1 in 84 risk to have a fetus with trisomy 18. Whereas a woman age 25 has a 1 in 1040 mid-trimester risk to have a fetus with Down syndrome and a 1 in 4053 risk to have a fetus with trisomy 18, (California Department of Health Services). Additionally, some couples may choose to seek out a gamete donor if one of them has a genetic condition they do not want to pass down to their biological offspring.

Single individuals and lesbian, gay, bisexual, transgender, and queer (LGBTQ) individuals make up a large portion of the people who choose to reproduce via gamete donation. The Donor Sibling Registry is an organization that aids individuals conceived as a result of either sperm, egg, or embryo donation that are seeking to make mutually desired contact with others whom they are related to genetically. Individuals registered through this program were asked what their family type was, i.e. information on their parents' sexual orientation and relationship status. According to these results, 49.2% were born to single mothers by choice, 33.4% were born to parents from the LGBTQ community, and 17.4% were born to heterosexual mothers and fathers (Donor Sibling Registry).

As previously mentioned, same-sex couples can have children via ovum or sperm donation. The social stigma surrounding same-sex couples prolonged their having access to this technology for some time (Daar, 2013); however, in the 1970's lesbian couples began pursuing sperm donation through artificial insemination using donor

sperm. By the 1980's fertility programs were routinely accepting those identifying themselves as lesbians for fertility treatment. Gay male couples can either use a traditional surrogate, where the sperm from one member pf the couple is artificially inseminated into the surrogate, or through in-vitro fertilization (IVF) to create an embryo using donor eggs to be transferred into a gestational surrogate (Greenfeld, 2016).

The first successful pregnancy via oocyte donation took place in Australia in 1983, (Sargent, 2007). The first account of donor sperm insemination was documented in a 1954 journal article in The British Medical Journal. In 1963, a ruling in the United States stated a child conceived through donor insemination was born out of wedlock and therefore illegitimate. In this case, the mother was considered adulterous and her partner was not considered legally to be the father (Massey, 1963). By 1973 the Commissioners on Uniform State Laws approved the Uniform Parentage Act. This act provides that if a wife is artificially inseminated with donor semen under a physician's supervision and with her husband's consent, the law treats the husband as if he were the natural father of the child. The law also makes it clear that the sperm donor has no legal obligations to the child and is not legally considered the father of the child. In 2002, this law was updated to cover areas of parentage arising in unmarried couples (Uniform Law Commission, 2002). Currently, the estimate of donor-conceived children who are born in the U.S. each year is 30,000–60,000 children from sperm donation and over 8,000 from egg donation (Sabatello, 2015).

1.2 *Carrier Screening Definition, History, and Expanded Carrier Screening Technology*

1.2.1 *Defining Carrier Screening*

Carrier screening is the process of identifying individuals or couples at risk of conceiving a child affected by autosomal recessive or X-linked conditions (Gabriel, 2012). Carrier screening for genetic conditions in gamete donors is an important component of reproductive medicine. Identifying carriers of either autosomal recessive or X-linked disorders allows intended parents access to more information about the risk of having a child with an inherited condition. When both biological parents are identified as carriers of the same autosomal recessive disease, they have 25% chance in each pregnancy of having a child affected by this disease. For X-linked disorders, half of the male offspring of a woman who carriers an X-linked recessive disorder will typically be affected with the disorder (Henneman, 2016).

1.2.2 *History of Carrier Screening*

Cystic Fibrosis screening for individuals of Caucasian and Ashkenazi Jewish ethnic backgrounds was the first carrier test recommended for donors (American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG, 2001). In 2005, these organizations expanded this recommendation to include individuals of all ethnic backgrounds (Lazarin, 2012). In 2008, the ACMG recommended that spinal muscular atrophy (SMA) screening be offered to all ethnicities. Recently, ACOG came out with a committee opinion agreeing with the ACMG, that screening for spinal muscular atrophy should be offered to all women who are considering pregnancy (ACOG, 2017). Typically, aside from cystic fibrosis and spinal muscular atrophy, in the absence of family history, diseases that donors are screened for are the more common conditions associated with their ethnicity (Lazarin, 2012). For example, individuals African and of certain Asian ancestries are

advised to have carrier testing for hemoglobinopathies. Individuals of Ashkenazi Jewish ancestry are advised to be tested for a panel of diseases more common in that population. Most recently, ACOG has come out with a committee opinion on carrier screening in the age of genomic medicine for all individuals who are pregnant, or are wanting to become pregnant. Though these recommendations aren't specific to gamete donation, they provide guidelines on how to proceed with testing and what type of testing should be performed, which can easily be applied to gamete donation. These recommendations are listed below.

1.2.3 *Carrier Screening in the Age of Genomic Medicine, A Committee Opinion*

Recommendations

- Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Each obstetrician–gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. After counseling, a patient may decline any or all carrier screening.
- If a patient requests a screening strategy other than the one used by the obstetrician–gynecologist or other health care provider, the requested test should be made available to her after counseling on its limitations, benefits, and alternatives.
- All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and

screening for thalassemias and hemoglobinopathies. Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome, or women with a personal history of ovarian insufficiency. Additional screening also may be indicated based on family history or specific ethnicity

- Couples with consanguinity should be offered genetic counseling to discuss the increased risk of recessive conditions being expressed in their offspring and the limitations and benefits of carrier screening.
- Carrier screening will not identify all individuals who are at risk of the screened conditions. Patients should be counseled regarding residual risk with any test result.
- Prenatal carrier screening does not replace newborn screening, nor does newborn screening diminish the potential benefit of prenatal carrier screening.
- If a woman is found to be a carrier for a specific condition, her reproductive partner should be offered screening to provide accurate genetic counseling for the couple with regard to the risk of having an affected child. Additional genetic counseling should be provided to discuss the specific condition, residual risk, and options for prenatal testing.
- If a carrier couple (i.e., carriers for the same condition) is identified before pregnancy, genetic counseling is encouraged so that reproductive options (egg, donor gametes, preimplantation genetic diagnosis, prenatal diagnosis) can be discussed.

- Individuals with a family history of a genetic disorder may benefit from the identification of the specific familial mutation or mutations rather than carrier screening. Knowledge of the specific familial mutation may allow for more specific and rapid prenatal diagnosis.
- Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth.
- Carrier screening panels should not include conditions primarily associated with a disease of adult onset.

1.2.4 Expanded Carrier Screening Technologies

Technologies such as next generation sequencing make it possible to screen for many conditions simultaneously while being cost efficient. Next generation sequencing technology became available for clinical use in 2005 (Rollins, 2012). Through next generation sequencing, millions of small fragments of DNA can be sequenced simultaneously. Software programming is used to piece together these fragments by mapping the individual sequences to the human reference genome. Each of the three

billion bases in the human genome is sequenced multiple times, providing a depth of coverage enough to make a call on whether a genetic alteration is present or not (Behjati, 2013). There are multiple companies taking advantage of this technological advancement, and advertise expanded carrier screening panels that include hundreds of conditions. For example, Counsyl offers a panel screening for 113 conditions, including autosomal recessive conditions as well as some X-linked recessive conditions. Natera offers a multi-disease, expanded carrier screening panel that consists of up to 274 conditions. Other companies offer screening of over 400 conditions.

With the advent of this new technology, issues regarding the interpretation of results have become more complex. As with most genetic testing, screening "negative" does not completely eliminate the risk of having a child with that condition. Even after a "negative" result, the laboratories will calculate a residual risk. A residual risk is the risk of being a carrier of a condition after testing has been reported negative. Residual risk is based on Bayesian analysis which is a statistical calculation used to incorporate additional information to give a more accurate posterior risk (in this case the remaining risk of being a carrier of a condition). The calculation incorporates a screening test's sensitivity, specificity, and the a-priori ethnic based carrier rate to calculate the chance that the test did not accurately detect a carrier of a condition.

Individuals and couples who use a donor to help have a child should be counseled on the residual risk that either one of them, or the chosen donor, is a carrier of a condition after receiving a negative carrier test result. Couples and/or individuals who are not counseled could assume their chosen donor screened negative for "genetic conditions," without receiving adequate counseling about both the residual risk of the

specific conditions being screened for and understanding that these large carrier panels cannot screen for every genetic condition.

The detection rate is how often a test will pick up a genetic change (also known as a “mutation” or variant) which is actually present in the individual. Mutation detection rates depend upon the ethnicity of the individual being tested, and the prevalence of the specific disease in that population. The lower the frequency of the disease in a population, the lower the detection rate will be, making the test not as efficient at detecting these mutations.

An example of varying detection rates by ethnic background can be found in cystic fibrosis (CF). Individuals of Northern European and Ashkenazi Jewish ancestry have the highest carrier frequency for CF, 1 in 28, and 1 in 29 respectively (Moskowitz, 2008). Whereas the carrier rate in individuals of African American ancestry is 1 in 61. The carrier rate for CF is even less in people of Asian American ancestry (1 in 93) (Zvereff, 2013). ACOG and ACMG recommend a minimum 23-mutation panel when performing CF carrier testing for individuals. The 23-mutation panel includes the most common gene mutations found in people of Northern European and/or Ashkenazi Jewish ancestry. However, this panel will be less likely to detect carriers of Asian or African ancestry, since they often have gene mutations which are not included on the panel. Consequently, if an individual of Ashkenazi Jewish ancestry tests negative using this 23-mutation panel, their residual risk to be a CF carrier is 1 in 380. Whereas an individual of Asian ancestry who tests negative using this same 23-mutation panel has a higher residual CF carrier risk of 1 in 180 (ACOG, 2017).

1.3 *Different Types of Follow-up Testing for the Intended Biological Parent*

Once a donor has been chosen by a couple or an individual often some type of genetic carrier screening is performed on the donor to determine if he or she is a carrier of a genetic condition. If that donor is a carrier of a recessive condition, he or she would not experience any symptoms of the condition, but would have a 50% chance to pass on their mutated allele to future offspring. If the intended biological parent is also a carrier of the same condition, the future offspring would have a 25% chance of being affected with the condition, a 50% chance of a being a carrier, and a 25% chance of have two normal functioning alleles.

In order to minimize the chance of having a child affected with a recessive condition, if the donor is found to be a carrier of a disorder, genetic testing of some type is often performed on the intended biological parent to determine if they are also a carrier of the condition. The way in which the intended biological parent is tested can vary by the clinician ordering the test. Clinicians can order an expanded carrier screening panel on the partner to see if they are also a carrier of the condition. These panels screen for up to hundreds of conditions, not just the one the gamete donor carries. In addition, these panels screen for the most common gene mutations causing the conditions. Depending upon the ethnic background of the intended biological parent, the mutation detection pickup rate may be so low in some cases, that one could argue that the common mutation panels are not the most informative method to detect carrier status.

Other clinicians choose to order carrier screening on the intended biological parent by targeted mutation analysis for only the condition for which the donor carries a mutation. For example, if a donor was found to be a carrier of cystic fibrosis, the

clinician could test the intended biological parent to see if he or she was also a carrier using a 23-mutation panel for cystic fibrosis. As mentioned previously the residual risk to be a carrier of cystic fibrosis after having the 23-mutation panel varies based on the ethnic background of the individual. For all ethnicities, there remains a residual risk to be a carrier, with some ethnic backgrounds having higher residual risks than others. There are over 2,000 mutations in the cystic fibrosis transmembrane protein (CFTR) gene, with some of them being very rare (McGarry, 2017). The methodology of testing for the most common 23-CFTR gene mutations in those of Northern European backgrounds does not consider the fact that an individual can be a carrier of a rarer mutation in the CFTR gene, which is not included in the panel. In this case a CF carrier could test negative, but still have a 50% chance on passing on that mutation to their offspring. If both the intended biological parent and the gamete donor were carriers, their future offspring would each have a 25% chance of being affected with cystic fibrosis.

Other clinicians choose to order carrier screening by sequencing and deletion/duplication analysis for only the condition for which the donor is a carrier. In the example of cystic fibrosis, this methodology would sequence the entire CFTR gene, and look for deletions and duplications to make sure the intended biological parent not only wasn't a carrier for any of the CFTR mutations in the 23-mutation panel, but also other mutations in the CFTR gene. While being more thorough and comprehensive, no genetic testing is 100% perfect. The residual risk for being a CF carrier after having sequencing and deletion/duplication testing would be much lower that if that individual only had targeted mutation analysis, or an expanded carrier screening panel, but it

would still not be eliminated, and varies based on ethnic background. The residual risk to be a carrier of cystic fibrosis after full sequencing and deletion and duplication testing for individuals of Ashkenazi Jewish ancestry is 1 in 2301, in Caucasian individuals the residual risk is 1 in 2401, in African Americans the residual risk in 1 in 6001, in Hispanic Americans the residual risk is 1 in 5701, and in Asian Americans the residual risk is 1 in 9301 (Ambry, 2017).

Navigating how to test the intended biological parent when the donor is a carrier of a condition can be complex. Some providers undoubtedly would prefer to not use a carrier donor altogether to minimize any potential risk. Others would prefer to refer the intended parent(s) to a genetic counselor to discuss the various carrier testing options. As stated in the joint American Society for Reproductive Medicine, and the Society for Assisted Reproductive Technology committee opinion listed below, information regarding the residual risk and further carrier testing options is best provided by a genetic counselor.

1.4 *Genetic Screening Recommendations for Gamete and Embryo Donation: A Committee Opinion.*

In 2013, the practice committee of the American Society for Reproductive Medicine and the practice committee of the Society for Assisted Reproductive Technology came out with a joint statement regarding the genetic screening of gamete (egg and sperm) donors. In addition to the specific recommendations for sperm and egg donors, the committee published what they call a “minimum genetic testing for gamete and embryo donors,” listed below.

1.4.1 *Genetic Screening Recommendations for Sperm Donors*

"Genetic screening for heritable diseases should be performed on potential sperm donors. Testing for cystic fibrosis carrier status should be performed on all donors. Other genetic testing should be performed as indicated by the donor's ethnic background and in accordance with recommendations after obtaining a proper family history. Chromosomal analysis on sperm donors are not required, "(ASRM, 2013).

1.4.2 *Genetic Screening Recommendations for Oocyte Donation*

"The donor should undergo appropriate genetic evaluation based on history, in accordance with ethnic background and current guidelines. Cystic fibrosis testing should be performed on all donors. Consideration should be given to fragile X testing on donors, but is not required," (ASRM, 2013).

