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Recipients' Perspectives Regarding Expanded Carrier Screening of Gamete Donors

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Recipients' Perspectives Regarding Expanded Carrier Screening of Gamete
Donors

by

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Abstract

Purpose: This study explored the perspectives of intended parents regarding genetic carrier screening of a gamete donor. The main goal of this study was to determine how much genetic carrier screening information a recipient would prefer to receive about potential donors. The study also aimed to identify factors that potentially influence a recipient's choice of donor based on genetic screening results. **Methods:** An online questionnaire was developed to assess intended parents' preferences regarding expanded carrier screening (ECS) of their donors. Participants were recruited from various online support groups and were eligible if they had previously utilized or were currently utilizing donor gametes. A total of 58 usable responses were collected and reflect insight into the perspectives of intended parents regarding which factors associated with genetic carrier screening influence their choice of donor. The questionnaire consisted of demographic questions, general questions about carrier screening, a genetics knowledge quiz, and questions about hypothetical scenarios in which a donor was a carrier for one of four distinct conditions: hemochromatosis, Usher syndrome, Bardet-Biedl syndrome, and GRACILE syndrome. **Results:** The majority of women (91.4%, 53/58) opted for ECS of their potential gamete donor, preferred over traditional ethnicity- or family history-based screening. Participants were comfortable proceeding with a donor with the knowledge that he/she was a carrier for a mild genetic condition (hemochromatosis, 83.3%). Fewer respondents were comfortable proceeding with a donor who was a carrier for a more severe condition (Usher, 37.0%; BBS, 39.1%; GRACILE, 39.1%). **Conclusion:** Intended

parents prefer ECS for their donors over traditional ethnicity- or family history-based screening. Participants were uncomfortable with a donor who is a carrier for severe, life-limiting conditions, regardless of statistical risk. Expanded carrier screening is desired and could be beneficial for use in gamete donation; however, given the overall discomfort with identification of positive carrier status, ECS would significantly alter clinical decision making in these settings. Increased genetic education of recipients on the implications of ECS carrier results is indicated, and access to genetic counseling services may be indicated for optimal implementation.

Keywords: gamete donation, expanded carrier screening, recipient perspectives.

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List of Abbreviations

| | |
|------------|---|
| ACMG | American College of Medical Genetics and Genomics |
| ACOG | American College of Obstetrics and Gynecology |
| AJ | Ashkenazi Jewish |
| AR..... | Autosomal Recessive |
| ART..... | Assisted Reproductive Technology |
| ASRM | American Society for Reproductive Medicine |
| ECS | Expanded Carrier Screening |
| IVF | In Vitro Fertilization |
| PGD | Preimplantation Genetic Diagnosis |
| XL | X-Linked |

Chapter 1: Background

1.1 Impaired fertility and assisted reproductive technology (ART)

Impaired fertility is the reduced ability to achieve or maintain pregnancy, while infertility is the inability to conceive altogether. According to the most recent data published by the Center for Disease Control and Prevention (CDC, 2015), approximately 6.7 million women and 1.5 million women aged 15-44 are affected by impaired fertility and infertility, respectively. Fertility problems can arise through male or female factors, or have an unknown etiology. Depending on the cause, there are several management options for couples struggling with fertility issues, and the CDC has estimated that 7.4 million women aged 15-44 have ever utilized infertility services. In addition to women with impaired fertility or infertility, same-sex couples and single women also commonly seek fertility care. Fertility treatment options for anyone seeking fertility care include the use of ovulation predictor kits, oral and injectable ovulation-inducing agents, intrauterine insemination, and assisted reproductive technologies (Gunn & Bates, 2016).

Assisted reproductive technology (ART) is defined as any fertility treatment that utilizes eggs or embryos handled in a laboratory. Although ART includes in vitro fertilization (IVF), gamete intrafallopian transfer, and zygote intrafallopian transfer, IVF constitutes 99% of all ART procedures performed. In a typical IVF cycle, a woman's eggs are stimulated with medication and surgically retrieved. Once retrieved, the eggs are combined with sperm to facilitate fertilization. Viable embryos are either selected for

transfer into the uterus or cryopreserved for use at a later time. By definition, ART does not include any procedures in which only sperm are handled (i.e. intrauterine insemination) or treatments in which women take medication to stimulate ovulation or egg production but do not have their eggs retrieved (Sunderam et al., 2015).

Assisted reproductive technology and other fertility treatments facilitate the use of donor gametes for couples unable to conceive using their own eggs or sperm. Indications for therapeutic donor insemination, or the use of donor sperm, include significant sperm or seminal fluid abnormalities (e.g. azoospermia, oligospermia), ejaculatory dysfunction, or other male factor infertility in the male partner, male partner carrier status of a genetic condition, or females without a male partner. Utilization of donor oocytes may be indicated when the woman is of advanced maternal age, has premature ovarian insufficiency or diminished ovarian reserve, is a carrier of a genetic condition, or had poor oocyte/embryo quality in previous ART cycles (ASRM, 2013). The use of donor gametes to facilitate family formation is now well established.

1.2 Current guidelines, recommendations, and concerns regarding gamete donation

Gamete donation is regulated by the Food and Drug Administration (FDA) because of its classification within donation of human cells, tissues, and cellular and tissue-based products (HCT/Ps). As such, the practice must follow clear guidelines for the screening of donors (ASRM, 2013). The American Society for Reproductive Medicine (ASRM) has issued their own recommendations for the evaluation of sperm, oocyte, and embryo donors, which includes the minimum federal requirements set by the FDA. The latest recommendations from the ASRM, which also recommend testing of recipients, include semen testing for males, thorough medical history evaluation, physical

examination, psychological examination, laboratory testing, including infectious disease and hormone testing, and genetic evaluation. While the FDA does not require genetic evaluation of donor HCT/Ps, it is recommended by the ASRM that all donors undergo genetic screening (ASRM, 2013).

Specifically, the ASRM recommends testing all potential donors for cystic fibrosis carrier status. While chromosomal analyses are not required for all donors, other genetic carrier screening should be implemented as indicated by the donor's ethnic background and medical and family history. While it is not required, consideration for fragile X carrier screening should be considered for egg donors (ASRM, 2013). Genetic carrier screening based on ethnic background should follow current available recommendations by the American College of Obstetrics and Gynecology (ACOG) and American College of Medical Genetics and Genomics (ACMG). The ASRM adds that, because over time, tests improve and new tests become available, cryopreserved specimens may not meet current standards at the time of use. In these instances, every effort should be made to re-contact and rescreen the donor to meet current guidelines.

When obtaining personal and family history information, careful attention should be given to look for heritable diseases. According to the current guidelines, the donor should not have any major Mendelian disorder, major malformations of complex causes, significant familial disease with major genetic components, or a known karyotypic abnormality that may result in chromosomally unbalanced gametes. If the family history reveals a disorder for which carrier screening is available, the donor should be referred for genetic counseling (ASRM, 2013).

Individual gamete donation programs have different policies regarding screening for heritable disorders. A 2013 study on the genetic screening practices of thirteen sperm banks in the United States revealed that while all facilities followed the genetic screening guidelines of at least one professional organization, there were many discrepancies as to which organization's guidelines they followed. Some directly followed the guidelines of relevant organizations such as ACMG or ACOG; however, many facilities frequently followed the guidelines of tissue banking and reproductive organizations such as the ASRM or the American Association of Tissue Banks (AATB). Regardless, all facilities stated that they would perform additional testing if requested by the recipients (Isley & Callum). Because of the lack of consistent guidelines from professional organizations, there is great variation in genetic screening protocols across programs in the United States. This variation can lead to insufficient genetic screening of donors, which may in turn lead to avoidable high-risk pregnancies. Gamete donation programs may benefit from consensus guidelines for achieving consistency in the genetic screening of donors. Frith, Sawyer, and Kramer (2012) called for greater uniformity to ensure that recipients are well informed of their options and are better able to choose between programs and donors.

There are other limitations to the screening of donors. Because the medical and genetic status of a person affects donor eligibility, it is essential that donors are truthful of their personal medical, family, and social histories. The responsibility of protecting the health of the donor-conceived offspring falls on the gamete donation programs, so it is imperative that qualified clinicians evaluate the donor's personal medical, family, and social histories (Ethics Committee of the ASRM, 2014). While the ASRM (2013) states

that a family history review is best performed by a genetic counselor, not all programs follow this guideline. The aforementioned study revealed that while all facilities obtain a three-generation family history from their prospective donors, the review of family history was performed by different professionals at each clinic, including nurse practitioners, reproductive endocrinologists, medical geneticists, genetic counselors, and medical directors (Isley & Callum, 2013). This variation may also contribute to some of the variation of screening practices in gamete donation programs.

1.3 Perspectives of patients utilizing donor gametes

While research is limited, there have been several studies exploring the perspectives of the recipients – the intended parents – of donor gametes. The factors that influence the recipient’s choice of donor are relatively well characterized. A few studies found that non-genetic parents felt it important to them to choose a donor that would create offspring who were “passable” as their own genetic children (Frith, Sawyer, & Kramer, 2012; Rubin et al., 2015). Specifically, a 2012 study found that sperm recipients matched donors by ethnicity (83%), skin coloring (70%), and interests (53%). In the same study, matching for height and build were also found to be important to intended parents (Frith, Sawyer, & Kramer, 2012). Physical health was found to be equally, if not more, important to physical characteristics in all studies (Frith, Sawyer, & Kramer, 2012; Sawyer et al., 2013; Hershberger, 2004; Rubin et al., 2015). A 2013 study found that the majority of parents identified the donor’s personal and family health among the most important attributes, and about half of the participants disclosed that they would reject donors who fit their criteria but had health issues in their personal and family histories (Sawyer et al.). The 2012 study participants were concerned about the health of the

donors and explicitly stated that donor medical screening practices were very important to them (Frith, Sawyer, & Kramer).

One area of research that is lacking is the recipients' preferences regarding the genetic screening of donors. A study from 2008 revealed that couples had varying preferences when it came to genetic screening of their donor. Many couples chose to decline recommended screening tests. It was also clear from this study that the outcome of screening may affect a couple's decision to continue with that particular donor (Baker, Rone, & Adamson, 2008). When prompted, another study found that 67% of recipients agreed that all sperm banks should be required to perform comprehensive genetic screening on their donors, and 84% would pay more for donors who had undergone more comprehensive screening (Sawyer et al., 2013). While not specific to genetic screening, one study found that more specific information placed more focus on donor imperfections and added to the burden of choosing (Rubin et al., 2015). Additional research into recipient preferences may be incorporated into the development of new donor screening guidelines.

1.4 Current guidelines, recommendations, and concerns regarding genetic carrier screening

Screening for Mendelian disorders originated more than 50 years ago and is widely implemented in obstetric care. It is able to achieve two different outcomes: screening for a disease in an individual (the goal of newborn screening), and screening for carrier status in an unaffected individual (the goal of carrier screening). While newborn screening (NBS) is a required practice to screen newborns for Mendelian disorders, carrier screening may be implemented based on ethnicity, family history, or

personal request (Rose & Wick, 2015). Genetic carrier screening is the identification of potential inherited disorders in unaffected patients without a previous history of disease, which may later affect themselves or their offspring (Gil-Arribas, Herrer, & Serna, 2016; Edwards et al., 2015). Carrier screening is generally performed during the prenatal or preconception periods. If performed during pregnancy, carrier screening of the parents during pregnancy can determine need for genetic testing of the embryo or fetus, which can provide obstetric options or information for neonatal care. Preconception carrier screening provides information for reproductive risk and prevention strategies such as preimplantation genetic diagnosis (PGD) or the use of donor gametes.