1.4.3 *Minimum Genetic Testing for Gamete and Embryo Donors*

A. The Donor:
    a. Should not have any major mendelian disorder. Mendelian disorders fall into the following categories:
        i. Autosomal dominant or X-linked disorders. Providers should be aware that some autosomal dominant or X-linked disorders can have variable expressivity (meaning that mutation carriers may not have noticeable symptoms) or have an age of onset that extends beyond the age of the donor (one example is Huntington disease).
        ii. Autosomal recessive disorders. **Donors who are heterozygous need not necessarily be excluded if the reproductive partner has had appropriate carrier screening.** The recipient and reproductive partner (as appropriate) should be counseled about

the accuracy of the carrier screening test and the residual risk to be a carrier following a negative test. Counseling regarding residual risk is complex and may best be provided by a genetic counselor.

b. Should not have (or have had) any major malformation of complex cause (multifactorial/polygenic), such as spina bifida or cardiac malformation. A major malformation is defined as one that carries serious functional or cosmetic handicap. However, the definition of “major” is a matter of judgement.

c. Should not have any significant familial disease with a major genetic component. Note: Assessment of hereditary risk factors by family history review is performed best by a genetic counselor. However, this screening may be performed by any professional trained in medical genetics at the discretion of the individual program.

d. Should not have a known karyotype abnormality that may result in chromosomally unbalanced gametes. In the general population, the chance of having a chromosomal rearrangement that could be transmitted in unbalanced form to offspring is small, provided the family history is negative for risk factors. Therefore, routine karyotyping of all donors is optional.

e. Should undergo general population and ethnicity (ancestry)-based screening. Donors should give informed consent prior to carrier screening. Informed consent should include discussion of the natural history of the condition being screened, carrier frequency in the respective ethnic group, detection rate of the test, residual risk to be a carrier when testing negative, and options for persons testing positive. If a prospective donor is identified as a carrier, genetic counseling for both the donor and recipient is recommended. All gamete donors should be evaluated by the current tests recommended at the time of donation. Note: It is not appropriate to screen donors for adult onset conditions (such as cancer predisposition, Huntington disease, etc.) without full consent of the gamete donor, including formal genetic counseling.

f. Should be generally healthy and young. Advanced maternal age is associated with an increased risk for aneuploid offspring. Advanced paternal age is associated with a moderately increased risk for new mutations in the offspring, and an emerging body of evidence suggests an increased risk for complex disorders, including some congenital anomalies, schizophrenia, autism spectrum disorders, and specific forms of cancer.

B. The donor's first degree relatives (parents, siblings, and offspring) should be free of:

a. Mendelian disorders as described above.

b. Major malformations as described above.

c. Significant familial disease with a major genetic component.

d. A chromosomal abnormality, unless the donor has a normal karyotype.

e. Mental retardation of undocumented etiology, (ASRM, 2013).

1.5 *Current Legislation on Gamete Donation and Carrier Screening*

As mentioned previously, gamete donation, particularly oocyte donation, is a relatively new technology. Legislation has been slow to keep up with the rapidly expanding technology involved in artificial reproductive technologies. Little has been written into law pertaining to what testing is mandatory for sperm and egg donors. Currently, federal regulations regarding testing that have been outlined for donors of reproductive tissue only include testing for communicable diseases such as, HIV, chlamydia, and gonorrhea, (21 CFR Part 1271 - Human cells, tissues, and cellular and tissue-based products).

1.6 Aim of Current Study

As testing costs continue to decrease, intended parents are expecting more comprehensive screening of gamete donors. A recent article surveyed 1,025 women who used a sperm donor and found that "67.1% of them agreed that sperm banks should be legally required to perform comprehensive genetic testing on all sperm donors," (Sawyer, 2013). The article did not define what the intended parents defined “comprehensive genetic testing” as. The use of expanded carrier screening in reproductive clinics will inevitably increase the number of known carriers of autosomal recessive conditions. While there is research on the preferences of intended parents

regarding carrier screening, as well as position statements from some professional societies in regards to expanded carrier screening in general, this thesis project aims at exploring the possibility of incorporating known carriers into the donor pool.

With the inevitable increase in the number of gamete donors who are carriers of one or more recessive condition(s) identified by an expanded carrier screening panel, this study is designed to assess the opinions of reproductive health clinicians (physicians, nurses, and genetic counselors) on what follow up testing, if any, should be done on the other biological parent. Given the nuances and rapidly expanding technology of genetic testing, knowing what the professionals in the field think about this technology is critical. Identifying whether disagreement is present and, if so, which items providers may disagree upon is a major aim of this study.

1.7 Statement of Hypothesis

Due to the decreasing cost of carrier screening and the technological advances allowing donors to be screened for up to hundreds of recessive conditions simultaneously, there will inevitably be an increase in the number of donors who are found to be carriers of one or more recessive condition(s). Due to these technological advancements and the minimal federal regulations on gamete donors, different providers from different clinics will vary on their opinion(s) of whether or not to proceed with using a gamete donor who is a carrier of a known recessive condition(s), and if they proceed, what type of testing on the biological partner would be the most appropriate.

1.8 Significance

This study aims to gather the opinions of the clinicians working in this area of reproductive healthcare to identify if opinions on the topic are widely similar, or have varying degrees of differences. Identifying areas of disagreement or confusion among clinicians would support that standardized guidelines on how best to proceed with a carrier donor should be followed.

2. METHODS

2.1 *Recruitment*

Participants were recruited to partake in an anonymous web-based survey through Survey Monkey, an online survey company. No researcher had direct contact with the participants. Recruitment was via the National Society of Genetic Counselor's Artificial Reproductive Technology special interest group contact sheet. On the contact sheet, members had their contact information available and checked whether or not students were permitted to contact them. Those who checked yes were emailed the survey.

An email blast was sent out via the National Society of Genetic Counselors. The email encouraged all genetic counselors working in infertility and/or gamete donation centers to fill out the survey. A reminder email blast was sent out two weeks after the initial email invitation.

A web based search for clinics specializing in reproductive technologies and gamete donation agencies was done through the Society for Assisted Reproductive Technology search engine. This generated contact information for clinics across the

United States. Those clinics which had contact information provided were emailed the survey. 380 clinics in total were emailed the survey.

2.2 *Participants*

The survey was available to all genetic counselors, physicians, nurses, administrative personnel, and other medical professionals involved in infertility and gamete donation. All participants needed to be at least 18 years of age or older. If at the beginning of the survey they checked yes to being under the age of 18, the survey ended. Aside from having to be 18 years or older, there was no discrimination based on age, ethnicity, sex, years of practice, or education level. The survey was only available in English, so participants were required to be able to read in English. To ensure the privacy of those participating in the survey, Survey Monkey was adjusted to prevent IP addresses from being collected.

2.3 *Informed Consent*

Informed consent was obtained through an information sheet that appeared as the first page of the survey. By clicking “next,” participants indicated that they consented to participate in the research study. The online consent form described the approximate time it would take to complete the survey, any risks associated with taking the survey, and the goal of the survey. The consent stated that the survey could be stopped at any time, and that no personal identifiers would be collected. At the end of the consent an email address and phone number for the University of California Irvine Institutional Review Board was provided to the respondents if they had any ethical or privacy concerns.

2.4 *Survey*

The survey was constructed through Survey Monkey, an online survey service. It was accessible through a link sent out by email. The survey was estimated to take approximately ten minutes. The survey consisted of 13 multiple choice questions that solicited information including personal demographics, current screening practices, opinion on testing strategies, opinion on their willingness to use donors who are carriers for a recessive condition(s), and resources available to them in their clinic. An additional question asked participants to rank a set of resources by anticipated helpfulness.

2.4.1 *Survey Scoring*

For the question, "what state do you practice in" those who answered "California" were given a score of "1." Those who answered "other" were given a score of "2" and were labeled "other." For the question "what is your role" those who answered, "genetic counselor" were given a label "genetic counselors" and given a score of "1." For those who answered, "physician," "nurse," "administrator" or "other" they were labeled "Non-Genetic Counselors" and given a score of "2."

For the question "What type of facility do you work at," groups were combined due to small sample size. Those who answered, "Fertility clinic" were labeled "Fertility clinic" and given a score of "1." Those who answered "Obstetrics/Gynecology" were labeled "ObGyn" and given a score of "2." For those who answered "Egg/Sperm bank" or "Other" were labeled "Other" and given a score of "3." For the question "What is your age" due to small sample size, certain groups were combined. For those who answered "18-25 years old" and "26-35 years old," they were labeled "18-35" and given a score of "1." Those who answered "36-45 years old" were labeled "36-45 years old" and given a score of "2." Those who answered "46-55 years old" were labeled "46-55 years old" and

given a score of “3.” Those who answered “56-65 years old” and “66-75+ years old” were labeled “56+ years old” and given a score of “4.”

For the question “How long have you been practicing,” due to small sample size, those who answered, “under 5 years” and “5-10 years” were labeled “0-10 years” and given a score of “1.” For those who answered “11-20 years” were labeled ’11-20 years” and given a score of “2.” For those who answered “21-30 years” and “31+ years” were labeled “21+ years” and given a score of “3.”

For the question “what types of screening practices does your facility currently have in places when using donor gametes,” due to low sample size those who answered an “expanded carrier screening panel” were given a score of “1.” Those who answered, “no screening requirements,” “ethnicity based screening for the conditions most common in the donor’s specific ethnic group,” “ethnicity based screening, spinal muscular atrophy, and cystic fibrosis screening,” “don’t know,” and “other” were all categorized as “other” and given a score of “2.”

For both the questions “Canavan Disease is a progressive neurological disease in which treatment is extremely limited, and individuals typically die in childhood. If a donor was found to be a carrier of a classic mutation, how would you typically proceed?” and “Phenylketonuria (PKU) is metabolic disorder that causes a toxic buildup of the amino acid phenylalanine. With early intervention, we are able to keep these toxic levels down and the individual can live a healthy long life. If a donor was found to be a carrier of PKU, how would you typically proceed?” due to small sample size, those who answered, “would not use the donor under any circumstance” were given the label “would not use the donor” and given a score of “1.” Those who answered, “proceed with

donor as long as the patient was properly counseled," "proceed only if the patient is not a carrier of the same condition," and "allow patient to choose the next best step(s)" were labeled "Would consider using the donor" and given a score of "2."

For the question, "What would be the best way to proceed if you have a patient who is interested in using gametes from a donor who is a carrier for one or more recessive condition(s)," due to few respondents answering, "Perform carrier screening on the patient by targeted mutation analysis for only those condition(s) for which the donor carries a mutation(s)," and "No routine management. It depends on the patient," those who answered one of these two choices was not involved in the statistical analysis. Those who answered, "Advise the patient to meet with a genetic counselor" were given a score of "1." Those who answered, "Perform an expanded carrier screening panel on the patient" were given a score of "2." Those who answered, "Perform carrier screening on the patient by sequence analysis for only those condition(s) for which the donor is carries a mutation in" were given a score of "3."

For the question "Expanded carrier screening has the capability to screen donors for hundreds of conditions simultaneously without significantly increasing the cost. This type of screening would be…," due to small sample size, groups were re-categorized. Those who answered, "Appropriate for all donors" were labeled "Appropriate for all donors" and given a score of "1." For those who answered either "Not Appropriate for donors" or "Appropriate only if the intended parents request such testing" were labeled "Not appropriate, or it depends" and given a score of "2."

2.5 *Statistical Analysis*

Survey analysis was conducted using the statistical software Statistical Package for Social Sciences (SPSS). This is a descriptive study comparing data on information about current practices and recommended follow-up screening for gamete donors. All data are categorical and thus described using frequencies and percents. Group differences for categorical response variables were tested using Pearson chi-square tests. A McNemar test was used to determine homogeneity among responses between Canavan disease and Phenylketonuria. A p-value less than 0.05 was used to indicate statistical significance.

3. RESULTS

3.1 Sample size and demographic information

There were 192 participants who began the survey. Of those, 133 completed the entire survey. 137 completed over half of the survey, and these responses were included in the analysis. Of the 137 participants who completed most the survey, 57% (n=78) of them work at a fertility clinic, 5% (n=7) of them work at an egg/sperm bank, 15% (n=21) work at an Obstetrics/Gynecology clinic, and 24% (n=31) work at “other.” Of those who checked other, some free response answers included maternal fetal medicine, private companies, and laboratories. 33% (n=45) of the participants were physicians, 9% (n=13) were nurses, 2% (n=3) were administrators, 49% (n=67) were genetic counselors, and 7% (n=9) were “other.”

Of the 137 participants, 4% (n=6) were ages 18-25 years, 35% (n=48) were ages 26-35 years, 18% (n=25) were ages 36-45 years, 20% (n=28) were ages 46-55 years,

20% (n=27) were ages 56-65 years, and 2% (n=3) were ages 66-75 years or older. 135 participants answered what ethnicity they identified as. Of the 135 participants who answered this question, 90% (n=121) were White or Caucasian, 2% (n=3) were Hispanic or Latino, 1% (n=1) were Black or African American, 3% (n=4) were Asian/Pacific Islander, and 4% (n=6) were “other.”

One hundred thirty-five participants answered how long they have been practicing. Of the 135 participants, 27% (n=36) have been practicing for less than five years, 19% (n=25) have been practicing between five and ten years, 22% (n=30) have been practicing between eleven and twenty years, 22% (n=30) have been practicing between twenty-one and thirty years, and 10% (n=14) have been practicing for over thirty years. 137 participants answered how long they have been at their current facility. Of the 137 participants who answered, 11% (n=15) have been at their facility for less than one year, 37% (n=51) have been at their facility between one and five years, 13% (n=18) have been at their facility between six and ten years, 15% (n=20) have been at their facility between eleven and fifteen years, 24% (n=33) have been at their facility for over fifteen years.

One hundred thirty-five participants answered in what state they practice. Of the 135 participants, 1.94% (n=2) practice in Alabama, 1.94% (n=2) practice in British Columbia, 23.70% (n=32) practice in California, 0.97% (n=1), practice in Colorado, 3.88% (n=4) practice in Connecticut, 0.97% (n=1) answered practicing in the “east coast,” 3.88% (n=4) practice in Florida, 5.83% (n=6) practice in Georgia, 2.91% (n=3) practice in Illinois, 0.97% (n=1) practice in Iowa, 0.97% (n=1) practice in Louisiana, 1.94% (n=2) practice in Maryland, 8.74% (n=9) practice in Massachusetts, 6.80% (n=7)

practice in Michigan, 5.83% (n=6) practice in Minnesota, 2.91% (n=3) practice in Missouri, 1.94% (n=2) practice in Montana, 0.97% (n=1) practice in New Hampshire, 4.85% (n=5) practice in New Jersey, 6.80% (n=7) practice in New York, 6.80% (n=7) practice in North Carolina, 0.97% (n=1) practice in Ohio, 1.94% (n=2) practice in Oregon, 2.91% (n=3) practice in Pennsylvania, 3.88% (n=4) practice in Tennessee, 6.80% (n=7) practice in Texas, 2.91% (n=3) practice in Virginia, 5.83% (n=6) practice in Washington, and 1.94% (n=2) practice in Wisconsin.

Table 1 summarizes the participant demographic information and table 2 summarizes the participant geographical information.