Screening panels most commonly include variants of genes associated with autosomal recessive (AR) conditions, which require two mutated copies of a gene at a particular locus in order to express that particular trait or disorder. Affected individuals typically inherit two mutated copies of a gene, one from each of their parents (Rose & Wick, 2015). Most of the conditions included in carrier screening panels significantly affect an individual's quality of life, either cognitively or physically, and have an early onset (i.e. fetal, neonatal, early childhood) with well-defined phenotypes (Edwards et al., 2015).

Carrier screening can identify individuals who are at risk of passing on mutated genes to their offspring, which is particularly important for couples considering pregnancy. If both partners are carriers of a specific gene mutation for a particular AR condition, each conception would have a 25% chance of inheriting both mutated copies of the gene and being affected with the condition (Rose & Wick, 2015). Carrier screening for couples can occur simultaneously or sequentially. If a couple opts for simultaneous

screening, both individuals are screened at the same time for the same set of disorders. When performed sequentially, one person is screened first; if he or she is found to be a carrier of a mutation, screening for the other partner would be recommended. If the first partner is not a carrier of any mutations, screening of the second partner would be unnecessary, as the child would not be at increased risk of being affected with the AR conditions tested. Sequential screening is beneficial because it may eliminate the unnecessary need to test both partners; however, it may delay an eventual diagnosis and limit the available options (Rose & Wick, 2015).

While most carrier screening panels focus on AR conditions, individuals can also be tested for X-linked (XL) conditions. X-linked conditions occur from a mutation of a gene on the X chromosome. Female carriers of a mutation for an XL condition may or may not exhibit the phenotype, depending on the distribution of X inactivation. Female carriers have a 50% chance of passing their mutation on to their children, and males inheriting an XL mutation have a high likelihood of being affected. Males with XL mutations (who are typically symptomatic of the associated condition), on the other hand, will transmit their mutation to all of their daughters. Their sons, however, will not be at risk of inheriting the mutation (Rose & Wick, 2015).

Genetic carrier screening for some conditions, such as cystic fibrosis and spinal muscular atrophy, are routinely offered to couples before or during pregnancy (Rose & Wick, 2015). Certain mutations for several AR conditions have been found to be more common in individuals of Ashkenazi Jewish (AJ) descent, and screening guidelines have been established for these disorders. The ACMG currently recommends carrier screening in the AJ population for the following AR conditions: cystic fibrosis, Tay-Sachs disease,

Canavan disease, familial dysautonomia, Fanconi anemia group C, Niemann-Pick disease type A, mucopolysaccharidosis IV, Bloom syndrome, and Gaucher disease (2008). The ACOG Committee on Genetics recommends that all AJ individuals be offered screening for cystic fibrosis, Tay-Sachs disease, Canavan disease, and familial dysautonomia, while individuals should be able to inquire about the other listed AJ disorders (2009). Several other disorders for which other ethnicities are at a higher risk also exist; therefore, genetic carrier screening has historically been ethnicity-based. (Rose & Wick, 2015).

Genetic carrier screening based on ethnicity, while helpful, is problematic for several reasons. Mixed ethnicities, unknown ancestry, adoption, unclear definitions for race and ethnicity, and the fact that genetic conditions are not confined to certain ethnic groups all pose problems in determining the best screening to offer individuals (Rose & Wick, 2015; Nazareth, Lazarin, & Goldberg 2015; Gil-Arribas, Herrero, & Serna, 2016; Edwards et al., 2015; Lazarin et al., 2013). Furthermore, conflicting or otherwise inconsistent guidelines from professional organizations and relatively limited guidelines leads to inconsistencies across practices (Nazareth, Lazarin, & Goldberg, 2015). Aided by an increasingly multi-ethnic population and the idea that NBS is not ethnicity-based, there has been a trend away from ethnicity-based carrier screening towards a more pan-ethnic approach (Nazareth, Lazarin, & Goldberg, 2015; Edwards et al., 2015; Lazarin & Hague, 2015; Henneman et al., 2016). A joint position statement by the National Society of Genetic Counselors (NSGC), ACMG, ACOG, Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine has laid out points to consider for carrier screening for women of reproductive age before conception, and suggested carrier screening of gamete donors be considered as part of all screening programs (Edwards et al., 2015).

1.5 Current guidelines, recommendations, and concerns regarding expanded carrier screening

The incorporation of next-generation sequencing technologies has made carrier screening both more available and more cost effective (Rose & Wick, 2015; Lazarin & Hague, 2015; Lazarin et al., 2014). This allows for the detection of increasingly larger numbers of mutations at one time, which allow for more expanded panels of conditions. Clinically introduced in 2009, expanded carrier screening (ECS) panels can test for more than 100 genetic conditions at one time (Edwards et al., 2015). Expanded carrier screens typically include conditions that are included on traditional carrier screening panels, with the addition of other rare AR and XL conditions. These conditions may have significant variation in their presentation or more undefined phenotypes. While conditions on expanded panels vary in severity, many are associated with cognitive impairment, decreased life expectancy, and need for medical or surgical intervention (Edwards et al., 2015; Lazarin & Hague, 2015). Taking into account the fact that Mendelian diseases account for about 20% of both infant mortality and infant hospitalizations, many find it reasonable to consider an expanded disease list for all populations (Lazarin & Hague, 2015; Henneman et al., 2016).

Conditions included on ECS vary between laboratories and clinical practices. While the list of conditions is not regulated, professional organizations have set forth guidelines for which conditions should be considered to be included on panels. Conditions being screened for should be a health problem that encompasses either cognitive disability, need for surgical or medical intervention, or an affected quality of life, and should include conditions for which prenatal diagnosis may result in

intervention, delivery management, or prenatal education, or a combination. Genes and variants for these conditions should have a well-understood phenotypic relationship based on strong evidence that is not limited solely to case reports (Edwards et al., 2015; Grody et al., 2013). Testing for conditions characterized by incomplete penetrance or variable expressivity, or conditions associated with mild phenotypes, should be made optional for individuals undergoing expanded carrier screening. Additionally, when adult-onset disorders are included in panels, individuals must be well informed about the chance of finding out about a potentially unexpected health risk before providing consent (Grody et al., 2013).

Recently, a taxonomy has been developed to group disorders into categories based on their impact on affected offspring: significantly shortened lifespan, serious medical problems, mild medical problems, unpredictable medical outcomes, and adult-onset conditions. This taxonomy has potential to be used to describe groups of conditions, and it was suggested that patients could opt out of receiving information for types of conditions that were not important to them (Leo et al., 2016).

Benefits of ECS include better identification of at-risk pregnancies and couples for greater availability and utilization of pregnancy management options. For potential offspring, ECS may lead to reduction of diagnostic time and costs, earlier availability and utilization of treatments and preventions, reduction of unnecessary treatments, and improvement of quality of life (Kingsmore, 2012). Expanded carrier screening, when implemented in practice, is able to identify many more at-risk couples compared with traditional ethnicity-based carrier screening. A 2013 study of ECS for 96 conditions identified 24% of individuals as heterozygous for at least one condition. Furthermore,

among identified mutations, 77% were for conditions not included in ACOG screening guidelines and 69% were for conditions not included in ACMG guidelines (Lazarin et al., 2013). Other studies have cited carrier rates ranging from 25% to 85% (Franasiak et al., 2016; Martin et al., 2015; Abuli, Rodriguez-Santiago, & Coroleu, 2016). These differences can be attributed to the variation of conditions and variants screened for among different expanded panels. In addition to identifying individuals as carriers, Martin et al. (2015) identified 5% of couples in an infertility practice to be at high risk for conceiving an offspring with an AR condition, and Abuli, Rodriguez-Santiago, and Croleu (2016) identified 3% of pre-assigned donor-recipient matches to have high reproductive risk. By identifying carriers and at-risk couples, ECS may lead to a reduction in the number of children born with the conditions that are screened for (Henneman et al., 2016).

Due to the identification of more at-risk couples, ECS may result in more couples undergoing prenatal diagnosis or choosing to utilize PGD or donor gametes as a way of managing increased reproductive risks. Gil-Arribas, Herrero, and Serna (2016) explained that ECS provides maximum benefits in gamete donor programs, since current prevention of genetic disorders relies on medical history and limited genetic testing. Several studies have even suggested the implementation of donor matching programs based on carrier screening results in order to efficiently avoid genetically high-risk pregnancies (Gil-Arribas, Herrero, & Serna, 2016; Martin et al., 2015; Silver et al., 2016).

While there are many benefits, concerns about ECS revolve around the counseling burden it poses. Because expanded panels screen for more disorders, a higher proportion of individuals tested will be found to be carriers and may require counseling about their

results (Benn et al., 2014). Other concerns include unnecessary prenatal diagnosis and termination for mild disorders, false reassurance for those who test negative, and a false understanding that ECS tests for “everything.” Additionally, it is unreasonable to provide detailed descriptions of each condition being tested for prior to screening, which may hinder informed decision-making and consent.

1.6 Attitudes toward genetic carrier screening

While ECS is not widely implemented across practices, attitudes towards ECS are generally favorable among medical professionals. One study found that most (78%) women’s healthcare providers would prefer to be tested for a larger number of diseases, if costs were the same as a smaller panel (Ready et al., 2012). Similarly, 90% of genetic counselors felt they would want to be screened for conditions beyond the ACMG and ACOG recommendations (Lazarin et al., 2015). In general, providers had positive attitudes towards carrier screening and believed it to be “socially responsible” behavior (Ready et al., 2012).

A focus group of individuals who had previously undergone preconception carrier screening revealed that patients were somewhat divided on undergoing ECS. While some individuals desired any and all information possible to achieve a sense of control in reproductive decision making, other hesitant individuals stated that more information would be anxiety-provoking and would ultimately not affect their reproductive decisions (Schneider et al., 2015). A European study found that among individuals of reproductive age, 34% stated that they would undergo ECS while 51% remained undecided. The same study cited prevention of and preparation for serious heritable disease as among the most important reasons to undergo expanded carrier screening (Plantinga et al., 2016). Most

recently, a study in the Netherlands found that among individuals in the Dutch Jewish community, genetic carrier screening is generally perceived as favorable and having high benefits. The same study found that slightly more than half (53.8%) of the participants preferred pan-ethnic ECS over ethnicity-based carrier screening. Important reasons for this preference revolved around potential stigmatization with ethnicity-based screening, and the difficulty in determining individuals at risk in an increasingly ethnically-diverse population (Holtkamp et al., 2016).

Among genetics professionals surveyed in a 2013 study, benefits of ECS revolved around the prevention of heritable diseases. They also felt that patients undergoing ART may be more interested in ECS, as couples have already undertaken the financial burden of IVF and therefore would find additional costs (e.g. ECS or PGD) less demanding. Additionally, participants felt that expanded screens had more financial value than traditional carrier screens. Perceived limitations included the lack of guidelines provided by professional organizations on the use of ECS, and the inability to fully eliminate risks of other rare conditions for which screening was not performed. Many agreed that the decision to recommend ECS was highly individualized and would need to consider the specific informational needs of each individual or couple. Furthermore, it is important to consider that as the number of conditions being screened for increases, the possibility of finding a variant of unknown significance (VUS) increases significantly. In general, genetics professionals felt that ECS has major limitations and is not ready for routine reproductive care (Cho et al., 2013).

A recent study explored the attitudes of European geneticists towards ECS (Janssens et al., 2017). All participants recognized the potential benefits of ECS,

including the identification of at-risk couples without a preexisting risk; however, they identified several major limitations. Many geneticists noted that ECS is unable to identify many carriers because of rare or novel pathogenic mutations not included in ECS panels. They felt that this residual risk would lead to undue anxiety in couples where only one partner was found to be a carrier. Some participants anticipated a lower prevalence of AR conditions with the implementation of ECS, which they felt could lead to perceived eugenic undertones of carrier screening and negative implications for people with the screened disorders (Janssens et al., 2017).

Current literature identified pretest counseling as a major limitation of ECS. Ninety-two percent of genetic counselors surveyed stated that pretest counseling should be required for all patients prior to having ECS (Lazarin et al., 2015), and a study of other genetics professionals had similar findings (Cho et al., 2013). One difficulty with pretest counseling is due to the large number of disorders on expanded screening panels. It would be impractical for any healthcare provider to provide details of each condition, particularly given the current shortage of genetic counselors available to have these discussions (Benn et al., 2014; Leo et al., 2016). Only 31% of genetic counselors agreed that pretest counseling could be administered through informational pamphlet/brochure or video (Lazarin et al., 2015). Considering that online information about ECS is often distributed by for-profit companies (Holton, Canary, & Wong, 2016), there is room for additional research to identify the best practices to educate patients in a non-biased manner to allow for an informed decision about ECS (Abuli, Rodriguez-Santiago, & Coroleu, 2016).

1.7 The use of expanded carrier screening in ART

Genetic carrier screening in a gamete donor population is markedly different from carrier screening of couples. Firstly, donors provide gametes for offspring that they will not parent. This may reduce informational need or the feelings of genetic burden that typical genetic parents may face. Therefore, donors' preferences regarding genetic testing is not generally the predominant factor that determines which evaluations are performed (Isley & Callum, 2013). Donors generally do not go to ART clinics to learn of their genetic reproductive risks (Abuli, Rodriguez-Santiago, & Coroleu, 2016). Additionally, all screening in donor programs would occur before conception, reducing the need for prenatal decision making faced by many couples undergoing carrier screening during pregnancy.

Although a potential drawback for carrier screening of donors is the psychosocial harm of positive results for donors and their families, research shows that while carriers scored higher in emotional and psychological impact questionnaires than non-carriers, none of the subjects had pathologic HADS-D and STAI scores. Furthermore, ECS seemed to be well tolerated and accepted by participants (Abuli, Rodriguez-Santiago, & Coroleu, 2016).

Still, ECS is not a routine practice in ART or gamete donation clinics, though several studies have explored its potential utility. A study in 2015 revealed that ECS in a population of individuals undergoing ART identified 85% of the population to be carriers for at least one pathogenic or likely pathogenic mutation. Furthermore, ECS was able to identify 2% of egg donors as carriers of XL disorders. These donors were discarded from their program, when they otherwise may not have been (Martin et al., 2015). A similar

study identified 56% of ART patients to be carriers of mutations and 1.7% of egg donors to be carriers of XL conditions (Abuli, Rodriguez-Santiago, & Coroleu, 2016). One study screened previously negative sperm donors, who were initially screened only for cystic fibrosis. After four additional carrier assessments, including an expanded panel, all donors were found to carry at least one defined variant of a genetic condition (Silver et al., 2016). These results suggest that the current standard of care (i.e. limited or ethnicity-based screening) is perhaps insufficient in reproductive medicine. In order to provide accurate risk assessments, it is important to detect carriers of genetic conditions, and screening standards should be updated to reflect the high variant carrier rates in an increasingly multi-ethnic population.

In a recent retrospective study of individuals who had undergone ECS, Haque et al. (2016) attempted to quantify the modeled risk of recessive conditions. Using random pairings of individuals from within and across different ethnic backgrounds, they were able to quantify the proportion of hypothetical fetuses who would be homozygous or compound heterozygous for mutations known to cause disease. From a study population of almost 350,000 individuals, it was calculated that the frequency of fetuses potentially affected by hereditary conditions ranged from 94.5 to 392.2 per 100,000 couples, depending on ethnicity. When compared with current genetic carrier screening practices, this study found that ECS was able to identify more hypothetical fetuses at risk (Haque et al., 2016). Because this study only analyzed the screening results of individuals without infertility or a personal/family history of genetic disease, the results may potentially be more representative of the cohort who may be selected for gamete donation, especially in a population with diverse races and ethnicities.

While ECS may identify more potential gamete donors as carriers of AR conditions, the risks of other inherited disorders must not be overlooked and should be included in patient counseling. A retrospective review of outcome reports of donor-conceived offspring revealed that of the 108 semen donors where vial distribution was restricted for suspected or confirmed heritable conditions, only 35 were due to AR conditions. Eleven donors were restricted for suspected or confirmed autosomal dominant (AD) conditions; however, the majority were restricted for multifactorial disorders (Isley, et al. 2016). Expanded carrier screening may identify more individuals at risk for AR conditions; however, it is unable to reduce the risk of most AD and multifactorial conditions.

Relatively little is known about the intended parents' preferences regarding ECS of their donors. Since AR diseases require inherited mutations from both genetic parents, a high-risk donor – one who carries a variant in the same AR condition as the other genetic parent – for one recipient is likely to be a low-risk donor for most other recipients (Silver et al., 2016). More information about recipients' genetics knowledge may be helpful in understanding the factors that influence choice of screening and/or donor. One study showed that among patients at reproductive genetics clinics who were counseled on ECS, only 4% and 12% in academic and private settings, respectively, accepted such screening. Still, as ECS becomes increasingly common it may become the “standard of care” and may be better received by the general population (Schoen et al., 2015).

1.8 Need for current study

Exploring the perspectives of intended parents about how genetic screening results influence their choice of donor would be helpful in determining the potential utility of

ECS in gamete donation practices. These perspectives may identify potential areas of improvement in educating patients about genetic carrier screening results. Increased knowledge of the implications of carrier status on future offspring may help to reduce the unnecessary discarding of variant-positive donors. Additionally, understanding the genetic screening preferences of parents utilizing donor gametes may lead to increased uniformity of genetic screening practices in gamete donation programs. Consistent and increased genetic screening practices will increase identification of at-risk conceptions and subsequent prevention of heritable conditions.

Chapter 2: Recipients' Perspectives Regarding Expanded Carrier Screening of Gamete Donors

2.1 Abstract

Purpose: This study explored the perspectives of intended parents regarding genetic carrier screening of a gamete donor. The main goal of this study was to determine how much genetic carrier screening information a recipient would prefer to receive about potential donors. The study also aimed to identify factors that potentially influence a recipient's choice of donor based on genetic screening results. **Methods:** An online questionnaire was developed to assess intended parents' preferences regarding expanded carrier screening (ECS) of their donors. Participants were recruited from various online support groups and were eligible if they had previously utilized or were currently utilizing donor gametes. A total of 58 usable responses were collected and reflect insight into the perspectives of intended parents regarding which factors associated with genetic carrier screening influence their choice of donor. The questionnaire consisted of demographic questions, general questions about carrier screening, a genetics knowledge quiz, and questions about hypothetical scenarios in which a donor was a carrier for one of four distinct conditions: hemochromatosis, Usher syndrome, Bardet-Biedl syndrome, and GRACILE syndrome. **Results:** The majority of women (91.4%, 53/58) opted for ECS of their potential gamete donor, preferred over traditional ethnicity- or family history-based screening. Participants were comfortable proceeding with a donor with the knowledge

that he/she was a carrier for a mild genetic condition (hemochromatosis, 83.3%). Fewer respondents were comfortable proceeding with a donor who was a carrier for a more severe condition (Usher, 37.0%; BBS, 39.1%; GRACILE, 39.1%). **Conclusion:** Intended parents prefer ECS for their donors over traditional ethnicity- or family history-based screening. Participants were uncomfortable with a donor who is a carrier for severe, life-limiting conditions, regardless of statistical risk. Expanded carrier screening is desired and could be beneficial for use in gamete donation; however, given the overall discomfort with identification of positive carrier status, ECS would significantly alter clinical decision making in these settings. Increased genetic education of recipients on the implications of ECS carrier results is indicated, and access to genetic counseling services may be indicated for optimal implementation.

Keywords: gamete donation, expanded carrier screening, recipient perspectives.

2.2 Introduction

Couples utilizing donor gametes (egg and/or sperm) consider many factors when selecting a donor. Many couples seek donors who will provide offspring that are “passable” as their own biological children, and so will select donors based on ethnicity and other factors such as eye and hair color. Aside from physical characteristics, recipients have stated that health of the donor and donor’s family is among the most important attributes; however, screening for physical health relies largely on donors to be truthful about their personal and family health histories (Frith, Sawyer, & Kramer, 2012). Additionally, the majority of babies born with an autosomal recessive (AR) condition have no family history of the disease. Genetic carrier screening, however, can help ameliorate some of this uncertainty by identifying donors who are at risk of passing down

mutations for an AR condition, which may otherwise be missed by only assessing family history.

Gamete donation is regulated by the Food and Drug Administration as human tissue donation; to date, there are no clear guidelines for the genetic testing of gamete donors. The American Society for Reproductive Medicine (ASRM), however, has issued recommendations regarding the testing of donors. The ASRM recommends testing for cystic fibrosis carrier status in all potential donors and carrier screening for other conditions as indicated by the donor's ethnicity and family history (ASRM, 2013). Still, donor screening practices differ widely throughout the United States, creating variation in the number of conditions for which donors are tested. Furthermore, an increasingly multi-ethnic population makes it difficult to determine who should be screened for which conditions. Thus, consideration of a pan-ethnic expanded carrier screen for all potential gamete donors may be warranted.

Although there is general acceptance of ECS from healthcare professionals (Ready et al., 2012; Lazarin et al., 2015), little is known about gamete recipient preferences regarding expanded carrier screening of their donors. Therefore, exploring the perspectives of intended parents would be helpful in determining the potential utility of ECS in gamete donation practices.

2.3 Materials and Methods

2.3.1 Participants. This study targeted current and past recipients of donor gametes. Individuals were invited to participate if they were currently in the process of choosing or utilizing gamete donors, or if they had a child conceived through the use of donor gametes. Either the genetic or non-genetic parent of a donor-conceived child may have

participated. No exclusion regarding method of conception (intrauterine insemination vs. in vitro fertilization) was established; however, as this study focused on recipients' preferences, gamete donors were excluded from this study.

Recruitment occurred through posting of an announcement (Appendix A) about the research study, which provided a brief introduction, invitation, and link to the questionnaire on SurveyMonkey. The announcement was posted on various online support groups for infertility and donor conception, and included the Donor Conception Support Group Australia website, the Southwestern Ontario Donor Conception Support Network Canada website and Facebook group, the Single Mothers by Choice Facebook group, the Parents Via Egg Donation website, and the Resolve national infertility association website. Permission was obtained from representatives of each group prior to posting of the announcement. The invitation described the study to participants, provided the investigators' contact information, and allowed participants to access the study. Participants were then able to decide whether they wanted to continue with the questionnaire.

A total of 58 respondents completed the online questionnaire. Table 2.1 summarizes demographic information. All individuals identified as females aged 29-55. The sample population had a mean age of 40 years ($SD = 6.2$), with most women (63.2%) reporting their age as being between 36 and 45 years. The majority of women were single (81.0%), identified as Caucasian (93.1%), lived in the United States (77.6%), and had a graduate level degree (65.5%).

2.3.2 Study Methods. Potential participants were able to view the invitation to determine whether they were interested in and eligible for the study. Informed consent

was considered to be provided once a patient accessed the questionnaire, which was expected to take approximately 15 minutes to complete. Participants could withdraw from the study at any time by not completing the questionnaire.