Table 1

Participant Characteristics	Total	
	n	%
AGE (N=137)		
18-25	6	4.4
26-35	48	35.0
36-45	25	18.3
46-55	28	10.4
56-65	27	19.7
66-75+	3	2.2
ETHNICITY (N=135)		
White/Caucasion	121	89.6
Hispanic or Latino	3	2.2
Black or African American	1	0.7
Native American	0	0.0
Asian or Pacific Islander	4	3.0
Other	6	4.4
YEARS IN PRACTICE (N=135)		
<5 years	36	26.7
5-10 years	25	18.5
11-20 years	30	22.2
21-30 years	30	22.2
31+ years	14	10.4
LENGTH AT CURRENT FACILITY (N=137)		
<1 year	15	10.9
1-5 years	51	37.2
6-10 years	18	13.1
11-15 years	20	14.6
16+ years	33	24.1
TYPE OF FACILITY (N=137)		
Fertility Clinic	78	56.9
Egg/Sperm Bank	7	5.1
Obstectrics/Gynecology	21	15.3
Other	31	22.6
ROLE (N=137)		
Physician	45	32.9
Nurse	13	9.5
Administrator	3	2.2
Genetic Counselor	67	48.9
Other	9	6.6

Table 2

State (N=135)		
Alabama	2	1.9
British Columbia	2	1.9
California	32	2.4
Colorado	1	1.0
Connecticut	4	3.9
East Coast	1	1.0
Florida	4	3.9
Georgia	6	5.8
Illinois	3	2.9
Indiana	1	1.0
Iowa	1	1.0
Louisiana	1	1.0
Maryland	2	1.9
Massachusetts	9	8.7
Michigan	7	6.8
Minnesota	6	5.8
Missouri	3	2.9
Montana	2	1.9
New Hampshire	1	1.0
New Jersey	5	4.9
New York	7	6.8
North Carolina	7	6.8
Ohio	1	1.0
Oregon	2	1.9
Pennsylvania	3	2.9
Tennessee	4	3.9
Texas	7	6.8
Virginia	3	2.9
Washington	6	5.8
Wisconsin	2	1.9

3.2 Types of screening requirements in place

One hundred thirty-six of the participants answered, “what types of screening requirements does your facility have in place when screen donor gametes.” Of the 136 participants, 9% (n=12) have no screening requirements, 5% (n=7) use ethnicity based screening for conditions most common in the donor’s specific ethnic group, 15% (n=21) use ethnicity based screening, and screen for spinal muscular atrophy, and cystic fibrosis. 43% (n=58) use an expanded carrier screening panel, 6% (n=8) didn’t know what screening practices were used at their facility, 21% (n=29) answered “other.” Table 3 summarizes screening practices used by the participants.

Table 3

Screening Requirements	Total (n=136)	
	n	%
No Screening Required	12	8.8
Ethnicity Based Screening Testing for Conditions Most Common in the Donor's Specific Ethnic Group	7	5.2
Ethnicity Based Screening, Spinal Muscular Atrophy Screening, and Cystic Fibrosis Screening	21	15.4
Expanded Carrier Screening Panel	59	43.4
Don't Know	8	5.9
Other	29	21.3

3.3 Which donors should have expanded carrier screening

One hundred thirty-six participants answered the question, “expanded carrier screening has the capability to screen donors for hundreds of conditions simultaneously without significantly increasing the cost.” 77% (n=105) answered this screening would

be appropriate for all donors, 4% (n=6) answered this screening is not appropriate for donors, and 18% (n=25) answered appropriate only if the intended parents request such testing. Table 4 summarizes for whom the participants thought expanded carrier screening would be most appropriate.

Table 4

Expanded Carrier Screening	Total (n=136)	
	n	%
Appropriate For All Donors Appropriate For All Donors	105	77.2
Not Appropriate For Donors	6	4.4
Approprate Only if the Intended Parents Request Such Testing	25	18.4

3.4 How to proceed with the intended parent(s) when the donor is a carrier of one or more recessive condition(s)

Participants were asked what would be the best way to proceed if you have a patient who is interested in using gametes from a donor who is a carrier for one or more recessive condition(s). Of the 137 participants, 44% (n=60) would advise the patient to meet with a genetic counselor, 5% (n=7) would recommend the patient use a different donor (to minimize risk and expenses associated with the donor), 26% (n=35) would perform an expanded carrier screening panel on the patient, 18% (n=25) would perform carrier screening on the patient by sequence analysis for only those condition(s) for which the donor carriers a mutation(s), 2% (n=3) would perform carrier screening on the patient by targeted mutation analysis for only those condition(s) for which the donor carries a mutation(s), and 5% (n=7) said no routine management, it depends on the patient. Table 5 summarizes what the participants answered as the best way to proceed

when a patient is interested in using gametes from a donor who is a carrier for one or more recessive condition(s).

Table 5

How to Proceed When a Patient is Interested in Using Gametes From a Donor Who is a Carrier for One or More Recessive Condition(s):	Total (n=137)	
	n	%
Advise the patient to meet with a genetic counselor	60	43.8
Recommend the patient use a different donor (i.e. to minimize risk and expenses associated with the donor)	7	5.1
Perform an expanded carrier screening panel on the patient	35	25.5
Perform carrier screening on the patient by sequence analysis for only those condition(s) for which the donor carries a mutation(s)	25	18.3
Perform carrier screening on the patient by targeted mutation analysis for only those analysis for only those condition(s) for which the donor carries a mutation(s)	3	2.2
No routine management. It depends on the patient	7	5.1

3.5 Carriers of Canavan disease vs. Phenylketonuria

Participants were given a brief description of both Canavan disease and phenylketonuria. 136 participants answered “if a donor was found to be a carrier of a classic mutation (Canavan disease), how would you typically proceed.” 17% (n=23) said they would not use the donor under any circumstance, 17% (n=23) said they would proceed with the donor so long as the patient was properly counseled, 44% (n=60) said they would proceed only if the patient is not a carrier of the same condition, 22% (n=30) said they would allow the patient to choose the next best step(s).

One hundred thirty-seven participants answered “if a donor was found to be a carrier of phenylketonuria how would you typically proceed.” 15% (n=20) said they

would not use the donor under any circumstance, 21% (n=29) said they would proceed with the donor so long as the patient was properly counseled, 42% (n=58) said they would proceed only if the patient is not a carrier of the same condition, and 22% (n=30) said they would allow the patient to choose the next best step(s). Table 6 summarizes participant responses to how they would proceed if a donor was a carrier for either Canavan disease or phenylketonuria.

Table 6

How You Would Proceed if a Donor Was a Carrier of:				
	Canavan Disease (n=136)		Phenylketonuria (n=137)	
	n	%	n	%
Would not use the donor under any circumstance	23	16.9	20	14.6
Proceed with donor as long as patient was properly counseled	23	16.9	29	21.2
Proceed only if the patient is not a carrier of the same condition	60	44.1	58	42.3
Allow patient to choose the next best step(s)	30	22.1	30	24.9

3.6 Access to a Genetic Counselor

Participants were asked if their facility has a genetic counselor available to donors and/or intended parents. Of the 135 participants that responded, 57% (n=77) answered yes: employed by their facility, 30% (n=40) answered yes: through a genetic testing company, 9.6% (n=13) answered yes: through an independent (non-testing company), and 3.7% (n=5) answered no. Table 7 summarizes participant responses to their access to a genetic counselor. When analyzed looking at only non-genetic counselors, 69 total

non-genetic counselors responded. Of the 69 participants that responded, 33.3% (n=23) answered yes: employed by their facility, 49.3% (n=34) answered yes: through a genetic testing company, and 14.5% (n=10) answered yes: through an independent (non-testing company), and 2.9% (n=2) answered no. Table 8 summarized non-genetic counselors' access to a genetic counselor.

Table 7

Does Your Facility Have Access to a Genetic Counselor	Total (n=135)	
	n	%
Yes, employed by our facility	77	57.0
Yes, through a genetic testing company	40	29.6
Yes, through an independent (non-testing company) service	13	9.6
No	5	3.7

Table 8

Does Your Facility Have Access to a Genetic Counselor		Total (n=69)	
		n	%
Non-Genetic Counselors	Yes, employed by our facility	23	33.3
	Yes, through a genetic testing company	34	49.3
	Yes, through an independent (non-testing company) service	10	14.5
	No	2	2.9

3.7 Resources

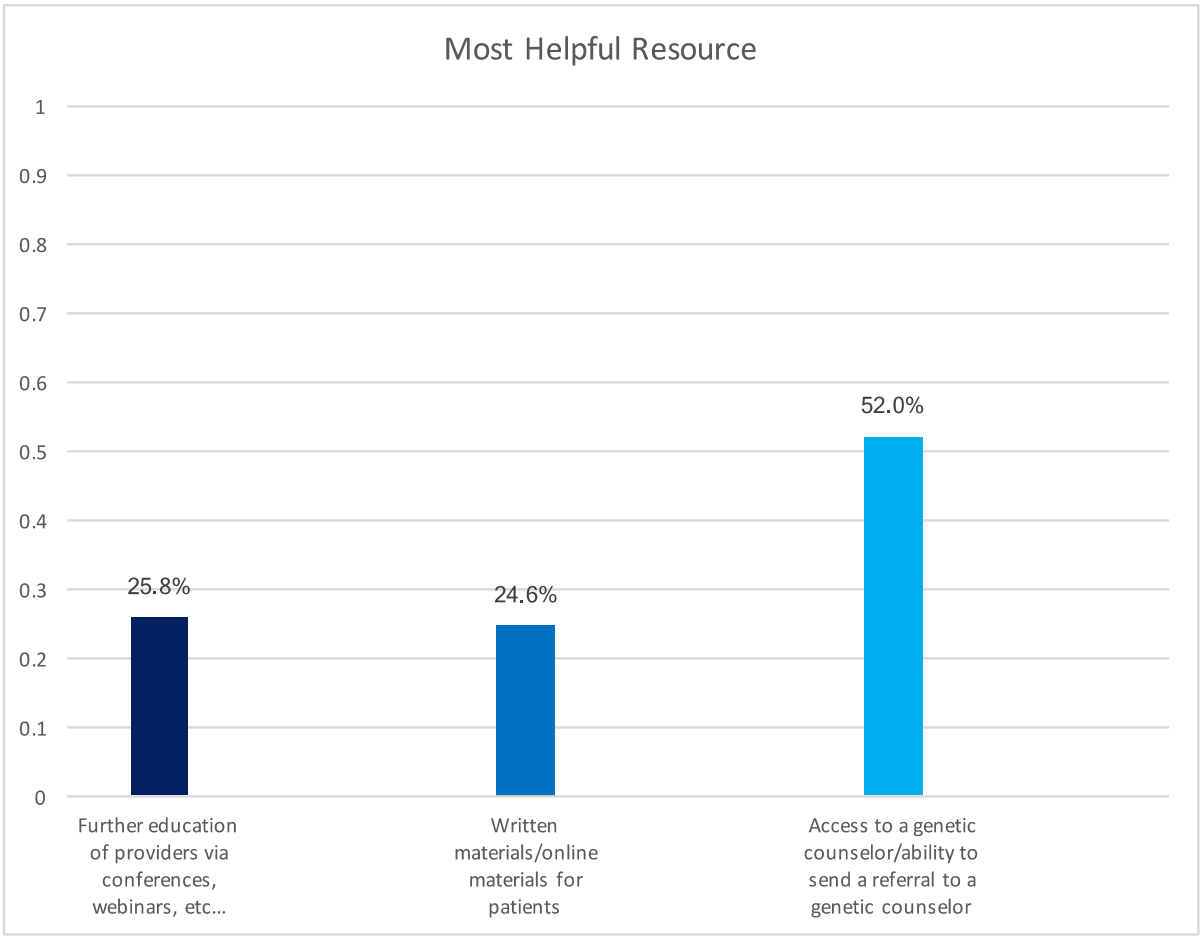
Participants were asked to rank in order of most helpfulness a list of resources. The three options were 1: further education of providers via conferences, webinars, etc…, 2: written materials/online materials for patents, and 3: access to a genetic counselor/ability to send a referral to a genetic counselor. Of the 133 participants who responded, 52% (n=66) rated access to a genetic counselor/ability to send a referral to a genetic counselor as number one, 26% (n=33) rated further education of providers via

conferences, webinars, etc… as number one, and 25% (n=31) rated written materials/online materials for patients as number one. Table 9 and figure 1 summarize participant responses to what they answered as the most helpful resource.

Table 9

Ranking of Most Helpful Resources	Total (n=133)					
	1		2		3	
	n	%	n	%	n	%
Further education of providers via conferences, webinars, etc…	33	25.8	43	33.4	52	40.6
Written materials/online materials for patients	31	24.6	59	46.8	36	28.6
Access to a genetic counselor/ability to send a referral to a genetic counselor	60	52.0	25	19.7	36	28.4

Figure 1



As mentioned above, respondents were categorized by role as either genetic counselor or non-genetic counselor. Table 10 shows the similarity in responses between physicians, nurses, administrators, and others, to justify grouping these respondents together. Their answers on other questions showed a similar trend.