2.3.3 Study Measures. An original online questionnaire developed through SurveyMonkey.com was designed with questions to identify intended parents' preferences regarding genetic carrier screening of gamete donors, as well as characterize factors that influence a recipient's choice of gamete donor based on genetic carrier screening results.

Quantitative questions were asked to assess categorical information about the participants, such as gender, age, ethnicity, and education level of the intended parents. Additionally, the data collected was used to provide information about the preferences of recipients regarding genetic carrier screening, as well as donor selection based on genetic results. Factors influencing donor selection were assessed through a series of questions intended to assess the importance of various elements, such as comparisons of carrier status and family history. The intended parents' understanding of genetics concepts and nature of genetic carrier screening was also assessed. Finally, the potential utility of a genetic counselor in explaining the relevant concepts for recipients during the donor selection process was assessed. The questionnaire contained multiple choice, select all that apply, ranking, and open-ended questions.

2.3.4 Statistical Analysis. Quantitative questions from the online survey were analyzed using descriptive statistics. The data produced was categorical. Calculation of frequencies and percentages for these questions was completed to quantify and summarize the preferences and factors identified. Independent t-tests were performed to

explore differences in the way participants answered questions amongst four distinct conditions. Qualitative analysis of open-ended responses was performed using grounded theory methods.

2.4 Results

2.4.1 Personal history with use of donor gametes. Table 2.2 shows the participants' personal histories with use of donor gametes. Of the study participants, 87.9% (51/58) had previously attempted to conceive with a sperm or egg donor and 74.5% (38/51) had achieved a live birth. At the time of the study, 18.9% (11/58) were currently seeking sperm or egg donors. The majority of participants (82.8%) reported that single motherhood was their main reason for using a donor.

2.4.2 Preferences for level of genetic carrier screening. Participants were given a brief introduction to genetic carrier screening and the differences between ethnicity or family history-based carrier screening and ECS. Twenty-one women (36.2%) reported that they personally had carrier screening previously. When prompted to provide the number of conditions for which they were screened, the range provided was between one and 500 conditions. In contrast, 67.9% reported that their donor had carrier screening. The number of conditions for which their donors were reportedly screened ranged between five and 100 conditions.

When asked to choose between ethnicity or family-history based carrier screening and ECS, the majority of women opted for ECS for themselves (72.4%) and their donors (91.4%). Significantly more women had no preference when deciding between different screening options for themselves than when they were deciding for their donors. A chi-square test for association was conducted between preference of genetic screening for self

and genetic screening for donor. Cell frequencies were greater than five for ECS, but not for ethnicity/family based screening or no preference. There was a statistically significant association between preference of genetic screening for self and genetic screening for donor, $\chi^2(4) = 36.674, p < .001$. There was a moderately strong association preference of genetic screening for self and genetic screening for donor, $\phi = 0.554, p < .001$.

2.4.3 Genetics knowledge. A seven question analysis highlighted respondents' understanding of AR inheritance, inherited disorders, and genetic carrier screening (Table 2.3). Twenty-two respondents (37.9%) were able to achieve a perfect score of seven. A majority (79.3%) were able to correctly answer five of the seven questions.

2.4.4 Genetic carrier screening opinions. Participants were asked to consider a series of statements regarding genetic carrier screening results and disclose their level of agreement for each statement. The results are summarized in Table 2.4 and Figures 2.1 and 2.2. A majority of women (69.4%) at least slightly agreed that if their donor has negative testing for a condition, they would not be worried about the other genetic parent (either herself or her partner) being a carrier for that condition. Fewer women (60.7%) at least slightly agreed that if one genetic parent (either herself, her partner, or another donor) has negative testing for a condition, they would not be worried about their donor being a carrier for that condition.

When asked to compare aspects of donor selection, 23.3% of women at least slightly agreed that the physical characteristics of their donor were more important to them than genetic carrier screening results. More women (35.8%) at least slightly agreed that their donor's family history was more important to them than genetic carrier screening results. Eleven women (19.6%) agreed that carrier screening results were

equally as important as donor family history, while only four (7.1%) said the same for the physical characteristics of the donor.

2.4.5 Donor selection scenarios. Respondents were asked to consider four distinct scenarios in which their donor, who met all of their physical and family history requirements, had ECS and was found to be a carrier of one of four different AR conditions: hereditary hemochromatosis, Usher syndrome, Bardet-Biedl syndrome (BBS), and GRACILE syndrome. Descriptions of each condition were provided (Appendix B). An independent-samples t-test was run to determine if there were statistically significant differences in how women answered a series of questions regarding use of a donor, between four distinct conditions. The results are summarized in Table 2.5.

The first question asked whether they would proceed with the donor, provided that the other genetic parent had negative screening for the condition. More women were comfortable proceeding with a donor who was a carrier for hemochromatosis ($M = 1.17$, $SD = 0.38$, $t(47) = 21.46$, $p < 0.001$) than for any other condition. Next, women were asked to consider whether they would give up an important physical or social characteristic in order to proceed with a donor free of carrier status for each condition. More women said that they would give up an important attribute in order to find a donor that was not a carrier for Usher syndrome ($M = 1.28$, $SD = 0.46$, $t(45) = 19.11$, $p < 0.001$), BBS ($M = 1.28$, $SD = 0.46$, $t(45) = 19.11$, $p < 0.001$), or GRACILE syndrome ($M = 1.39$, $SD = 0.49$, $t(45) = 19.12$, $p < 0.001$), than for hemochromatosis. They were then asked whether they would prefer the donor who tested positive for each condition but negative for the remaining ECS panel, or a donor who was only screened for four

conditions but was negative for all four. More women said they would rather proceed with a donor who was only screened for four conditions, when comparing it to a donor who was a carrier for Usher syndrome ($M = 1.39$, $SD = 0.49$, $t(45) = 19.12$, $p < 0.001$), BBS ($M = 1.47$, $SD = 0.50$, $t(44) = 19.50$, $p < 0.001$), or GRACILE ($M = 1.43$, $SD = 0.50$, $t(45) = 19.42$, $p < 0.001$), than for hemochromatosis. Finally, they were asked about their level of worry about the chance of their child being an unaffected carrier of each condition. More women reported being worried about the chance of their child being an unaffected carrier for Usher syndrome ($M = 2.46$, $SD = 0.86$, $t(45) = 19.34$, $p < 0.001$), BBS ($M = 2.50$, $SD = 0.84$, $t(45) = 20.27$, $p < 0.001$), and GRACILE ($M = 2.61$, $SD = 0.95$, $t(45) = 18.55$, $p < 0.001$), than for hemochromatosis.

2.4.6 Open-ended responses. For each condition and corresponding set of questions, women were given the opportunity to provide their overall thoughts about the donor. Grounded theory methods revealed these major themes: (1) level of concern; (2) carrier status of offspring; and (3) knowledge of genetic evaluation.

Theme 1: Level of concern.

Women voiced varying levels of concern for each donor. Most women were not worried about their donor being a carrier for hemochromatosis, citing the mild nature of the condition and the ease of treatment for affected individuals. Of the women who provided their own input, 75% (24/32) stated that they would have little to no concern using a donor who was a carrier for hemochromatosis. One respondent explained, “If he was a carrier for one easily treatable disease, I would likely go for it.” As long as the donor met all of their other criteria, many women felt that a donor who was a carrier for hemochromatosis would be a strong candidate.

“If all other desired attributes were present, and there were no other donors who matched up, I would still select this donor. I feel the odds of inherited health problems in his potential offspring are low, and at least he has been pretty thoroughly screened. Natural conceptions do not usually have this level of genetic screening.”

In contrast, few women stated that they would use a donor who was a carrier for Usher syndrome, BBS, or GRACILE syndrome without concern. Regarding a donor who was a carrier for Usher syndrome, one woman explained:

“My opinions of this donor are tainted by knowing that he tested positive as a carrier for a condition with such severe effects. Just the knowledge of the positive test creates a paranoia that potential offspring could develop or pass on the condition.”

Women were generally well informed of the low overall risk for an affected pregnancy with only one parent as a carrier but felt uncomfortable with the severity of Usher, BBS, and GRACILE: “Low chance but the condition is too severe to knowingly use a donor who is a carrier.”

Theme 2: Carrier status of offspring.

Many women mentioned their concerns about their offspring with each donor being a carrier for the respective condition. For a donor who is a carrier of hemochromatosis, respondents’ concerns revolved around testing the carrier status of any offspring with that donor. Women felt that allowing them to inform their child of any reproductive risks would be beneficial for them:

“I would want to do more research into how it would affect them and knowing that [the donor] is a carrier for it I would want to get my child with them tested so that they can be fully informed before they decide to have kids.”

In regard to donors who were carriers of Usher, BBS, or GRACILE, however, women expressed considerable concern for their children being carriers. Again, severity of disease often influenced this concern: “I would want to minimize the risk of my child being a carrier for any condition that substantially reduces life expectancy.”

Theme 3: Knowledge of genetic evaluation.

There was a spectrum of opinions on the level of genetic screening the hypothetical donors were receiving. A few women discussed the “unknown” in pregnancies that were achieved without donor gametes, and one woman expanded by stating, “I would rather the known than the unknown so if I know that it is a possibility then I can plan for it and make sure my child is tested so they know if they are a carrier.” Some women mentioned that guidance from their clinic would be beneficial in helping them to decide to proceed with a donor: “I would consider this donor if he met all my other requirements but would want to talk with a genetic counselor first,” and “[if] the advice from my clinic was positive, I would feel reassured.”

One woman was uncomfortable with the decision to reject a donor based on genetic carrier screening results. She explained:

“Children created without the use of donor sperm have the chance of being affected by many disorders. The worry of using genetic testing to select a donor is a bit like creating ‘designer babies.’ I would choose this donor

based on a combination of traits particularly their openness to contact with the child after birth, not based on the fact that they have completed genetic testing.”

This participant’s responses remained consistent through the different donors, stating, “I struggle to understand why someone would choose a donor or disregard a donor based on a genetic test result.”

2.4.7 Ranking of donors. Participants were asked to rank five donors, based on how likely they were to choose that donor based on genetic screening results (Figure 2.3). A one-sample Kolmogorov-Smirnov test was performed to determine if there were statistically significant differences in rankings between donors based on genetic screening results. There were statistically significant differences ($p < 0.01$), with individuals ranking donor 2 first, donor 3 second, donor 1 third, donor 5 fourth, and donor 4 fifth (Table 2.6). One woman reported that she had no preference regarding these donors, and six women preferred not to select one of these donors at all.

The women were then asked to identify factors that influenced their ranking of the donors. The results are summarized in Table 2.7. The severity of disorder was the most influential factor, followed by the number of tested conditions.

2.4.8 Utility of genetic counselors. Women were provided with the National Society of Genetic Counselors’ (NSGC) description of genetic counseling and asked to consider the utility of genetic counselors in explaining carrier screening during the donor selection process. Most women (53.3%) reported that it would be extremely helpful to have a genetic counselor explain carrier screening to them. An additional 40% of women said that it would be helpful or somewhat helpful. One person (2.2%) reported that she

received enough information from someone at her donor clinic/program who was not a genetic counselor.

2.5 Discussion

This is the first study to assess the opinions of intended parents regarding ECS of gamete donors. There are currently limited consensus guidelines for genetic carrier screening of donors. Therefore, there is much variability in how gamete donors are screened at different clinics. Study findings have potential implications for implementing ECS in a gamete donation setting. This study explored the perspectives of recipients of donor gametes to gain insight into how much genetic information they may prefer to receive about their potential donors and how they would utilize the results.

2.5.1 Preferences for ECS. Most of the participants preferred ECS over traditional ethnicity-based screening, even more so for their donor than for themselves. This finding was to be expected, since individuals are expending resources to utilize gamete donors, and thus, may have a stronger preference for a higher level of genetic screening. Additionally, there is an added element of choice when considering genetic screening of donors versus screening of self or partner. Whereas a known carrier status in a donor may impact a recipient's choice of donor, there is no similar choice when carrier status is identified in self or partner.

The preference for obtaining a higher level of genetic information has been observed in other reproductive settings. A 2015 study explored women's preferences for prenatal testing, and found that pregnant women were inclined to choose a test that offered the most information on the chromosomal status of their unborn child (Beulen et al.). In this study, pregnant women placed the highest value on the level of information

gained from prenatal tests, compared to other qualities of the test, such as minimum age of gestation at which the test is offered, and waiting time for results.

In line with their carrier screening preferences, more of our participants felt they would worry if their donor was a carrier of a gene mutation than if she or her partner was. This may again relate to the element of choice, or it may indicate that recipients feel that donors should be free of risk for genetic disease overall. Anecdotally, recipients are often uncomfortable upon learning about positive carrier status of a previously chosen donor (A. Besser & L. Isley, personal communication, March 15, 2017). It is reasonable to believe they feel that given a choice, they would choose not to put their child at risk for being a carrier of a genetic condition. Additionally, there may be an unrealistic expectation for a donor to be genetically “perfect,” and once their chosen donor has been identified as a carrier, he/she may no longer fit their description of the ideal donor. This idea of a genetically “perfect” individual is unrealistic because as studies have shown, up to 85% of individuals may be identified as a carrier for an AR condition on ECS panels (Lazarin et al., 2013; Franasiak et al., 2016; Martin et al., 2015; Abuli, Rodriguez-Santiago, & Coroleu, 2016).

Only 19.6% (11/56) of women felt that the donor’s family history was as important as genetic carrier screening results. This suggests potential lack of genetic understanding, given the multifactorial nature of most common health problems and the importance of family history assessment as the sole way of determining risk for these. In one study, multifactorial conditions in donor-conceived offspring were documented to occur at a higher frequency than AR conditions (Isley, et al., 2016). One of the concerns of ECS is that there may be a false understanding that it tests for “everything,” and more

education into the limitations of ECS may be warranted. Patients need to be properly counseled that ECS is a valuable tool used to detect carriers of AR conditions; however, it is unable to reduce the risks for most autosomal dominant (AD) and multifactorial conditions. It is therefore important to recognize that ECS does not replace assessment of familial risk or formal genetic counseling.

2.5.2 Donor preferences based on carrier screening results. Our study found that unsurprisingly, women were more likely to proceed with a donor who was a carrier for hemochromatosis, a relatively mild condition, than for Usher, BBS, or GRACILE. In general, women were comfortable proceeding with a donor who was a carrier for hemochromatosis, and would not give up an important attribute to find a donor who was not a carrier. The rejection rate of a donor who was a carrier for hemochromatosis was 16.7%, compared to Usher, BBS, or GRACILE, which had rejection rates of 63%, 60.9%, and 60.9%, respectively. Importantly, 39.1%, 46.7%, and 43.5% of women, respectively, preferred a donor who was only screened for four conditions and negative for all four, over these donors who were screened for 300 conditions and positive for Usher, BBS, or GRACILE (Table 2.5). This is somewhat consistent with a 2016 study, which found that when sperm donors received supplemental screening (at the request of their recipients, who had been identified as carriers, often through ECS) and found to be a carrier of the same condition, the majority of recipients chose another, often untested, donor (Callum & Isley).

Many respondents expressed concern over their offspring with a potential donor being a carrier for a genetic condition. It was difficult to ascertain from this study the reasons behind this concern – whether recipients were concerned with reproductive risk

for their offspring or the chance for their offspring to develop the condition. Some participants mentioned the carrier status of their offspring in their open-ended responses; however, the meanings behind their statements were often unclear. Future studies would benefit from interviews with recipients, to extrapolate their true feelings and concerns.

In ranking donors based on carrier screening results, women ranked a donor who was a carrier for hemochromatosis as their first choice. Surprisingly, a donor who was only screened for four conditions (and found to be negative for all four) ranked higher than a donor who was a carrier for either BBS or GRACILE, both rare conditions with relatively low carrier frequencies, and negative for the remaining 299 conditions. Women most often cited the severity of condition as an influential factor in these donor choices. These results suggest that, in general, women are comfortable with a donor who is a carrier of a mild condition or a donor who has had limited testing, and less comfortable to proceed with a donor who is a carrier for a more severe condition. This is supported by the relatively high rejection rates of donors who were carriers for Usher, BBS, or GRCAILE, compared to hemochromatosis, and the tendency for women to give up an important physical or social characteristic to find a donor who was free of carrier status of these conditions. This is interesting because it contradicts the participants' interest in ECS, preferred over ethnicity- or family history-based screening. Women may state their desires for more genetic information on their donors (i.e. ECS); however, many may not be prepared for the realistic outcomes of ECS, which would identify the majority of donors as carriers for a genetic condition. It appears there may be an unrealistic expectation for a donor who meets all of a recipients' physical and social characteristic requirements and who screens negative on a panel consisting of several hundred

conditions. In our study, eight women stated that they would not proceed with a donor who was a carrier for hemochromatosis, even if the other genetic parent was not a carrier. This is interesting given the relatively mild nature and ease of treatment of the condition, in addition to the low statistical risk of having an affected child when only one genetic parent is identified as a carrier. Therefore, more research could be done to elicit reasoning behind rejection of these donors.

Anecdotally, from speaking with genetics professionals who have experience in gamete donation programs, intended parents may proceed with a donor who is a known carrier of a genetic disorder for a variety of reasons. In egg donation, intended parents often experience a level of attachment to their egg donors. In general, a more limited pool of egg donors exists as compared to sperm donors; thus, recipients using donor eggs typically have fewer options than recipients using donor sperm. Couples may experience difficulty finding an egg donor who matches their desired ethnicity or other physical characteristics, unlike in sperm donation, where there tends to be many more donor choices available (A. Besser & L. Isley, personal communication, March 15, 2017).

In sperm donation, couples who learn their donor is a carrier for an AR disorder after they have already chosen to use that donor's gametes may decide to continue using that donor for a couple of reasons. Financially, recipients often purchase multiple vials of sperm from one donor at one time. Discarding the vials upon knowledge of genetic risk could mean a significant financial loss, which may not be an option for some recipients. Another reason for continuing to use a donor is the opportunity to provide a full genetic sibling for their donor-conceived child, which is an important factor for some families (A. Besser & L. Isley, personal communication, March 15, 2017).

There may be psychological factors involved in donor selection that do not equally apply to parents who conceive without the use of a donor. As an intended parent actively chooses a particular donor (compared to parents who conceive with their own gametes), any actual or potential adverse health outcomes in a donor-conceived child may result in an additional burden of guilt for making the “wrong” choice. Most parents would likely agree that if given the choice, they would choose not to put their child at risk of being a carrier for any genetic conditions (A. Besser & L. Isley, personal communication, March 15, 2017).

Our findings suggest that implementation of ECS in a gamete donation program would significantly alter clinical decision making. Most of the women in our study stated that they would be uncomfortable proceeding with a donor who was a carrier for a severe genetic condition. The ACOG Committee on Genetics recently published new guidelines and points to consider on ECS. These guidelines highlight that conditions included on expanded panels should 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 (2017). Including milder conditions such as hemochromatosis on expanded panels may be going against established guidelines for ECS. It is important to remember that the inclusion of a condition on an expanded panel does not necessarily validate its appropriateness on that panel, and gamete programs should be especially wary of offering expanded panels which include conditions that do not fully comply with established guidelines.

It is important to recognize the importance of proper genetic evaluation of the intended parent, as genetic risk is not dependent solely on the donor. Genetic evaluation

of both genetic parents is necessary to perform accurate risk assessment and provide information for recipients to make the most informed decision about a donor.

2.5.3 Genetics knowledge. A genetics knowledge quiz was performed to assess potential areas of improvement in education about genetic disease. Twenty-two respondents (37.9%) were able to correctly answer all seven questions, indicating that they had a fair understanding of the nature of genetic diseases. However, up to 37.2% of respondents provided incorrect answers to questions regarding the implications of various carrier screening results (questions 1, 2, 5-7, Table 2.3). We speculated that poor overall understanding of carrier screening could affect women's preferences for or against a donor who was a carrier of a genetic condition; however, no significant differences were found between those who answered more questions correctly and those who answered less questions correctly. Further studies could include more detailed analyses on how genetics knowledge affects perspectives towards carrier screening results and donor selection. Additionally, increased education about carrier screening in this population may be beneficial to ensure that recipients are making informed decisions.

2.5.4 Study limitations. The major limitation of this study was the homogeneity of participants. Most of the participants were Caucasian, educated women; the results cannot be generalizable to the perspectives of all intended parents. It would be interesting to gather the perspectives of men in this population. Similarly, as most of the results represent the views of women who utilized donor sperm to become single mothers, they are not generalizable to the population of all individuals and couples who use donor gametes. Additionally, because very few respondents reported the use of donor eggs, comparisons could not be made between those who utilize donor sperm and those who

utilize donor eggs. As mentioned previously, there are fewer options for egg donors as there are for sperm donors, and this may have a significant impact on whether carrier status of a donor alters a recipient's choice to continue with that donor.

Our study attempted to discern differences in the way carrier screening was perceived based on which countries the participants lived in. Because the majority of participants resided in the United States, no such comparisons could be made. Carrier screening practices differ in countries around the world; therefore, general perceptions of carrier screening may differ. In some countries, such as Iran, Turkey, Saudi Arabia, and Cyprus, carrier screening for certain conditions (i.e. beta thalassemia) is mandatory and routinely performed in premarital couples. Some countries, such as Greece, Iran, and Italy, provide information about carrier screening through mass media to increase knowledge among the general population (Cousens et al., 2010). In these countries, carrier screening is normalized and general attitudes toward carrier screening may be more positive. It would be interesting to compare perspectives of gamete recipients residing in these countries, to see whether there is a difference in preference when carrier screening is normalized throughout the country.

Lastly, a limitation in our study was in the interpretation of open-ended responses of participants. Because their responses were written rather than obtained from oral interviews, their responses could not be clarified and there could be some discrepancy between what the participants meant and how their responses were interpreted. Future studies may utilize interviews to further clarify and understand the views of intended parents.

2.5.5 Genetic counseling practice implications. Women in our study felt it would be helpful to speak with a genetic counselor about reproductive risk in the setting of gamete donor selection. Future studies may focus on how genetic counseling could be helpful in gamete donation programs. It would be interesting to see whether genetic counseling during the donor selection process can impact a recipient's comfort level with choosing a donor who was identified as a carrier for a genetic condition. Allowing the recipients access to a genetic counselor to have discussions about residual risk, carrier frequencies, and other details surrounding carrier screening may be beneficial in gamete donation programs to ensure that they are making the most informed decisions.

2.6 Conclusion

Due to the emergence of new technologies and decreasing costs, carrier screening for hundreds of conditions at one time has become readily accessible. Gamete donation programs are an ideal setting for ECS, as all screening occurs in the preconception period, when carrier screening is most beneficial to maximize reproductive choice. With limited current consensus guideline recommendations for the level of carrier screening performed in the gamete donor population, updated guidelines may benefit from perspectives of intended parents. Our study found that although recipients were interested in ECS for their potential donors, they were uncomfortable choosing a donor who was a carrier for an AR condition. This would significantly limit the available donor pool, as ECS would identify most individuals as a carrier for at least one condition. It seems that in most cases, ECS in a gamete donation program would alter clinical decision making for the recipients.