Table 10

What would be the best way to proceed when you have a patient interested in using gametes from a donor who is found to be a carrier of one or more recessive condition(s)					
		Perform an expanded carrier screening panel on the patient		Perform carrier screening on the patient by sequence analysis for only those condition(s) the donor carries a mutation	
		n=35	%	n=25	%
What is your role	Genetic counselor	6	26.1	17	73.9
	Physician	19	79.2	5	20.8
	Nurse	4	57.1	3	42.9
	Administrator	2	100.0	0	0.0
	Other	4	100.0	0	0.0

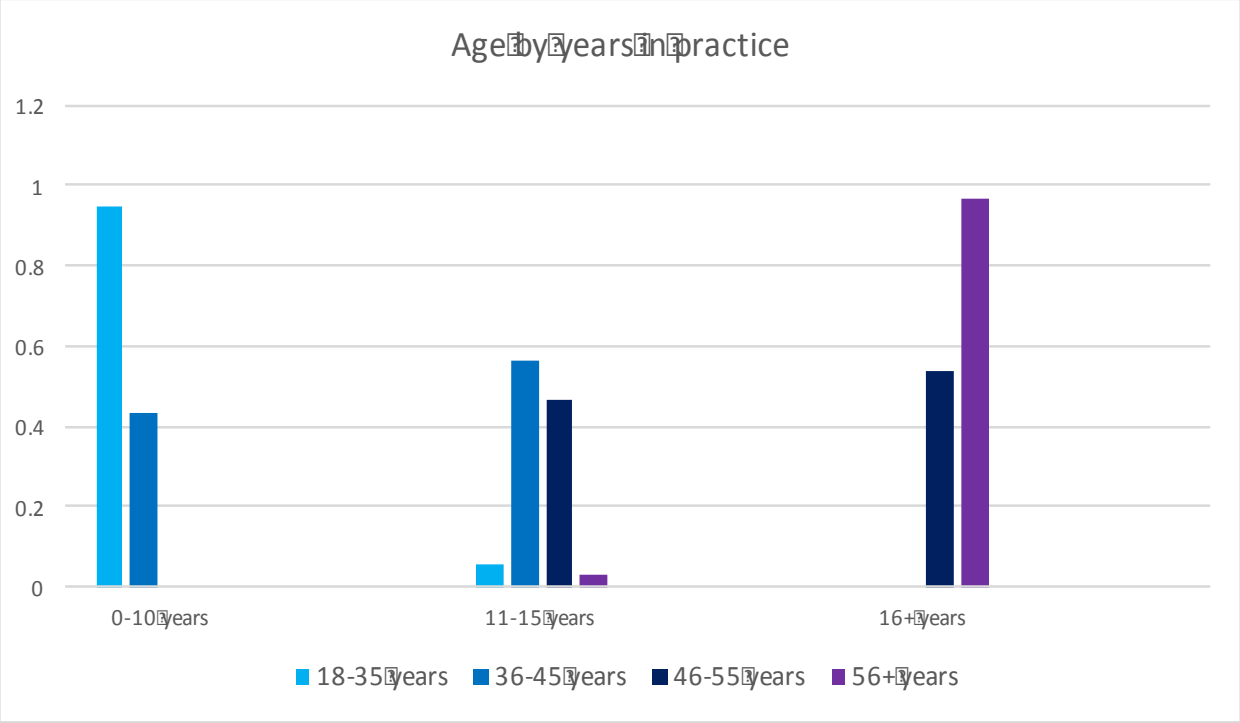
Respondent's age was largely correlated with their years in practice. Table 11 and figure 2 show these results. A significant p-value (<0.001) from a linear by linear trend shows the younger the respondent, the fewer years they have been in practice, similarly, the older the respondent, the longer they have been in practice.

Table 11

		Years in practice						
		0-10 years		11-15 years		16+ years		p-value
		n	%	n	%	n	%	
Age	18-35 years	51	94.4	3	5.6	0	0.0	<0.001
	36-45 years	10	43.5	13	56.5	0	0.0	
	46-55 years	0	0.0	13	46.4	15	53.6	
	56+ years	0	0.0	1	3.3	29	96.7	
	Total	61	45.2	30	22.2	44	32.6	

Linear by linear test → <0.001

Figure 2

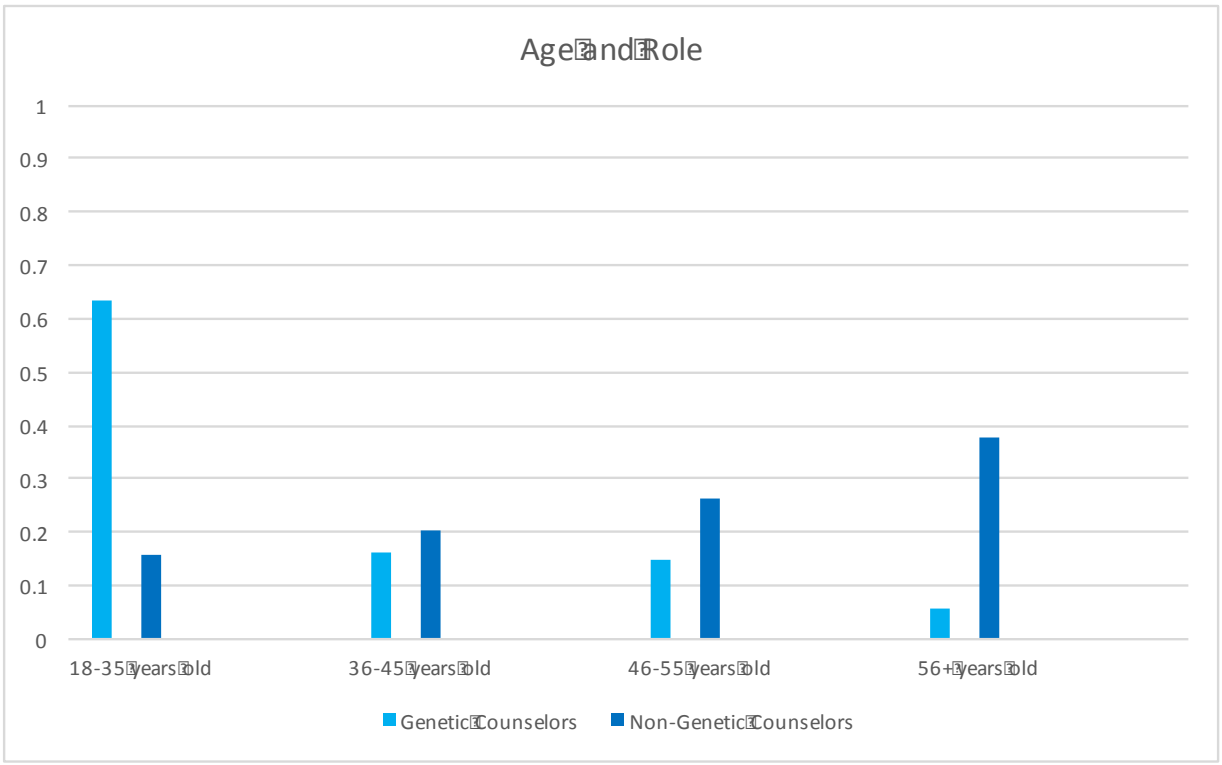


Respondent's age was differed significantly by role (p<0.001). Younger respondents were more likely to be genetic counselors than non-genetic counselors. Similarly, older respondents were more likely to be non-genetic counselors than genetic counselors. Table 12 and figure 3 illustrate these results.

Table 12

	18-35 years old		36-45 years old		46-55 years old		56+ years old		p-value
	n	%	n	%	n	%	n	%	
Genetic Counselors	43	63.2	11	16.2	10	14.7	4	5.9	<0.001
Non-Genetic Counselors	11	15.9	14	20.3	18	26.1	26	37.7	
Total	54	39.4	25	18.2	28	20.4	30	21.9	

Figure 3

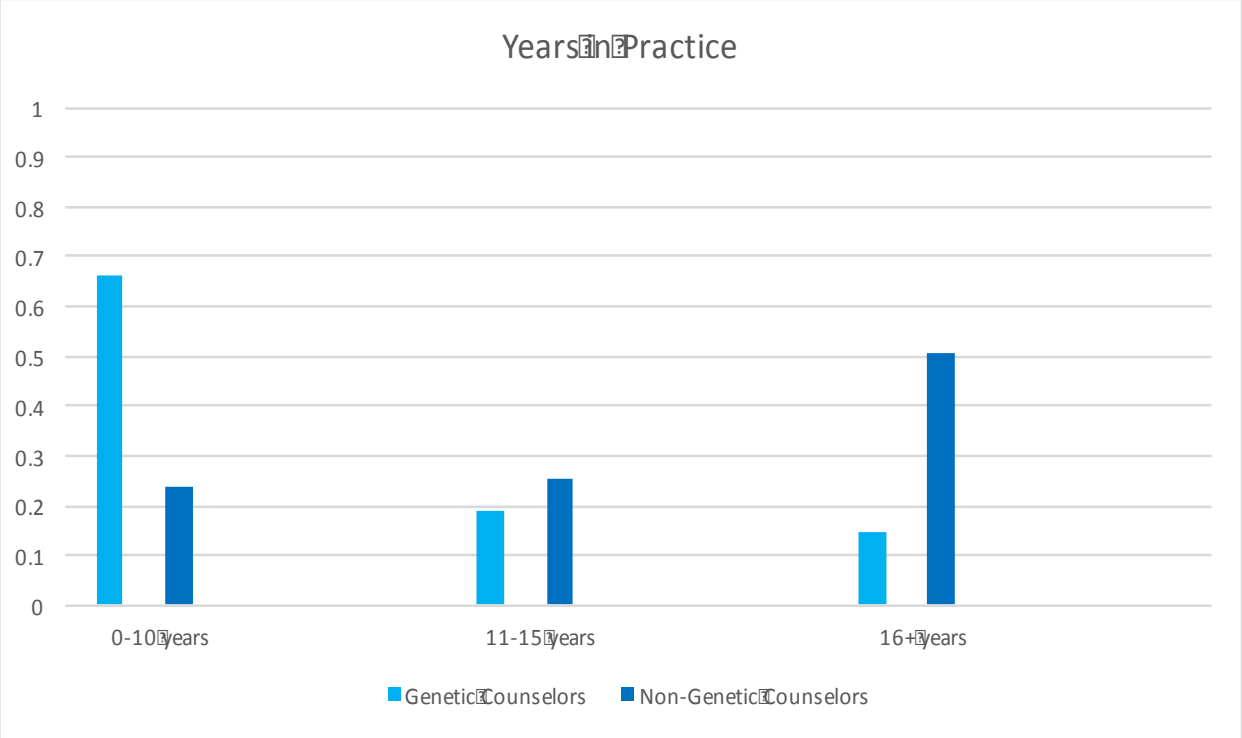


Respondent's years in practice was compared by role and a significant p-value was found (p=<0.001). Respondents who had fewer years in practice were more likely to be a genetic counselor. Similarly, respondents who had more years in practice were more likely to be non-genetic counselors. Table 13 and figure 4 illustrate these results.

Table 13

	Years in practice						
	0-10 years		11-15 years		16+ years		p-value
	n	%	n	%	n	%	
Genetic Counselors	45	66.2	13	19.1	10	14.7	<0.001
Non-Genetic Counselors	16	23.9	17	25.4	34	50.7	
Total	61	45.2	30	22.2	44	32.6	

Figure 4



Respondent's age was compared by state in which they practice; no significant difference was found for age of respondent when comparing those who practice in California vs. other states (p=0.681). Table 14 illustrates these results.

Table14

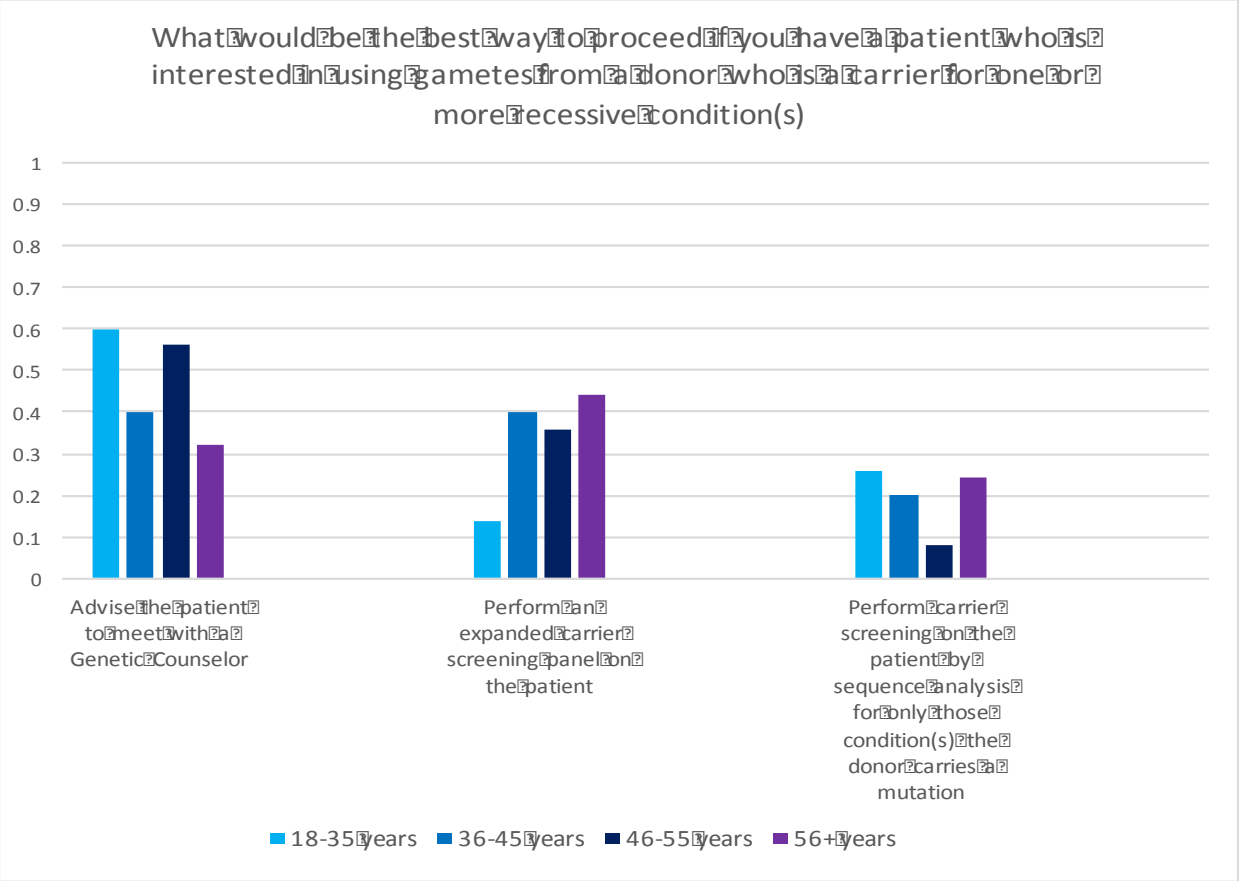
	18-35 years old		36-45 years old		46-55 years old		56+ years old		p-value
	n	%	n	%	n	%	n	%	
California	13	40.6	5	15.6	5	15.6	9	28.1	0.681
Other	41	39.8	19	18.4	23	22.3	20	19.4	
Total	54	40.0	24	17.8	28	20.7	29	21.5	

The question asking how best to proceed if you have a patient interested in using gametes from a donor who is a carrier for one or more recessive condition(s) was compared by age. A significant p-value (p=0.043) was found. The younger the respondent the more likely they were to advise the patient to meet with a genetic counselor. Table 15 and figure 5 illustrate these results.

Table15

What would be the best way to proceed if you have a patient who is interested in using gametes from a donor who is a carrier for one or more recessive condition(s)							
Age		Advise the patient to meet with a Genetic Counselor		Perform an expanded carrier screening panel on the patient		Perform carrier screening on the patient by sequence analysis for only those condition(s) the donor carries a mutation		p-value
		n=60	%	n=35	%	n=25	%	
	18-35 years	30	60.0%	7	14.0%	13	26.0%	0.043
	36-45 years	8	40.0%	8	40.0%	4	20.0%	
	46-55 years	14	56.0%	9	36.0%	2	8.0%	
	56+ years	8	32.0%	11	44.0%	6	24.0%	

Figure 5



The question asking how best to proceed if you have a patient interested in using gametes from a donor who is a carrier for one or more recessive condition(s) was compared by years of practice. No significant difference (p=0.27) was found. The results show respondents with fewer years in practice are more likely to advise the patient to meet with a genetic counselor, and those with more years in practice are more likely to perform an expanded carrier screening panel on the patient, however there was no statistical significance found. Table 16 illustrates these results.