There seemed to be a disconnect between what recipients think they desired and the level of information they would be comfortable with. This could be due to a lack of overall understanding of carrier screening, and/or an unrealistic expectation that donors should test negative when screened for carrier status of hundreds of conditions, despite the reality that most individuals screened will have at least one positive result. Increased knowledge among intended parents on the frequency and implications of positive carrier screening results is necessary before implementation of ECS in gamete donation programs would be successful. Additionally, intended parents need to be properly counseled that although ECS is a valuable tool to detect carriers of AR conditions, it is unable to reduce the risks for most AD and multifactorial conditions. Therefore, it is important to recognize that ECS does not replace genetic counseling or assessment of familial risk.

Recipients may benefit from increased genetic education about carrier frequencies, residual risk, and other details surrounding genetic carrier screening. As expressed by our participants, access to genetic counseling could be an integral part of the gamete donation process. Proper counseling can aid in decreasing the gaps in knowledge among intended parents regarding carrier screening, and ensure that recipients are making the most informed decisions.

Table 2.1 Patient demographics

| Demographic | Number of participants (%) |
|---|----------------------------|
| Gender | |
| Female | 58 (100) |
| Age | |
| 18-35 | 14 (24.6) |
| 36-45 | 36 (63.2) |
| 46+ | 7 (12.3) |
| Total | 57 (100) |
| Relationship status | |
| Single | 47 (81.0) |
| Married | 10 (17.2) |
| Partnered, not married | 1 (1.7) |
| Total | 58 (100) |
| Ethnicity/ancestry | |
| Caucasian | 54 (93.1) |
| Hispanic/Latino | 2 (3.4) |
| Jewish | 6 (10.3) |
| Mediterranean (Italian, Greek) | 1 (1.7) |
| Middle Eastern | 1 (1.7) |
| Native American | 1 (1.7) |
| Total | 58 (100) |
| Country of residence | |
| Australia | 1 (1.7) |
| Canada | 10 (17.2) |
| United Kingdom | 2 (3.4) |
| United States | 45 (77.6) |
| Total | 58 (100) |
| Highest education level | |
| High school diploma/GED | 2 (3.4) |
| Some college | 2 (3.4) |
| Associate's degree | 2 (3.4) |
| Bachelor's degree | 11 (19.0) |
| Some graduate school | 3 (5.2) |
| Graduate degree (Master's, PhD, MD, JD, etc.) | 38 (65.5) |
| Total | 58 (100) |

Table 2.2 Personal history with use of donor gametes

| | Number of participants (%) |
|--|----------------------------|
| Ever attempted to conceive with an egg or sperm donor in the past | |
| Yes, and had a live birth | 38 (65.5) |
| Yes, and have an ongoing pregnancy | 6 (10.3) |
| Yes, but the pregnancy did not result in a live birth | 3 (5.2) |
| Yes, but pregnancy was not achieved | 4 (6.9) |
| No, I have not attempted to conceive with a donor | 7 (12.1) |
| Total | 58 (100) |
| Currently seeking egg or sperm donor | |
| Yes – seeking egg donor | 1 (1.7) |
| Yes – seeking sperm donor | 10 (17.2) |
| No | 47 (81.0) |
| Total | 58 (100) |
| Reason for using an egg and/or sperm donor | |
| Female factor infertility | 10 (17.2) |
| Male factor infertility | 4 (6.9) |
| Single mother | 48 (82.8) |
| LGBTQ individual or couple | 6 (10.3) |
| Genetic condition in me/my partner | 1 (1.7) |
| Total | 58 (100) |

Table 2.3 Genetics knowledge results

| Question (True/False) | Correct Answer | Number of correct answers (%) |
|--|----------------|-------------------------------|
| If both genetic parents are found to be carriers of the same mutation, the child will definitely have the disorder | False | 42 (72.4) |
| If my donor is a carrier of a genetic mutation and I (or my partner) am not, the child will likely not be affected by the disorder | True | 39 (67.2) |
| Healthy parents can have a child with an inherited disorder | True | 58 (100) |
| Some genetic disorders occur more commonly in certain ethnic groups | True | 57 (98.3) |
| If somebody is found to be a carrier of an autosomal recessive disorder, that person will develop the disease | False | 50 (86.2) |
| If genetic carrier screening finds no mutations in one genetic parent, any child from that parent is not at risk for any conditions | False | 47 (81.0) |
| If neither parent is found to be carriers of a mutation, their child definitely will not develop a genetic condition | False | 37 (63.8) |

Table 2.4 Opinions about genetic carrier screening results

| Statement | Strongly Agree | Agree | Slightly Agree | Slightly disagree | Disagree | Strongly Disagree | |
|---|----------------|-----------|----------------|-------------------|-----------|-------------------|----------------------------|
| I am not worried about the other genetic parent (non-donor) being a carrier for a genetic condition if my donor has negative testing for that condition (n=49) | 7 (14.3) | 20 (40.8) | 7 (14.3) | 9 (18.4) | 5 (10.2) | 1 (2.0) | |
| I am not worried about my donor being a carrier of a genetic condition if the other genetic parent (donor or non-donor) has negative testing for that condition (n=56) | 8 (14.3) | 14 (25.0) | 12 (21.4) | 10 (17.9) | 8 (14.3) | 4 (7.1) | |
| Statement | Strongly Agree | Agree | Slightly Agree | Slightly disagree | Disagree | Strongly Disagree | They are equally important |
| The physical characteristics of my donor are more important to me than genetic carrier screening results (n=56) | 0 (0) | 3 (5.4) | 10 (17.9) | 7 (12.5) | 20 (35.7) | 12 (21.4) | 4 (7.1) |
| My donor's family history is more important to me than genetic carrier screening results (n=56) | 3 (5.4) | 8 (14.3) | 9 (16.1) | 10 (17.9) | 12 (21.4) | 3 (5.4) | 11 (19.6) |
| Note: Data are expressed as n (%). | | | | | | | |

Table 2.5 Donor selection scenarios

| | Hemochromatosis | Usher | BBS | GRACILE |
|--|-----------------|-----------|-----------|-----------|
| Would proceed with donor to build family (provided negative testing for other genetic parent) | | | | |
| Yes | 40 (83.3) | 17 (37.0) | 18 (39.1) | 18 (39.1) |
| No | 8 (16.7) | 29 (63.0) | 28 (60.9) | 28 (60.9) |
| Would give up an important attribute unrelated to health to proceed with donor free of carrier status | | | | |
| Yes | 19 (39.6) | 33 (71.7) | 33 (71.7) | 28 (60.9) |
| No | 29 (60.4) | 13 (28.3) | 13 (28.3) | 18 (39.1) |
| Donor preference | | | | |
| This donor (screened for 300, positive for 1) | 42 (87.5) | 28 (60.9) | 24 (53.3) | 26 (56.5) |
| Other donor (screened for 4, negative for all) | 6 (12.5) | 18 (39.1) | 21 (46.7) | 20 (43.5) |
| Level of concern for offspring being unaffected carrier | | | | |
| Not worried at all | 14 (29.2) | 6 (13.0) | 4 (8.7) | 4 (8.7) |
| Slightly worried | 28 (58.3) | 18 (39.1) | 21 (45.7) | 21 (45.7) |
| Worried | 5 (10.4) | 17 (37.0) | 15 (32.6) | 10 (21.7) |
| Extremely worried | 1 (2.1) | 5 (10.9) | 6 (13.0) | 11 (23.9) |
| Note: Data are expressed as n (%). | | | | |

Table 2.6 Ranking of donors

| Ranking | Donor | N | Mean |
|---------|---|----|------|
| 1 | 2: tested for 300 conditions, carrier for hemochromatosis | 42 | 1.24 |
| 2 | 3: tested for 300 conditions, carrier for Usher syndrome | 39 | 2.92 |
| 3 | 1: tested for 4 conditions, negative for all 4 | 38 | 3.13 |
| 4 | 5: tested for 300 conditions, carrier for GRACILE | 39 | 3.79 |
| 5 | 4: tested for 300 conditions, carrier for BBS | 39 | 3.87 |

Table 2.7 Factors influencing ranking of donors

| Factor | Number of participants (%) |
|--|----------------------------|
| Number of tested conditions | 27 (46.6) |
| Severity of disorder for which he/she is a carrier | 42 (72.4) |
| Incidence of disorder for which he/she is a carrier | 26 (44.8) |
| Availability of testing for me/my partner to assess the chance that I/he/she is not a carrier of the same disorder | 16 (27.6) |

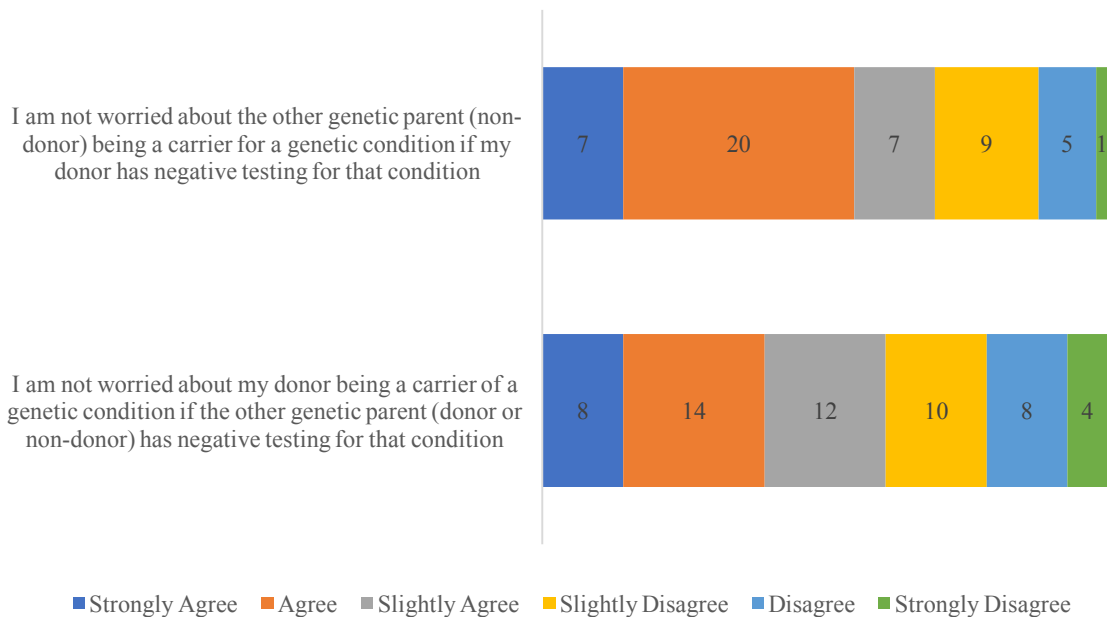


Figure 2.1
On a scale from strongly agree to strongly disagree, participants' level of agreement on statements about genetic carrier screening in gamete donors.

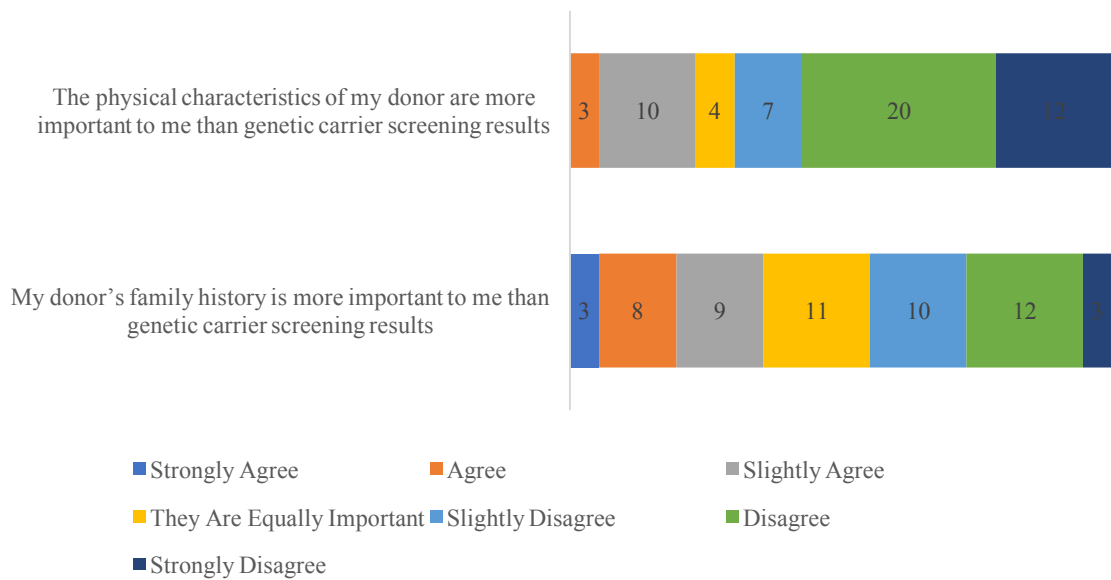


Figure 2.2
On a scale from strongly agree to strongly disagree, participants' level of agreement on statements about genetic carrier screening in gamete donors.

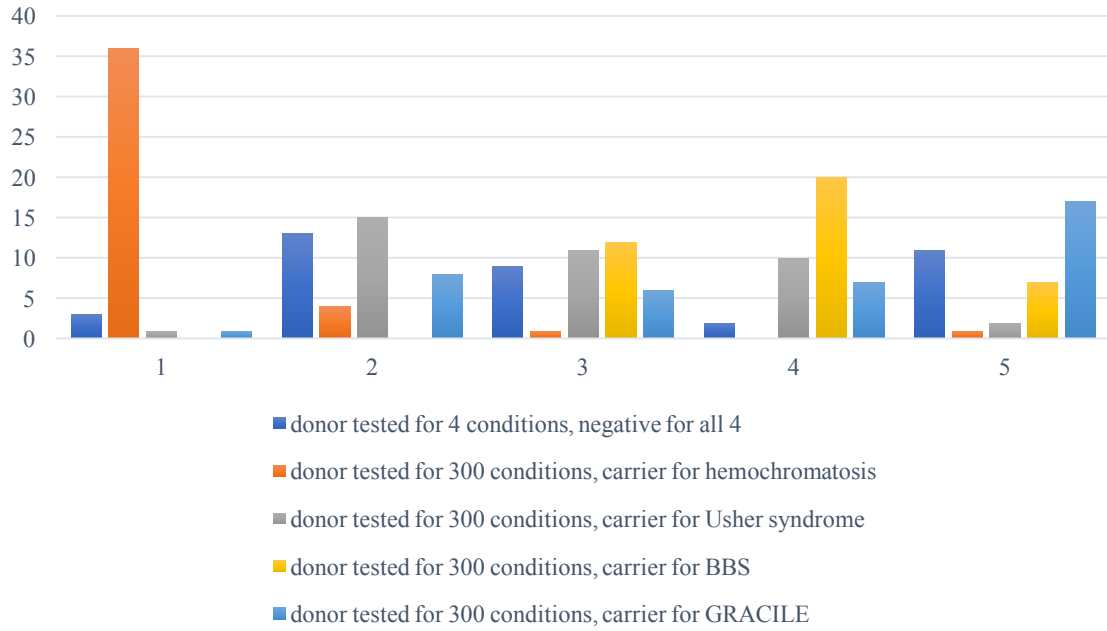


Figure 2.3
Participants' rankings of donors based on genetic carrier screening results.

Chapter 3: Conclusion

Due to the emergence of new technologies and decreasing costs, carrier screening for hundreds of conditions at one time has become readily accessible. Gamete donation programs are an ideal setting for expanded carrier screening (ECS), as all screening occurs in the preconception period, when carrier screening is most beneficial to maximize reproductive choice. With limited current consensus guideline recommendations for the level of carrier screening performed in the gamete donor population, updated guidelines may benefit from perspectives of intended parents. Our study found that although recipients were interested in ECS for their potential donors, they were uncomfortable choosing a donor who was a carrier for an autosomal recessive (AR) condition. This would significantly limit the available donor pool, as ECS would identify most individuals as a carrier for at least one condition. It seems that in most cases, ECS in a gamete donation program would alter clinical decision making for the recipients.

There seemed to be a disconnect between what recipients think they desired and the level of information they would be comfortable with. This could be due to a lack of overall understanding of carrier screening, and/or an unrealistic expectation that donors should test negative when screened for carrier status of hundreds of conditions, despite the reality that most individuals screened will have at least one positive result. Increased knowledge among intended parents on the frequency and implications of positive carrier screening results is necessary before implementation of ECS in gamete donation programs would be successful. Additionally, intended parents need to be properly

counseled that although ECS is a valuable tool to detect carriers of AR conditions, it is unable to reduce the risks for most autosomal dominant and multifactorial conditions. Therefore, it is important to recognize that ECS does not replace genetic counseling or assessment of familial risk.

Recipients may benefit from increased genetic education about carrier frequencies, residual risk, and other details surrounding genetic carrier screening. As expressed by our participants, access to genetic counseling could be an integral part of the gamete donation process. Proper counseling can aid in decreasing the gaps in knowledge among intended parents regarding carrier screening, and ensure that recipients are making the most informed decisions.

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Appendix A – Invitation to Participate

Invitation to Participate: Recipients' Perspectives Regarding Expanded Carrier Screening

Dear Potential Participant,

You are invited to participate in an **anonymous** master of science thesis research study at the University of South Carolina School of Medicine. The objective of this study is to determine how much genetic carrier screening information a recipient would prefer to receive about their potential egg and sperm donors. The study will also aim to identify factors that influence an intended parent's choice of donor based on genetic screening results.

We are inviting both parents of donor-conceived children and intended parents currently in the process of selecting/using a donor to participate. Participation in this study is meant to benefit intended parents by identifying whether increased education of genetic screening options could improve the donor selection process. We believe that the results of this study can add to the discussion concerning genetic screening of egg and sperm donors, which could lead to greater consistency among donor screening practices.

If you decide to participate, you will be asked to complete an **anonymous** online questionnaire about various issues surrounding the genetic screening of egg and sperm donors. All responses are kept **anonymous** and **confidential**. The data collected may be published or presented, but your responses will not be associated with any personally identifying information. The survey will take approximately 15 minutes to complete, and participation is completely voluntary. You do not have to answer any questions that you do not wish to answer and you may discontinue the survey at any time. By completing the survey, you are consenting that you have read and understand this information.

Thank you for your time and participation in this study. Your answers will help to improve the donor screening and selection process for future parents. If you have any questions, or would like more information, please contact me or my advisor, Janice Edwards, using the contact information below. Thank you for considering participating in this research project. Your input is invaluable and we appreciate your time.

Link to access survey: <https://www.surveymonkey.com/r/LJLSDP9>

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Appendix B – Questionnaire

You are being asked to participate in this study if you are using or have previously used an egg and/or sperm donor(s) to build your family. The purpose of this study is to explore the perspectives of intended parents regarding the genetic testing of a gamete donor.

Your participation in this study will increase our understanding of the factors that influence the decision to choose a donor based on their genetic screening results. We believe that the results of this study can add to the discussion concerning genetic screening of egg and sperm donors, which could lead to greater consistency among donor screening practices.

Your participation in the study is voluntary, and you can withdraw from the study at any time. Participating in the study involves completing an online survey. The survey is anonymous, meaning that we will not collect any personal information that could identify you or connect you to your responses. The survey should take approximately 15 minutes to complete. Questions in the survey will ask you about your perspectives regarding carrier screening of egg and sperm donors, as well as your preferences of donors based on hypothetical genetic carrier screening results. There are also some questions designed to assess your knowledge of genetic concepts.

This study is being conducted by Erika Jackson, a genetic counseling student at the University of South Carolina Medical School for a Master's Thesis project. Janice Edwards, a genetic counselor at the University of South Carolina, is the faculty thesis advisor for this study. If you have any questions about this study, you may contact us:

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For questions about your rights as a participant, you may contact the Office of Research Compliance at the University of South Carolina at (803) 777-7095.

By accessing the online survey by clicking the "Next" button below, you are indicating your consent to participate in this study.

Thank you for sharing your insight.

Demographic Questions

What is your gender?

What is your age?

What is your current relationship status?

What is your ethnicity/ancestry? (Please select all that apply.)

- Caucasian
- Asian / Pacific Islander
- African American
- Hispanic / Latino
- Jewish
- Mediterranean (Italian, Greek)
- Other (please specify)

What is your country of residence?

What is the highest level of education you have completed?

Demographic Questions

Have you ever attempted to conceive with an egg or sperm donor in the past?

Demographic Questions

How many children do you have?

Conceived by egg and/or
sperm donor(s)

Conceived without egg or
sperm donor

Are you currently seeking an egg or sperm donor?

What is/was your reason for using an egg and/or sperm donor(s)?

- Female factor infertility
- Male factor infertility
- Single mother
- LGBTQ individual or couple
- Genetic condition in me/my partner
- Prefer not to say
- Other (please specify)

Demographic Questions

Genetic carrier screening is a blood or saliva test that is performed to see whether an individual carries a genetic mutation that could cause an inherited disorder in his or her baby. Most disorders on carrier screening tests are inherited in an autosomal recessive (AR) manner, meaning that BOTH genetic parents (individual contributing sperm and individual contributing egg) would need to be carriers of a mutation in the same gene to have an affected child. It is likely that everyone carries one or more AR mutations, even without a family history of genetic disease. Being a “carrier” of a genetic mutation usually causes no health problems or symptoms for that individual. However, if both genetic parents carry a mutation in the same gene, there is a 1 in 4 (25%) chance of having an affected child in each conception.

Have you or your partner had any genetic carrier screening?

Do you know how many disorders you or your partner were screened for?

- No
- Yes (please specify a number)

Were you or your partner found to be a carrier of any disorder?

To your knowledge, was your donor(s) screened for genetic disorders?

Do you know how many disorders your donor was screened for?

- No
- Yes (please specify number)

Do you have any personal or family history of genetic or inherited disorders? If yes, please specify which disorder.

Genetic or inherited disorder(s)

Screening Preferences

Some genetic carrier screening tests only assess conditions that are more common among certain ethnicities or ancestries (ethnicity-based carrier screening) or for conditions that are known to be in an individual's family history (family history-based carrier screening). Ethnicity or family history-based genetic carrier screening tests typically test for fewer than 20 conditions. When testing for approximately 20 conditions, up to 25% of individuals will be identified as a carrier.

In contrast, expanded carrier screening is not specific to an individual's ethnicity or family history and typically tests for more than 100 disorders at one time. Some of these disorders may be severe, while others may be milder. When testing for over 100 conditions, up to 65% of individuals will be identified as a carrier of at least one disorder, and many will be carriers of multiple disorders.