Table16

What would be the best way to proceed if you have a patient who is interested in using gametes from a donor who is a carrier for one or more recessive condition(s)								
Years in Practice		Advise the patient to meet with a Genetic Counselor		Perform an expanded carrier screening panel on the patient		Perform carrier screening on the patient by sequence analysis for only those condition(s) the donor carries a mutation		p-value
		n	%	n	%	n	%	
	0-10 years	32	56.1	12	21.1	13	22.8	0.27
	11-15 years	13	56.5	6	26.1	4	17.4	
	16+ years	15	38.5	16	41.0	8	20.5	
	Total	60	50.4	34	28.6	25	21.0	

The question asking if expanded carrier screening was appropriate for all donors was compared by age. No significant value was found (p=0.12). The majority of all age groups answered expanded carrier screening was appropriate for all donors. Table 17 illustrates these results.

Table 17

Expanded carrier screening has the capability to screen donors for hundreds of conditions simultaneously without significantly increasing the cost. This type of screening would be:						
Age		Appropriate for All Donors		Not appropriate or only if the intended parents request it		p-value
		n	%	n	%	
	18-35 years	41	77.4	12	22.6	0.12
	36-45 years	23	92.0	2	8.0	
	46-55 years	18	64.3	10	35.7	
	56+ years	23	76.7	7	23.3	
	Total	105	77.2	31	22.8	

The type of screening requirements currently in place at the facility the participants work at was compared to the state in which they practice. No significance was found in the types of screening practices compared by state (p=0.11). The results show those respondents from California more often answered they use an expanded carrier screening panel on their gamete donors than respondents from states other than California, however no statistical significance was found. Table 18 illustrates these results.

Table 18

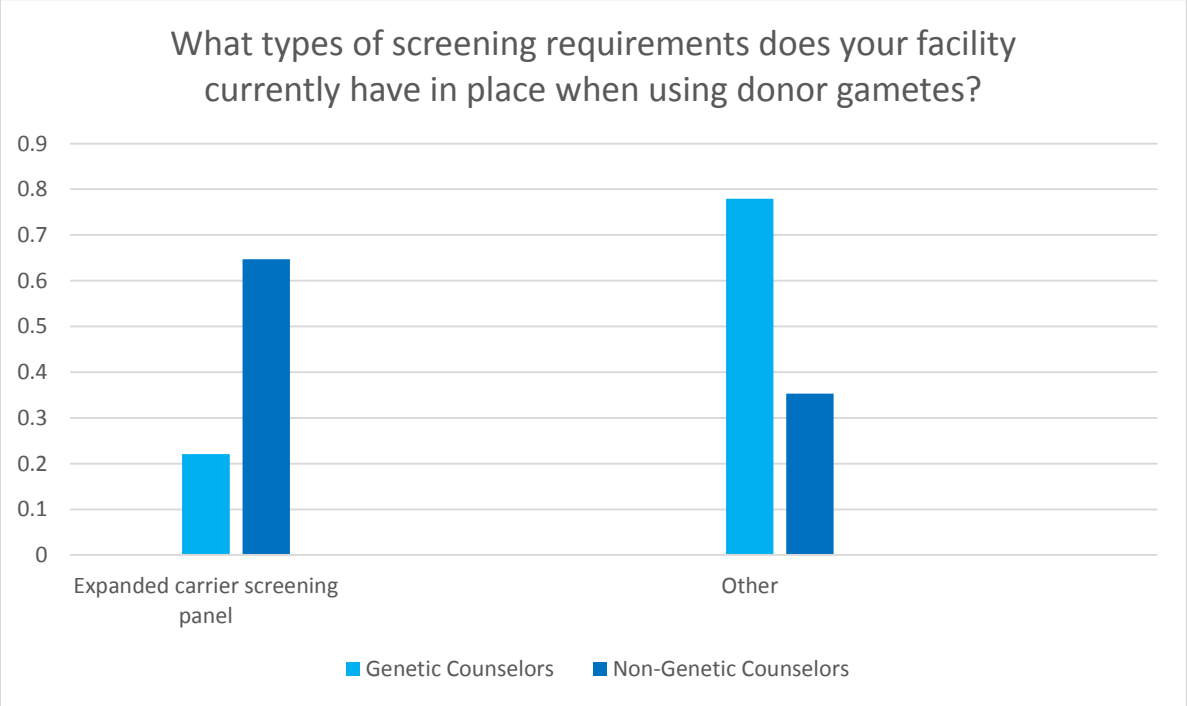
What types of screening requirements does your facility have in place when using donor gametes?					
	Expanded carrier screening panel		Other		p-value
	n	%	n	%	
California	18	56.3	14	43.8	0.11
Other	41	40.2	61	59.8	
Total	59	44.0	75	56.0	

The type of screening requirements currently in place at the facility the participants work at was compared by the role of the participants; genetic counselor or non-genetic counselor. A significant difference was found (p<0.001), with genetic counselors more often using something other than expanded carrier screening panel to screen their donors. Table 19 and figure 6 illustrate these results.

Table 19

What types of screening requirements does your facility have in place when using donor gametes?					
	Expanded carrier screening panel		Other		p-value
	n	%	n	%	
Genetic Counselors	15	22.1%	53	77.9%	<0.001
Non-Genetic	44	64.7%	24	35.3%	
Total	59	43.4	77	56.6	

Figure 6

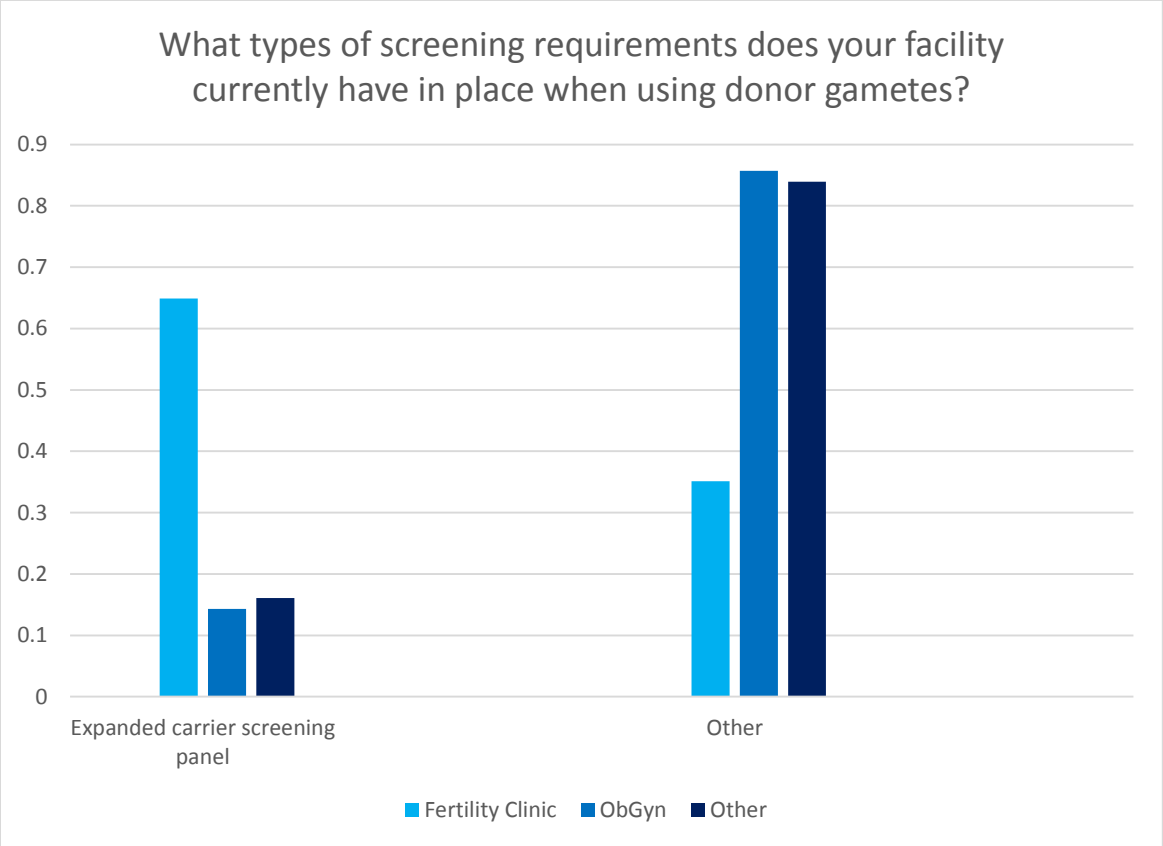


The type of screening requirements currently in place at the facility the participants work at was compared by type of clinic. A significant p-value was found ($p<0.001$), with those who work at a fertility clinic more likely to use an expanded carrier screening panel. Table 20 and figure 7 illustrate these results.

Table 20

What types of screening requirements does your facility have in place when using donor gametes?					
	Expanded carrier screening panel		Other		p-value
	n	%	n	%	
Fertility Clinic	50	64.9	27	35.1	<0.001
ObGyn	4	14.3	24	85.7	
Other	5	16.1	26	83.9	
Total	59	43.4	77	56.6	

Figure 7



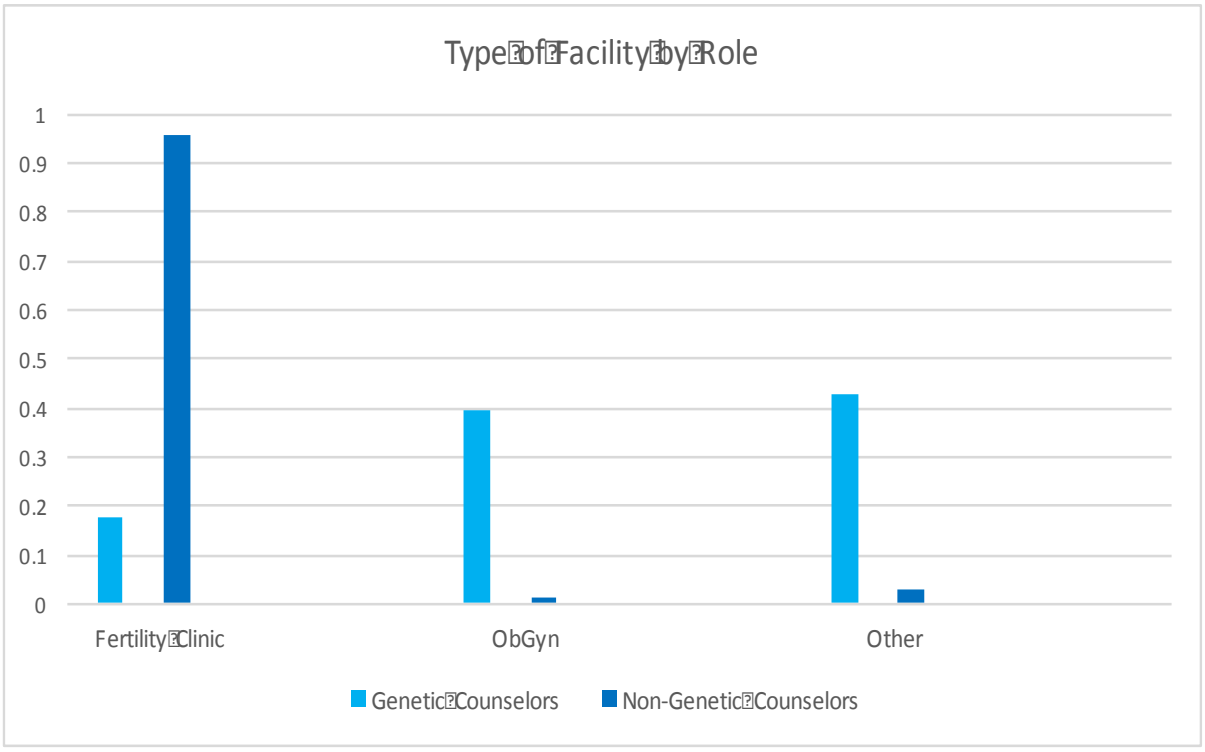
Respondents roles were compared by type of facility they practice in, a significant value was found of $p<0.001$. Non-genetic counselors were more likely to work at a fertility clinic than their genetic counselor counterparts. Similarly, genetic counselors

were more likely to work at an obstetrician gynecology office or other than their non-genetic counselor counterparts. Table 21 and figure 8 illustrate these results.

Table 21

	Type of Facility						p-value
	Fertility Clinic		ObGyn		Other		
	n	%	n	%	n	%	
Genetic Counselors	12	17.6	27	39.7	29	42.6	<0.001
Non-Genetic Counselors	66	95.7	1	1.4	2	2.9	
Total	78	56.9	28	20.4	31	22.6	

Figure 8



The question, would you consider using a donor who was a carrier of Canavan disease was compared by the role of the participants: genetic counselor or non-genetic

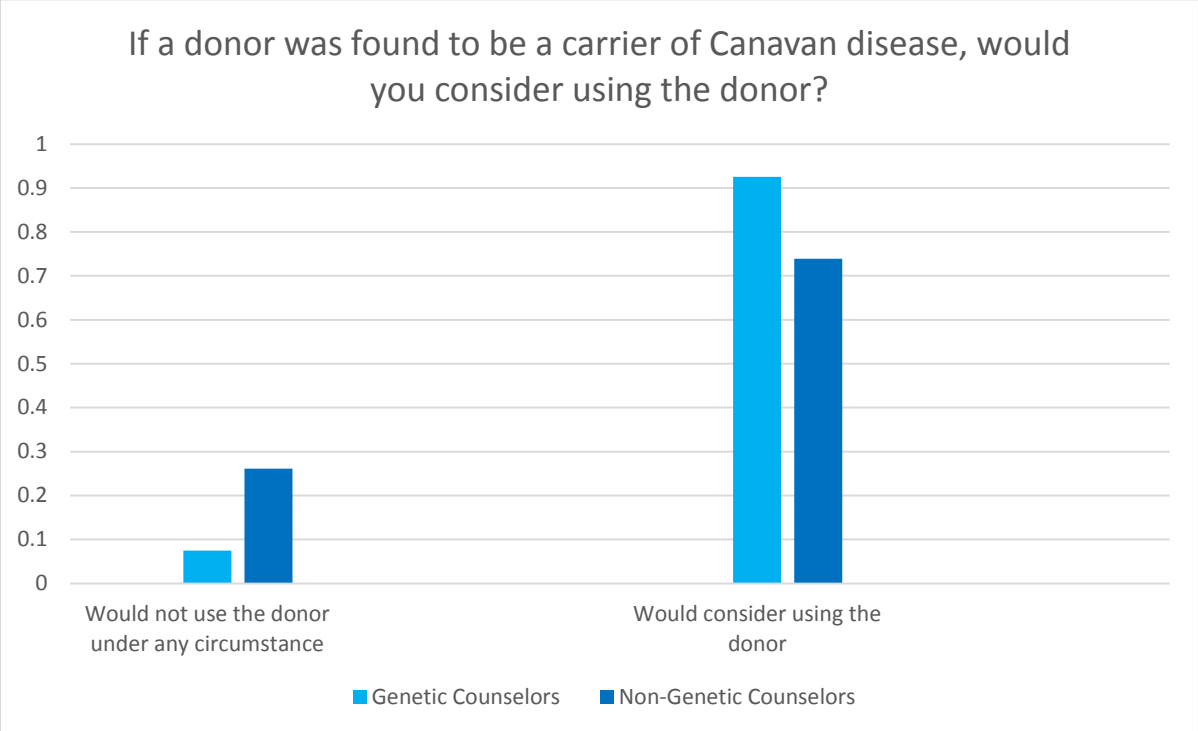
counselor. A significant p-value was found (p=0.004), with genetic counselors more likely to be use a donor who is a known carrier of Canavan disease. Table 22 and figure 9 illustrate these results.