It is important to note that a negative carrier screening result reduces the chance of being a carrier and thus, the chance of having an affected baby; however, someone still has a chance of being a carrier despite a negative result (although this chance is low).

To reiterate, for each genetic condition:

| | Chance of affected baby |
|--|-------------------------|
| Both genetic parents a carrier | high |
| One genetic parent a carrier, the other genetic parent tested negative | low |
| Both genetic parents tested negative | low |

Given this information, would you **yourself** prefer to be tested through only ethnicity or family history-based screening (1-20 conditions) or through expanded carrier screening (100+ conditions, more likely to identify carrier)?

Given this information, would you prefer your **potential egg and/or sperm donor(s)** to be tested through only ethnicity or family history-based screening (1-20 conditions) or through expanded carrier screening (100+ conditions, more likely to identify carrier)?

Genetics Knowledge

The following questions will gauge your understanding of autosomal recessive inheritance, inherited disorders, and genetic carrier screening. Please answer each question to the best of your knowledge. If you do not know the answer to a question, you may select "unsure."

If both genetic parents are found to be carriers of the same mutation, the child will definitely have the disorder.

- True
- False
- Unsure

If my donor is a carrier of a genetic mutation and I (or my partner) am not, the child will likely not be affected by the disorder.

- True
- False
- Unsure

Healthy parents can have a child with an inherited disorder.

- True
- False
- Unsure

Some genetic disorders occur more commonly in certain ethnic groups.

- True
- False
- Unsure

If somebody is found to be a carrier of an autosomal recessive disorder, that person will develop the disease.

- True
- False
- Unsure

If genetic carrier screening finds no mutations in one genetic parent, any child from that parent is not at risk for any conditions.

- True
- False
- Unsure

If neither parent is found to be carriers of a mutation, their child definitely will not develop a genetic condition.

- True
- False
- Unsure

* Besides your donor, who will be/was the genetic parent?

- Myself
- My partner
- Another donor

Please answer each statement with the option that most accurately reflects your opinion/preference:

I am not worried about being a carrier for a genetic condition if my donor has negative testing for that condition.

| | | | | | |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Strongly agree | Agree | Slightly agree | Slightly disagree | Disagree | Strongly disagree |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

I would not be worried about my donor being a carrier of a genetic condition if I have negative testing for that condition.

| | | | | | |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Strongly agree | Agree | Slightly agree | Slightly disagree | Disagree | Strongly disagree |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

The physical characteristics of my donor are more important to me than genetic carrier screening results:

| | | | | | | |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|----------------------------|
| Strongly agree | Agree | Slightly agree | Slightly disagree | Disagree | Strongly disagree | They are equally important |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

My donor's family history is more important to me than genetic carrier screening results.

| | | | | | | |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|----------------------------|
| Strongly agree | Agree | Slightly agree | Slightly disagree | Disagree | Strongly disagree | They are equally important |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

The following questions are regarding carrier status for autosomal recessive conditions, a group of conditions in which both copies of the responsible gene (one from each genetic parent) must be mutated for someone to have the disease and show symptoms. You will be asked about four distinct conditions.

Scenario #1

For these questions, please consider a donor who meets all of your requirements and was screened for 300 different conditions. The donor was found to be a carrier of a gene for hereditary hemochromatosis. Hemochromatosis is a common and treatable inherited disease in which the body absorbs and stores too much iron, potentially damaging the liver and other organs. Most people with two mutated copies of the gene do not develop the disease. In people who do develop the disease, symptoms generally start between ages 40-60. If the disease is diagnosed and treated before symptoms develop, people with hemochromatosis typically have a normal lifespan. If the disease is untreated, however, it can lead to fatal liver and heart failure. As many as 33% of individuals are carriers for this condition, depending on ethnicity. Carrier testing is available for this condition, and a negative test significantly decreases the chance to be a carrier.

If you have negative testing for hemochromatosis, would you proceed with this donor to build your family?

- Yes
- No

Would you give up an important attribute unrelated to health (i.e. physical/social characteristic) to proceed with a donor free of carrier status for this condition?

- Yes
- No

Given the choice, would you prefer this donor (who was screened for 300 conditions and positive for 1) or a donor who was screened for 4 conditions and not found to have any mutations?

- This donor
- Other donor

How worried are you about the chance of your child being an **unaffected carrier** of this condition (unaffected carrier would have no symptoms but can pass it on to their children in the same autosomal recessive manner)?

| | | | |
|-----------------------|-----------------------|-----------------------|-----------------------|
| Not worried at all | Slightly worried | Worried | Extremely worried |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

What are your overall thoughts about this donor?

Scenario #2

For these questions, please consider a donor who meets all of your requirements and was screened for 300 different conditions. The donor was found to be a carrier of a gene for Usher syndrome type 1F. Infants with Usher syndrome type 1F are profoundly deaf at birth. In adolescence, people with Usher syndrome type 1F develop retinitis pigmentosa, an eye disease which causes night blindness and a gradual loss of peripheral vision. People with Usher syndrome type 1F also have balance problems and may appear clumsy and have difficulty with athletic activities. Usher syndrome does not affect one's lifespan or intelligence, nor does it cause any other health problems. It is estimated that 1 in 70 (1.4%) people in the US are carriers of this disorder. Carrier testing is available, and negative testing significantly reduces the chance to be a carrier.

Testing for Usher syndrome is not 100% accurate, which means that there is still a chance to have an affected child even if one or both individuals test negative. If only the donor is a carrier and you are negative, there is an approximately 1/1,600 (0.06%) chance to have a child with Usher syndrome.

If you have negative testing for Usher syndrome, would you proceed with this donor to build your family?

- Yes
 No

Would you give up an important attribute unrelated to health (i.e. physical/social characteristic) to proceed with a donor free of carrier status for this condition?

- Yes
 No

Given the choice, would you prefer this donor (who was screened for 300 conditions and positive for 1) or a donor who was screened for 4 conditions and not found to have any mutations?

- This donor
 Other donor

How worried are you about the chance of your child being an **unaffected carrier** of this condition (unaffected carrier would have no symptoms but can pass it on to their children in the same autosomal recessive manner)?

| Not worried at all | Slightly worried | Worried | Extremely worried |
|-----------------------|-----------------------|-----------------------|-----------------------|
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

What are your overall thoughts about this donor?

Scenario #3

For these questions, please consider a donor who meets all of your requirements and was screened for 300 different conditions. The donor was found to be a carrier of a gene for Bardet-Biedl syndrome. Bardet-Biedl syndrome is an inherited disease that can cause some or all of the following problems: vision problems, kidney abnormalities, genital anomalies, extra fingers or toes, mild obesity. Also, about half of people with the disease have developmental delay or intellectual disability. About 1 in 400 (<1%) individuals are carriers for this condition. Carrier testing is available, and negative testing significantly reduces the chance to be a carrier.

Testing for BBS is not 100% accurate, which means that there is still a chance to have an affected child even if one or both individuals test negative. If only the donor is a carrier and you are negative, there is an approximately 1/4,000 (0.025%) chance to have a child with BBS.

If you have negative testing for BBS, would you proceed with this donor to build your family?

- Yes
 No

Would you give up an important attribute unrelated to health (i.e. physical/social characteristic) to proceed with a donor free of carrier status for this condition?

- Yes
 No

Given the choice, would you prefer this donor (who was screened for 300 conditions and positive for 1) or a donor who was screened for 4 conditions and not found to have any mutations?

- This donor
 Other donor

How worried are you about the chance of your child being an **unaffected carrier** of this condition (unaffected carrier would have no symptoms but can pass it on to their children in the same autosomal recessive manner)?

| | | | |
|-----------------------|-----------------------|-----------------------|-----------------------|
| Not worried at all | Slightly worried | Worried | Extremely worried |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

What are your overall thoughts about this donor?

Scenario #4

For these questions, please consider a donor who meets all of your requirements and was screened for 300 different conditions. The donor was found to be a carrier of a gene for GRACILE syndrome. GRACILE syndrome is an inherited and fatal metabolic disorder that causes infants to accumulate toxic substances during the first few days of life. Even with treatment, affected infants typically do not survive beyond 5 months. Approximately 1 in 600 (< 0.05%) individuals are carriers of GRACILE syndrome, except in the Finnish population, where the carrier frequency is 1 in 110 (1%). Carrier testing is available, and negative testing significantly reduces the chance to be a carrier.

Testing for GRACILE is not 100% accurate, which means that there is still a chance to have an affected child even if one or both individuals test negative. If only the donor is a carrier and you are negative, there is an approximately 1/16,000 (0.006%) chance to have a child with GRACILE.

If you have negative testing for GRACILE, would you proceed with this donor to build your family?

- Yes
- No

Would you give up an important attribute unrelated to health (i.e. physical/social characteristic) to proceed with a donor free of carrier status for this condition?

- Yes
- No

Given the choice, would you prefer this donor (who was screened for 300 conditions and positive for 1) or a donor who was screened for 4 conditions and not found to have any mutations?

- This donor
- Other donor

How worried are you about the chance of your child being an **unaffected carrier** of this condition (unaffected carrier would have no symptoms but can pass it on to their children in the same autosomal recessive manner)?

| | | | |
|-----------------------|-----------------------|-----------------------|-----------------------|
| Not worried at all | Slightly worried | Worried | Extremely worried |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

What are your overall thoughts about this donor?

Assuming only these 5 donors were available, which of these donors are you most likely to choose based on their genetic screening results? (Please rank from 1-5, with 1 being most likely and 5 being least likely to choose.)

If you have no preference or would prefer not to select any of these donors, please select the option below.

| | |
|--------------------------|---|
| <input type="checkbox"/> | Donor 1: tested for 4 conditions, negative for all 4 (unknown chance of affected child) |
| <input type="checkbox"/> | Donor 2: tested for 300 conditions, carrier for hemochromatosis (mild, treatable, most do not develop disease, unknown chance of affected child) |
| <input type="checkbox"/> | Donor 3: tested for 300 conditions, carrier for Usher syndrome (hearing and vision loss, no shortened lifespan, 1/1,600 chance of affected child) |
| <input type="checkbox"/> | Donor 4: tested for 300 conditions, carrier for Bardet-Biedl disease (multiple abnormalities, developmental delay or intellectual disability, 1/4,000 chance of affected child) |
| <input type="checkbox"/> | Donor 5: tested for 300 conditions, carrier for GRACILE syndrome (fatal metabolic disorder, infants die within 5 months, 1/16,000 chance of affected child) |

Please select a statement if it applies to you. (You may leave this question blank if you have already ranked the above donors)

- I have no preference regarding these donors.
- I would prefer not to select a donor at this time.

Which factors influenced your ranking of these donors? (select all that apply)

- Number of tested conditions
- Severity of disorder for which he/she is a carrier
- Incidence of disorder (how common or rare) for which he/she is a carrier
- Availability of testing for me/my partner to assess the chance that I/he/she is not a carrier of the same disorder
- Other reason (please explain)

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates:

- **Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.**
- **Education about inheritance, testing, management, prevention, resources and research.**
- **Counseling to promote informed choices and adaptation to the risk or condition.**

Genetic counselors can give you the personalized help you need when it comes to you and your family's genetic health. Genetic counselors can work with you – and your physician – to understand complex genetic information and help you make informed decisions.

How helpful would it be for a genetic counselor to explain carrier screening to you during the donor selection process?

| | | | | | | |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|---|
| | | | | | | I receive enough information from my donor clinic/program (not a genetic counselor) |
| Extremely helpful | Helpful | Somewhat helpful | Somewhat unhelpful | Unhelpful | Extremely unhelpful | |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

Survey Complete

Thank you for your time and input.