Table 22

Canavan Disease is a progressive neurological disease in which treatment is extremely limited, and individuals typically die in childhood. If a donor was found to be a carrier of a classic mutation, how would you typically proceed?

	Would not use the donor under any circumstance		Would consider using the donor		p-value
	n	%	n	%	
Genetic Counselors	5	7.5	62	92.5	0.004
Non-Genetic Counselors	18	26.1	51	73.9	
Total	23	16.9	113	83.1	

Figure 9

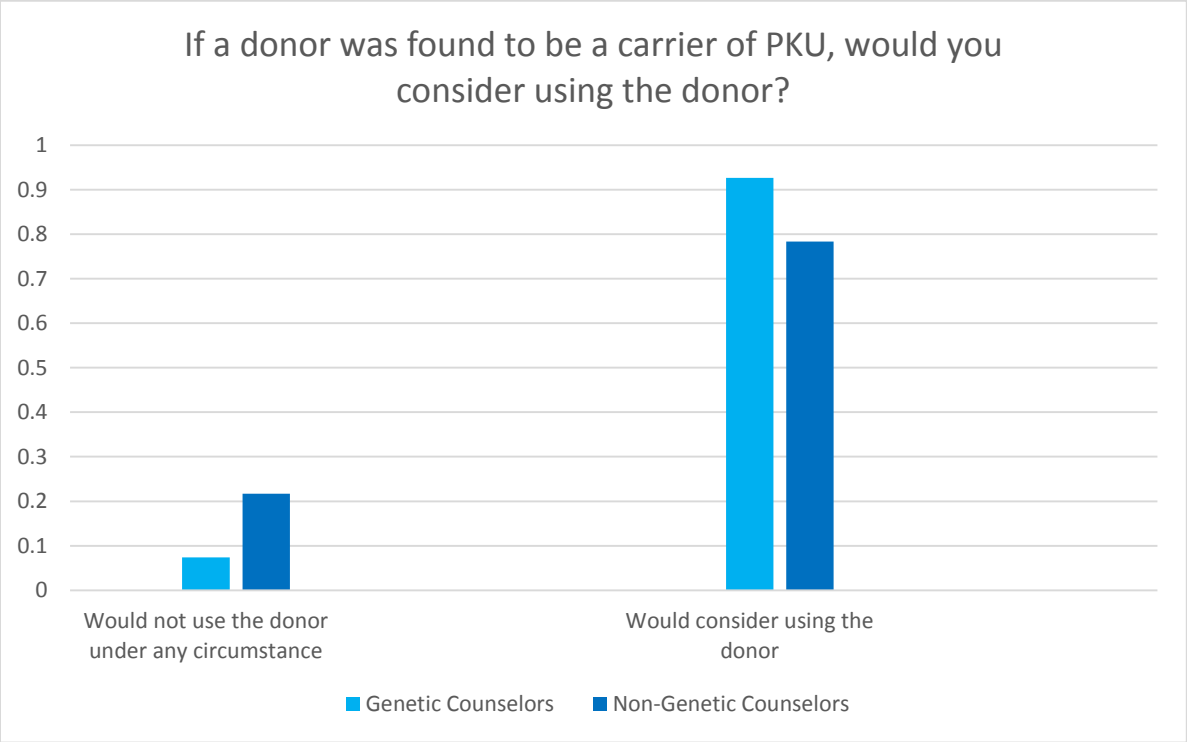


The question, would you consider using a donor who was a carrier of Phenylketonuria (PKU) was compared by the role of the participants: genetic counselor or non-genetic counselor. A significant p-value was found (p=0.02), with genetic counselors more likely to be use a donor who is a known carrier of PKU. Table 23 and figure 10 illustrate these results.

Table 23

Phenylketonuria (PKU) is a metabolic disorder that causes a toxic buildup of the amino acid phenylalanine. With early intervention, we are able to keep these toxic levels down and the individual can live a healthy long life. If a donor was found to be a carrier of PKU, how would you typically proceed?					
	Would not use the donor under any circumstance		Would consider using the donor		p-value
	n	%	n	%	
Genetic Counselors	5	7.4	63	92.6	0.02
Non-Genetic Counselors	15	21.7	54	78.3	
Total	20	14.6	117	85.4	

Figure 10



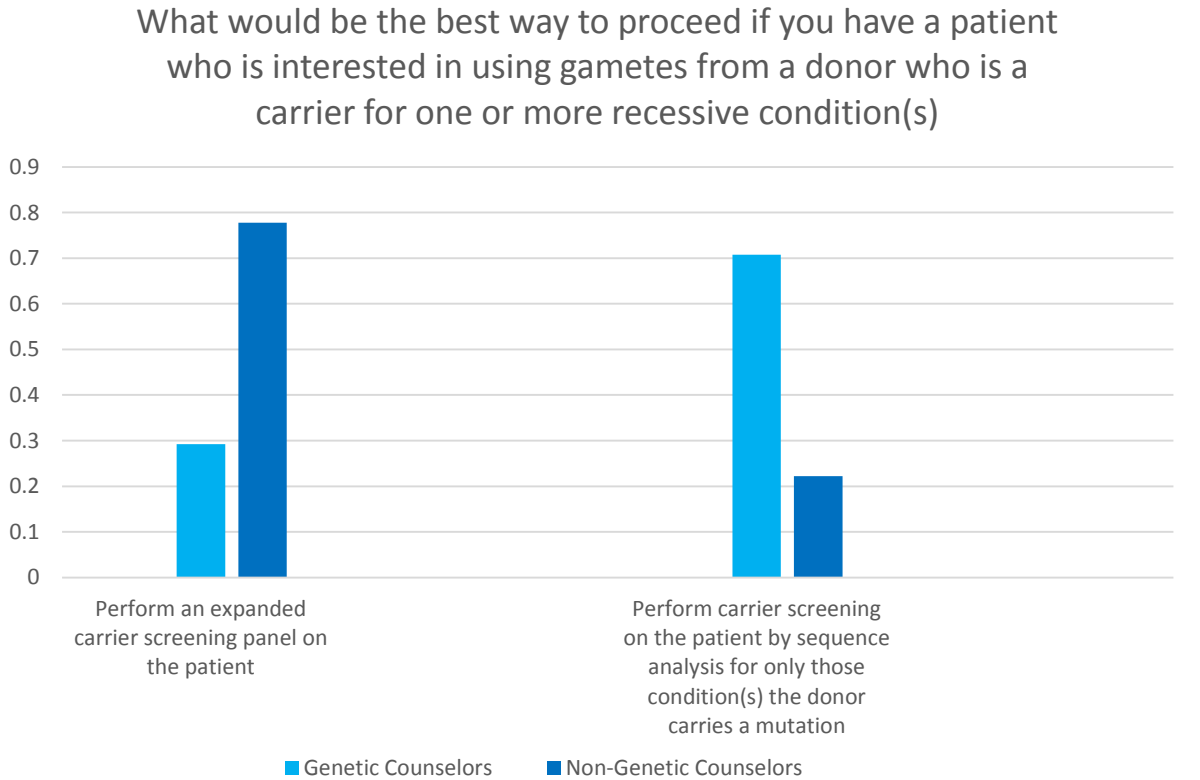
The question asking how best to proceed if you have a patient interested in using gametes from a donor who is a carrier for one or more recessive condition(s) was compared to role: genetic counselors and non-genetic counselors. A significant value was found ($p<0.001$), with non-genetic counselors more likely to perform an expanded carrier screening panel on the intended biological parent than genetic counselors. Table 24 and figure 11 illustrate these results.

Table 24

What would be the best way to proceed if you have a patient who is interested in using gametes from a donor who is a carrier for one or more recessive condition(s)

	Perform an expanded carrier screening panel on the patient		Perform carrier screening on the patient by sequence analysis for only those condition(s) the donor carries a mutation		p-value
	n	%	n	%	
Genetic Counselors	7	29.2	17	70.8	<0.001
Non-Genetic Counselors	28	77.8	8	22.2	
Total	35	58.3	25	41.7	

Figure 11



The question asking how best to proceed if you have a patient interested in using gametes from a donor who is a carrier for one or more recessive condition(s) was compared to state of practice. No significant p-value was found (p-value=0.15). The results show those respondents from California would perform an expanded carrier screening panel on the patient more often than those respondents from another state, however no statistical significance was found. These results are summarized in table 25.

Table 25

What would be the best way to proceed if you have a patient who is interested in using gametes from a donor who is a carrier for one or more recessive condition(s)							
	Advise the patient to meet with a Genetic Counselor		Perform an expanded carrier screening panel on the patient		Perform carrier screening on the patient by sequence analysis for only those condition(s) the donor carries a mutation		p-value
	n	%	n	%	n	%	
California	13	43.3	13	43.3	4	13.3	0.15
Other	46	52.3	22	25.0	20	22.7	
Total	59	50.0	35	29.7	24	20.3	

The question asking how best to proceed if you have a patient interested in using gametes from a donor who is a carrier for one or more recessive condition(s) was compared by type of clinic. No significant p-value was found (p=0.12). The results show those respondents who work in a fertility clinic were more likely to perform an expanded carrier screening panel on the patient than those who work an obstetrician gynecologist

office, or other. Similarly, those that work in either an obstetrician gynecologist office or other ere more likely to advise the patient to meet with a genetic counselor or perform carrier screening on the patient by sequence analysis for only those condition(s) the donor carries a mutation, however no statistical significance was found. Table 26 illustrates these results.

Table 26

What would be the best way to proceed if you have a patient who is interested in using gametes from a donor who is a carrier for one or more recessive condition(s)							
	Advise the patient to meet with a genetic counselor		Perform an expanded carrier screening panel on the patient		perform carrier screening on the patient by sequence analysis for only those condition(s) the donor carries a mutation		p-value
	n	%	n	%	n	%	
Fertility Clinic	29	43.3	28	41.8	10	14.9	0.12
ObGyn	16	64.0	3	12.0	6	24.0	
Other	15	53.4	4	14.3	9	32.1	
Total	60	50.0	35	29.2	25	20.8	

The question asking if expanded carrier screening was appropriate for all donors was compared by type of clinic. No significant p-value was found (p=0.29). The results show the majority of all respondents answered expanded carrier screening is appropriate for all donors. Table 27 illustrates these results.

Table 27

Expanded carrier screening has the capability to screen donors for hundreds of conditions simultaneously without significantly increasing the cost. This type of screening would be:					
	Appropriate for All Donors		Not appropriate or only if the intended parents request it		p-value
	n	%	n	%	
Fertility Clinic	64	82.1	14	17.9	0.29
ObGyn	20	71.4	8	28.6	
Other	21	70.0	9	30.0	
Total	105	77.2	31	22.8	

The question asking if expanded carrier screening was appropriate for all donors was compared by role. No significant p-value was found (p=0.13). The majority of both groups agreed that expanded carrier screening was appropriate for all donors. Table 28 illustrates these results.

Table 28

Expanded carrier screening has the capability to screen donors for hundreds of conditions simultaneously without significantly increasing the cost. This type of screening would be:					
	Appropriate for All Donors		Not appropriate or only if the intended parents request it		p-value
	n	%	n	%	
Genetic Counselors	48	71.6	19	28.4	0.13
Non-Genetic Counselors	57	82.6	12	17.4	
Total	105	77.2	31	22.8	

Differences in responses between willingness to use a donor who was a carrier of Phenylketonuria and willingness to use a donor who was a carrier of Canavan disease found no significant differences between the two diseases (p=0.45). The results show those that would use a donor who was a carrier of Phenylketonuria would also use a donor who was a carrier of Canavan disease. Similarly, those that would not use a donor who was a carrier of Phenylketonuria would also not use a donor who was a carrier of Canavan disease. Table 29 illustrates these results.

Table 29

Differences in reposonses between Canavan disease and Phenylketonuria		Phenylketonuria				
		Would not use donor		Would use donor		p-value
		n	%	n	%	
Canavan disease	Would not use donor	18	78.3	5	21.7	0.45
	Would use donot	2	18.0	111	98.2	
	Total	20	14.7	116	85.3	

4. DISCUSSION

Through the technological advances of expanded carrier screening, individuals interested in donating their gametes are now able to be screened for up to hundreds of conditions simultaneously. While the use of these technologies are being utilized in clinics across the United States, regulations regarding initial screening and follow-up testing have not be adequately established.

Previous studies have looked at the ethical concerns regarding genetic carrier screening and current screening practices across only sperm banks (Dondorp, 2014; Sims, 2010). This study examined the opinions of reproductive healthcare clinicians on

what follow up testing, if any, should be done on the biological parent. This study also examined the types of carrier screening that are routinely performed.

4.1 Age and Years in Practice of Respondents

The ages of the respondents were compared by years in practice, role, and state, to determine if age was diluting the meaning of the proceeding analyses. Respondents who were of younger ages also had been in practice for fewer years. Importantly, respondents who were of younger ages were also more likely to be genetic counselors than non-genetic counselors. Similarly, genetic counselors were more likely to have been practicing for a fewer amount of years, most likely due to this group being younger in age than their non-genetic counselor counterparts. There was no difference found in respondents age by state in which they practiced, therefore age was not a diluting the meaning of the results regarding state in which the respondents practice.

The question asking how best to proceed if you have a patient interested in using gametes from a donor who is a carrier for one or more recessive condition(s) was compared by age, with a significant p-value showing the younger the respondent the more likely they are to advise the patient to meet with a genetic counselor. Age is most likely to be a confounding variable, with younger respondents more likely to be genetic counselors than non-genetic counselors. The results are more likely to be reflecting attitudes of genetic counselors vs non-genetic counselors rather than age.

4.2 Current Donor Screening Practices

The type of screening practices currently being performed did not significantly differ by which state the participants practiced. However statistical significance was found in the comparison of genetic counselors to non-genetic counselors and by type of

facility. Genetic counselors were less likely to use an expanded carrier screening panel than their non-genetic counselor counterparts. Some of the answers genetic counselors chose instead of an expanded carrier screening panel were ethnicity based screening, spinal muscular atrophy, and cystic fibrosis, or they answered “other,” and wrote in their responses. These responses ranged from custom panels, to ethnicity based screening, spinal muscular atrophy, cystic fibrosis, and fragile-X, to not having requirements but suggestions, see appendix G for all free response answers.

Those who practiced in a fertility clinic were more likely to have donors undergo an expanded carrier screening panel rather than a less comprehensive form of screening. However, when the role of the respondent was compared by type of facility in which the respondent practiced, genetic counselors were less likely to work in a fertility clinic than their non-genetic counselor counterparts.

Often the type of carrier screening a provider orders will be based on the policy or standard of practice at the facility in which he or she works. From the results, we know genetic counselors are less likely to work at fertility clinics than non-genetic counselors. It is possible that the finding that genetic counselors are less likely to order an expanded carrier screening panel is due to the screening protocols in place at the different types of clinics rather than differences based on role. Furthermore, when asked who expanded carrier screening is most appropriate for, both genetic counselors and non-genetic counselors agree that expanded carrier screening should be offered to all donors.

4.3 Willingness to Use a Donor Who is a Carrier of Canavan Disease or Phenylketonuria

Participants were asked if they would have considered using a donor who was a carrier of either Canavan disease or Phenylketonuria. A brief description of both conditions was provided. For both Canavan disease and Phenylketonuria, genetic counselors were more likely to consider using a donor who is a carrier for one of these conditions than their non-genetic counselor counterparts. Participants who would consider using a donor who was a carrier of one of these conditions could choose either to proceed with the donor so long as the patient was properly counseled, proceed with the donor only if the patient is not a carrier of the same condition, or to allow the patient to choose the next best step(s). As mentioned previously, according to a joint statement by the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Medicine in 2013, donors who are carriers of recessive conditions need not necessarily be excluded from the donor pool, so long as the intended biological parent has had appropriate carrier screening and counseled about the accuracy of carrier screening and the residual risk to be a carrier following a negative test. Additionally, the joint statement acknowledges counseling regarding residual risk is complex and may best be provided by a genetic counselor (ASRM 2013).

The difference of opinion between genetic counselors and non-genetic counselors on their willingness to either use or not use a donor who is a carrier of one of these conditions argues in favor of standardized regulations among all practices and providers. This would ensure that donors who do not need to be excluded from the donor pool aren't excluded unnecessarily. It would also ensure the intended biological

parent receives appropriate counseling about residual risk and the accuracy of carrier testing.

To measure if there was a difference in the willingness to use a donor who was a carrier of a condition based on the severity of the condition, respondent answers for 'would they consider using a donor who was a carrier of Phenylketonuria' were compared to respondent answers for 'would they consider using a donor who was a carrier of Canavan disease', with no statistical significance found. If a respondent was likely to consider using a donor who was a carrier of Phenylketonuria, they were just as likely to consider using a donor who was a carrier of Canavan disease. Similarly, those unwilling to use a donor who was a carrier of Canavan disease were just as unlikely to consider using a donor who was a carrier of Phenylketonuria. These results suggest that the severity of the condition for which the donor is a carrier is not a factor in whether they would consider using the donor.

4.4 Type of Follow-up Recommended When a Donor is Found to be a Carrier of One or More Recessive Condition(s)

Participants were asked what type of follow-up testing would be most appropriate when a donor is found to be a carrier of one or more recessive condition(s). This question was compared across role, (genetic counselors vs non-genetic counselors), type of clinic, age, years of practice, and state in which the participant practices. As mentioned above, age and years in practice were found to be confounding variables, and were more likely to reflect the role of the respondent.

Genetic counselors were more likely to recommend the intended biological parent have follow-up screening via full gene sequence analysis for only the condition for which

the donor screened positive and non-genetic counselors were more likely to recommend using an expanded carrier screening panel on the intended biological parent. As discussed above, an expanded carrier screening panel would not be the most appropriate testing to perform on the intended biological parent, as the residual risk to be a carrier of a condition after an expanded carrier screening panel would be much greater than the residual risk to be a carrier after comprehensive full gene sequencing for the specific condition. This discrepancy among genetic counselors and non-genetic counselors argues in favor of having regulations in place to ensure proper follow-up testing and counseling for the intended biological parent, regardless of the role of the clinician.

At a minimum, patients should be advised of the different testing technologies available and counseled about the residual risk to be a carrier and the residual risk to have an offspring affected with the condition in question.

4.5 Access to a Genetic Counselor

Participants were asked about their access to a genetic counselor, either directly employed by their clinic or contracted out through a different company. 97.1% of non-genetic counselors answered “yes” to having access to a genetic counselor. Lack of access to genetic counselors has been a problem described in the literature (Hawkins, 2011); however in this sample access does not seem to be a barrier. Therefore, in cases where counseling regarding complex carrier testing and residual risk calculations is needed, a recommendation for referral to a genetic counselor should be included.

4.6 For Whom is Expanded Carrier Screening Most Appropriate

Participants were asked ‘for whom expanded carrier screening would be most appropriate’. Respondents either choose it would be appropriate for all donors, or not appropriate for all donors, or only appropriate if the intended biological parent requested such testing. This question was compared to role (genetic counselors vs non-genetic counselors) and type of clinic.

When this question was compared by role of the respondent, no significant difference was found. Both genetic counselors and non-genetic counselors agreed that expanded carrier screening is appropriate for all donors. Additionally, there was no statistically significant difference found when compared by type of clinic, with respondents from all types of clinics agreeing that expanded carrier screening is appropriate for all donors. This convergence across role and type of clinic that expanded carrier screening is most appropriate for all donors should be taken into consideration if new guidelines are to be made for carrier screening of gamete donors.

4.7 Limitations of This Study

This study was limited by the small sample size. At times answers were grouped together by likeness to account for small sample size. Additionally, a very small response rate was found for certain options, so analysis of those items was limited.

While this survey was available to individuals of all ethnicities and backgrounds, analysis for differences by ethnicity was not possible due to small sample size in many racial groups.

4.8 Future Studies

While this study illustrates important differences and similarities among different types of healthcare providers, it did not examine the opinions of either the intended

biological parent or the donor. Future studies should evaluate these types of questions among the intended biological parents and donors to gauge similarities and differences between providers and patients.

While the focus of this study was to gauge healthcare providers' opinions on carrier screening for gamete donors, there was no major analysis on how best to implement this screening. Additionally, there was not major analysis on whether regulations with established guidelines should become standard of care and, if so, how this should be done. Future studies should evaluate providers' opinions on how best to implement standardized carrier screening for gamete donors.

4.9 Conclusion

The results of this study demonstrate the differences in opinions among reproductive healthcare providers when it comes to appropriate carrier screening of donors, appropriate follow-up screening of the intended biological parent, and current screening practices being performed. To ensure patients are being appropriately cared for, it is recommended that new guidelines be implemented and adopted by all who practice in this specialty. The purpose of standardized guidelines put forth by professional societies is to better guarantee that the most appropriate type of care becomes the standard of care regardless of clinic type, state, or role.

Based on these results, it is suggested that new guidelines are established and implemented by providers. Suggestions for new guidelines include the following:

1. Expanded carrier screening panels should be offered to all gamete donors.

2. Appropriate pre-test counseling for the gamete donors regarding what this test can detect, the implications of being a carrier of a condition for either his or her donor status, and for his or her own reproductive health should be provided.
3. If a gamete donor is found to be a carrier of one or more recessive conditions the donor need not necessarily be excluded from the donor pool.
4. If a gamete donor is found to be a carrier of one or more recessive conditions, genetic counseling is recommended for both the donor and the intended biological parent. Counseling for the intended biological parent should include options regarding carrier testing for him or her, the option to have no follow-up carrier testing and the risks associated with no follow-up testing, and a brief overview of the natural history of the condition in question.
5. Full sequencing and deletion/duplication (if appropriate) testing for the condition(s) of which the donor is a carrier is recommended as the best way to give the intended biological parent the smallest residual risk to be a carrier, and thus the smallest residual risk to have an affected offspring.

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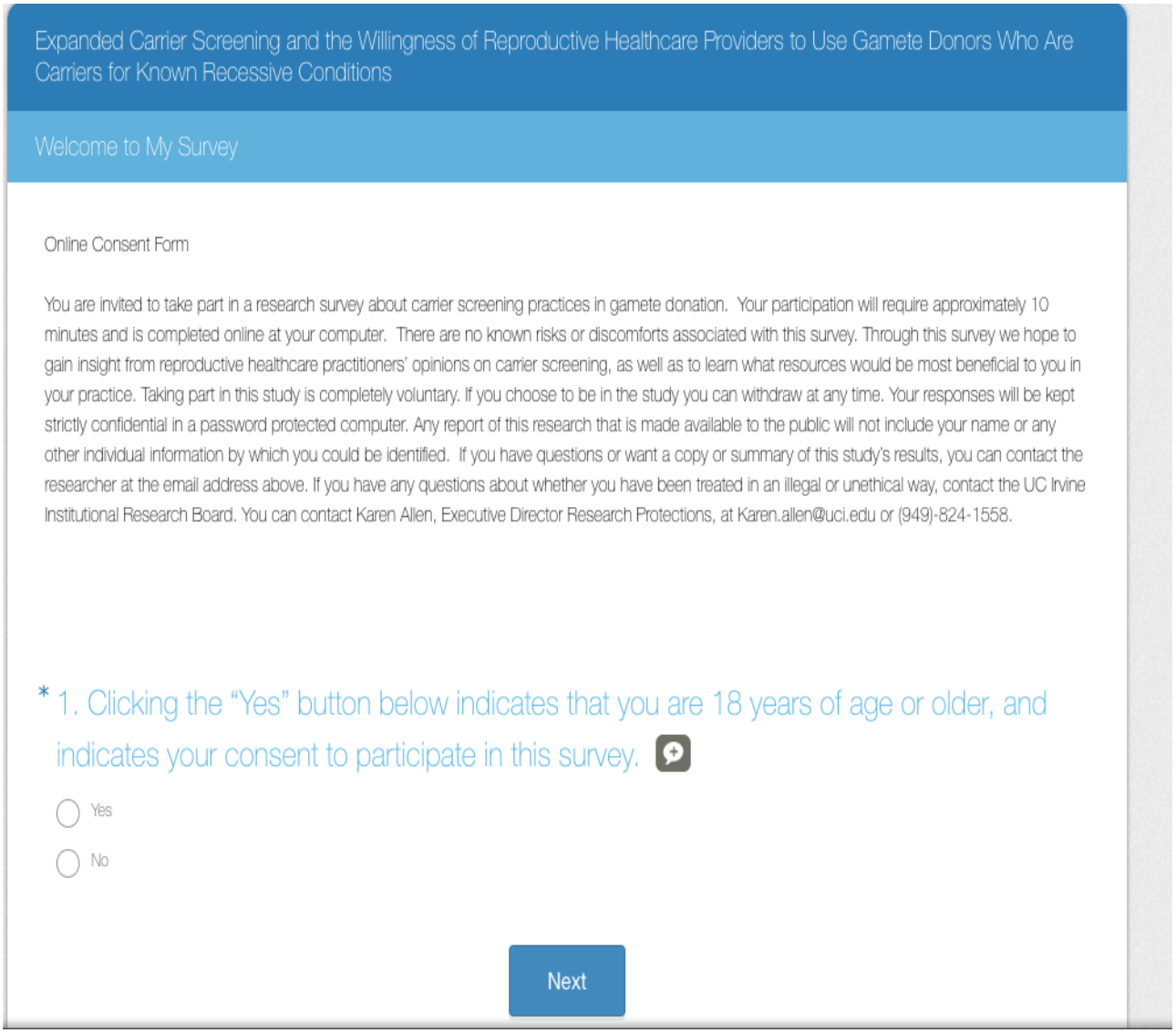
APPENDIX A: Survey



Expanded Carrier Screening and the Willingness of Reproductive Healthcare Providers to Use Gamete Donors Who Are Carriers for Known Recessive Conditions

Welcome to My Survey

Online Consent Form

You are invited to take part in a research survey about carrier screening practices in gamete donation. Your participation will require approximately 10 minutes and is completed online at your computer. There are no known risks or discomforts associated with this survey. Through this survey we hope to gain insight from reproductive healthcare practitioners' opinions on carrier screening, as well as to learn what resources would be most beneficial to you in your practice. Taking part in this study is completely voluntary. If you choose to be in the study you can withdraw at any time. Your responses will be kept strictly confidential in a password protected computer. Any report of this research that is made available to the public will not include your name or any other individual information by which you could be identified. If you have questions or want a copy or summary of this study's results, you can contact the researcher at the email address above. If you have any questions about whether you have been treated in an illegal or unethical way, contact the UC Irvine Institutional Research Board. You can contact Karen Allen, Executive Director Research Protections, at Karen.allen@uci.edu or (949)-824-1558.

* 1. Clicking the "Yes" button below indicates that you are 18 years of age or older, and indicates your consent to participate in this survey.

Yes

No

Next

Expanded Carrier Screening and the Willingness of Reproductive Healthcare Providers to Use Gamete Donors Who Are Carriers for Known Recessive Conditions

Carrier screening for genetic conditions in gamete donors is an important component of the donation process. With the advent of newer technologies we are now able to screen donors for hundreds of conditions simultaneously without dramatically increasing the cost. These tests are typically referred to as "expanded carrier screening panels." As these expanded carrier screening panels become more available, intended parents will be expecting more comprehensive screening on gamete donors. The use of expanded carrier screening panels in reproductive clinics will inevitably increase the number of known carriers of autosomal recessive conditions. This survey seeks to gain insight on the opinions of reproductive healthcare providers regarding their willingness to use donors who are carriers for a known recessive conditions and what, if any, follow up testing should be performed. We are also aiming to learn what carrier testing resources may best aid you in your practice.

Prev Next

Expanded Carrier Screening and the Willingness of Reproductive Healthcare Providers to Use Gamete Donors Who Are Carriers for Known Recessive Conditions

3. What type of facility do you work at?

- ◯ Fertility clinic (Reproductive Endocrinology)
- ◯ Egg/Sperm bank
- ◯ Obstetrics/Gynecology
- ◯ Other (please specify)

4. What is your role?

- ◯ Physician
- ◯ Nurse
- ◯ Administrator
- ◯ Genetic counselor
- ◯ Other (please specify)

5. What state do you practice in?

- ◯ California
- ◯ Other (please specify)

6. What is your age?

- ◯ 18-25 years old
- ◯ 26-35 years old
- ◯ 36-45 years old
- ◯ 46-55 years old
- ◯ 56-65 years old
- ◯ 66-75+ years old

7. What is your ethnicity?

- ◯ White
- ◯ Hispanic or Latino
- ◯ Black or African American
- ◯ Native American
- ◯ Asian/Pacific Islander
- ◯ Other (please specify)

8. How long have you been practicing?

- ◯ Under 5 years
- ◯ 5-10 years
- ◯ 11-20 years
- ◯ 21-30 years
- ◯ 31+ years

9. How long have you been at your current facility?

- ◯ Under 1 year
- ◯ 1-5 years
- ◯ 6-10 years
- ◯ 11-15 years
- ◯ 16+ years

10. What types of screening requirements does your facility have in place when using donor gametes?

- ◯ No screening required
- ◯ Ethnicity based screening testing for conditions most common in the donor's specific ethnic group
- ◯ Ethnicity based screening, Spinal Muscular Atrophy screening, and Cystic Fibrosis screening
- ◯ Expanded carrier screening panel
- ◯ Don't know
- ◯ Other (please specify)

11. Expanded carrier screening has the capability to screen donors for hundreds of conditions simultaneously without significantly increasing the cost. This type of screening would be:

- ◯ Appropriate for all donors
- ◯ Not appropriate for donors
- ◯ Appropriate only if the intended parents request such testing

12. What would be the best way to proceed if you have a patient who is interested in using gametes from a donor who is a carrier for one or more recessive condition(s):

- ◯ Advise the patient to meet with a genetic counselor
- ◯ Recommend the patient use a different donor (i.e. to minimize risk and expenses associated with the donor)
- ◯ Perform an expanded carrier screening panel on the patient
- ◯ Perform carrier screening on the patient by sequence analysis for only those condition(s) for which the donor carries a mutation(s)
- ◯ Perform carrier screening on the patient by targeted mutation analysis for only those condition(s) for which the donor carries a mutation(s)
- ◯ No routine management. It depends on the patient

13. Canavan Disease is a progressive neurological disease in which treatment is extremely limited, and individuals typically die in childhood. If a donor was found to be a carrier of a classic mutation, how would you typically proceed?

- ◯ Would not use the donor under any circumstance
- ◯ Proceed with donor as long as patient was properly counseled
- ◯ Proceed only if the patient is not a carrier of the same condition
- ◯ Allow patient to choose the next best step(s)

14. Phenylketonuria (PKU) is metabolic disorder that causes a toxic buildup of the amino acid phenylalanine. With early intervention, we are able to keep these toxic levels down and the individual can live a healthy long life. If a donor was found to be a carrier of PKU, how would you typically proceed?

- ◯ Would not use the donor under any circumstance
- ◯ Proceed with donor as long as patient was properly counseled
- ◯ Proceed only if the patient is not a carrier of the same condition
- ◯ Allow patient to choose the next best step(s)

15. Does your facility have a genetic counselor available to counsel donors and/or intended parents?

- ◯ Yes, employed by our facility
- ◯ Yes, through a genetic testing company
- ◯ Yes, through independent (non-testing company) service
- ◯ No

16. What resources would be most helpful to you in your practice? Please rank in order, 1 being most helpful, 3 being least helpful.

- ⠿ [ ] Further education of providers via conferences, webinars, etc...
- ⠿ [ ] Written materials/online materials for patients
- ⠿ [ ] Access to a genetic counselor/ability to send a referral to a genetic counselor

Prev Done

APPENDIX B: Confirmation of Exempt Research Registration

UCI University of California, Irvine

CONFIRMATION OF EXEMPT RESEARCH REGISTRATION

November 17, 2016

EMILY NICOLE MARSH
GENETIC AND GENOMIC MEDICINE

RE: HS# 2016-3189 *Expanded Carrier Screening and the Willingness of Reproductive Healthcare Providers to Use Gamete Donors Who Are Carriers for Known Recessive Conditions*

The human subjects research project referenced above has been registered with the UC Irvine Institutional Review Board (UCI IRB) as Exempt from Federal regulations in accordance with 45 CFR 46.101. This exemption is limited to the described activities in the registered UCI IRB Protocol Narrative and extends to the performance of such activities at the sites identified in your UCI IRB Protocol Application. Informed consent from subjects must be obtained unless otherwise indicated below. UCI IRB conditions for the conduct of this research are included on the attached sheet.

Information provided to prospective subjects to obtain their informed consent should, at a minimum, consists of the following information: the subject is being asked to participate in research, what his/her participation will involve, all foreseeable risks and benefits, the extent to which privacy and confidentiality will be protected, that participation in research is voluntary and the subject may refuse to participate or withdraw at any time without prejudice.

Questions concerning registration of this study may be directed to the UC Irvine Office of Research, 141 Innovation Drive, Suite 250, Irvine CA 92697-7600; 949-824-0665 (biomedical committee) or 949-824-6662 (social-behavioral committee).

Level of Review: Exempt Review, Category 2

Beverley W. Alberola, CIP
Vice Chair, Institutional Review Board
Registration valid from 11/17/2016 to 11/16/2021
UCI (FWA) 00004071, Approved: January 31, 2003

Determinations as Conditions of Exemption:

Informed Consent Requirements:

1. Signed Informed Consent Not Required
    a. Study Information Sheet Required

APPENDIX C: UCI IRB Conditions for All UCI Human Research Protocols

APPROVAL CONDITIONS FOR ALL UCI HUMAN RESEARCH PROTOCOLS

UCI RESEARCH POLICIES:
All individuals engaged in human-subjects research are responsible for compliance with all applicable UCI Research Policies. The Lead Researcher (and Faculty Sponsor, if applicable) of the study is ultimately responsible for assuring all study team members adhere to applicable policies for the conduct of human-subjects research.

LEAD RESEARCHER RECORDKEEPING RESPONSIBILITIES:
Lead Researchers are responsible for the retention of protocol–related records. The following web pages should be reviewed for more information about the Lead Researcher's recordkeeping responsibilities for the preparation and maintenance of research files: Lead Researcher Recordkeeping Responsibilities and Preparation and Maintenance of a Research Audit File.

PROTOCOL EXPIRATION:
The UCI IRB approval letter references the protocol expiration date under the IRB Chair's signature authorization. A courtesy email will be sent approximately 60 to 90 days prior to expiration reminding the Lead Researcher to apply for continuing review. For studies granted Extended IRB Approval, a courtesy e-mail will be sent annually to verify eligibility for the continuation of extended approval. **It is the Lead Researcher's responsibility to apply for continuing review to ensure continuing approval throughout the conduct of the study.** Lapses in approval must be avoided to protect the safety and welfare of enrolled subjects.

MODIFICATIONS & AMENDMENTS:
Per federal regulations, once a human research study has received IRB approval, any subsequent changes to the study must be reviewed and approved by the IRB prior to implementation *except when necessary to avoid an immediate, apparent hazard to a* subject. **Accordingly, no changes are permissible (*unless to avoid an immediate, apparent hazard to a subject*) to the approved protocol or the approved, stamped consent form without the prior review and approval of the UCI IRB.** All changes (e.g., a change in procedure, number of subjects, personnel, study locations, new recruitment materials, study instruments, etc.) must be prospectively reviewed and approved by the IRB before they are implemented.

APPROVED VERSIONS OF CONSENT DOCUMENTS, INCLUDING STUDY INFORMATION SHEETS:
Unless a waiver of informed consent is granted by the IRB, the consent documents (consent form; study information sheet) with the UCI IRB approval stamp must be used for consenting all human subjects enrolled in this study. Only the current approved version of the consent documents may be used to consent subjects. **Approved consent documents are not to be used beyond the expiration date provided on the IRB approval letter.** Current consent documents are available on the IRB Document Depot.

UNANTICIPATED PROBLEMS REPORTING:
In accordance with Federal regulations and HRP policies, only internal (where UCI serves as the IRB of record), Unanticipated Problems must be reported to the UCI IRB. Unanticipated Problems should also be reported to the UCI IRB when UCI is relying on an external IRB, and the incident occurred at UCI or the incident occurred at an offsite location on a study conducted by a UCI LR. Unanticipated Problems must be submitted to the IRB via the Unanticipated Problems (UP) Report within 5 business days upon the Lead Researcher's (LR) knowledge of the event. For additional information visit the updated HPR webpage on Unanticipated Problems.

CHANGES IN FINANCIAL INTEREST:
Any changes in the financial relationship between the study sponsor and any of the investigators on the study and/or any new potential conflicts of interest must be reported immediately to the UCI Conflict of Interest Oversight Committee (COIOC). If these changes affect the conduct of the study or result in a change in the text of the currently-approved informed consent document, these changes must also be reported to the UCI IRB via a modification request. Research subject to COIOC oversight is not eligible for Extended IRB Approval.

CLOSING REPORT:
A closing report should be filed with the UCI IRB when the research concludes. Visit the HRP webpage Closing a Protocol for complete details.

APPENDIX D: Recruitment Email to the National Society of Genetic Counselors

Dear NSGC Member,

You are invited to participate in a University of California, Irvine genetic counseling student survey exploring the willingness of reproductive healthcare providers to use gamete donors who are carriers for known recessive conditions. The survey seeks to gain insight on the opinions of different medical professionals involved in infertility on using donors who are carriers for one or more recessive condition.

Our study is open to genetic counselors currently working in infertility, in a gamete donation facility, or prenatal genetic counselors that work closely or have worked closely in infertility and/or gamete donation.

The online, anonymous survey should take no more than 10 minutes to complete and does not need to be filled out in one sitting. You can skip any questions you do not want to answer, and you may choose to quit the survey at any time.

This study has been approved by the Institutional Review Board at the University of California, Irvine. If you have any questions, you can contact me at enmarsh@uci.edu

Thank you very much

Survey Link: https://www.surveymonkey.com/r/HFP6973

APPENDIX E: Recruitment Email to the Society for Assisted Reproductive Technology

Hello,

I hope this finds you well. My name is Emma Marsh and I am a second year genetic counseling graduate student at UC Irvine. I am interested in the A.R.T. world and am working on collecting data for my thesis looking at physicians, nurses, & genetic counselors opinions on genetic carrier screening of egg and or sperm donors. My thesis is titled, "Expanded Carrier Screening and the Willingness of Reproductive Healthcare Providers to Use Gamete Donors Who Are Carriers for Known Recessive Conditions." I have a SHORT 15 question survey I'm hoping you could either take or forward to any physician, nurse, or genetic counselor on staff. I'd be happy to answer any questions regarding the survey and my thesis. I really appreciate the help.

Survey link: https://www.surveymonkey.com/r/HFP6973

Again thank you so much for your time and help,

Emma Marsh
Genetic Counseling Intern
Division of Genetic and Genomic Medicine
University of California, Irvine
Fax: (714)-456-5330 Phone: (714)-456-5837
Email: enmarsh@uci.edu

APPENDIX F: List of “Other” Responses for “What Type of Facility do you Work at?”

List of “Other” Responses for “What Type of facility do you Work at?”
“MFM clinic”
“Maternal Fetal Medicine”
“PGD testing facility”
“Industry lab now, but up to 1 year ago I was the primary GC in a IVF clinic with donor gamete and PGD programs. I will answer the questions based on my 12 work experience at that clinic”
“Prenatal Diagnosis Center”
“Private Company”
“I work as an independent GC for an egg donor company as well as a prenatal GC for LabCorp”
“Lab”
“Maternal Fetal Medicine”
“Carrier Screening Laboratory”
“Maternal Fetal Medicine”
“I do both prenatal and reproductive genetic counseling”
“Hospital, but not in the B/GYN Dept.”
“carrier screen, PGD lab”
“private company providing GC”
“I work in the Ob/Gyn department (mostly perinatal center) but also work with our reproductive endocrinology center”
“laboratory”
“Egg donor agency”
“Fertility clinic that also has an in-house egg donor agency”
“laboratory”
“Maternal Fetal Medicine”
“PGD laboratory”
“PGD testing lab”
“Reproductive testing company”
“Clinical testing lab (but previously sperm/egg bank)”
“PGD lab”
“PGD lab”
“PGD lab”
“Company that provides ECS”
“Maternal Fetal Medicine”
“telegenetics non-profit providing expanded carrier screening”

APPENDIX G: List of “Other” Responses for “What Types of Screening Requirements Does Your Facility Have in Place When Using Donor Gametes?”

List of “Other” Responses for “What Types of Screening Requirements Does Your Facility Have in Place When Using Donor Gametes?”
“we use gametes from other facilities, so they choose the screening. We work with banks that use a variety of screening”
“Expanded if the practice is working with the donor directly; if family has gone through a bank the practice defers to the screening requirements of the bank”
“Counsel people about using donor gametes, but not from the same facility.”
“I don't know that they have their own requirements. Each clinic they work with tests the donors differently while taking into account our recommendations.”
“We typically only see patients that have used donors and are not involved in the screening process of donors or the donation process.”
“I work with facilities using our carrier screening”
“We are often using donor gametes from other sources who have their own screening guidelines, if a patient desires to use a known gamete donor, we offer and recommend expanded carrier screening”
“We do not typically see donors prior to donation”
“lab that does screening”
“ethnicity based, fragile X, SMA and CF”
“All donors must have CF, SMA, and ethnicity based screening; however, expanded carrier screening is offered as an option to the recipient of the egg donor”
“Screened per external bank's protocols”
“Fragile X, SMA,CF,Thal,Tay Sachs and ethnicity based”
“Ethnicity based screening and Cystic Fibrosis screening”
“panel specifically for donors-SMA, CF, Fragile X and askenazi jewish panel”
“Expanded for the oocyte donors we recruite; rely on sperm banks for their screening of sperm donors”
“Varies if its male or female or the bank that provides them.Usually expanded carrier”
“I do donor counseling for several programs all with different screening requirements”
“N/A”
“No requirements - but suggestions.”
‘‘Currently n/a”
“Does not apply”
“Lab, so no requirements”
“We counsel those who get ECS so N/A”
“N/A”
“we don't test donor gametes”
“We typically use anonymous third party egg and sperm donors recruited through American banks. In this case they organize the screening. If we use a known donor screening is based on ethnicity; however screening would not be required.”
“We have an expanded panel of 22 diseases plus fragile X.”
“We use a small "expanded" panel of 22 conditions that contain all the ethnicity specific conditions as well as CF, SMA and Fragile X.”

APPENDIX H: List of “Other” Responses for “What is Your Role?”

List of “Other” Responses for “What is Your Role?”
“Director”
“IVF Lab Director”
“nurse practitioner”
“Director”
“Owner of company”
“embryologist”
“Physician assistant”
“Physician Assistant”
“Genetic counselor/Variant curator”

APPENDIX I: List of “Other” Responses for “What is Your Ethnicity?”

List of “Other” Responses for “What is Your Ethnicity?”
“Biracial”
“Half Asian/Half Caucasian”
“Asian/White”
“Mixed: Asian and Caucasian”
“1/2 Caucasion 1/2 South Asian”
“Mixed”