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Walking the Edge with Controversial Use of Preimplantation Genetic Diagnosis (PGD): Opinions and Attitudes of Genetic Counselors

Kristen Everton
University of South Carolina - Columbia

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by

Kristen Suzanne Everton

Bachelor of Science
Wingate University, 2009

Master of Science
Washington State University, 2011

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Accepted by:

Janice Edwards, Director of Thesis

Andria Besser, Reader

Patricia Hershberger, Reader

Lacy Ford, Vice Provost and Dean of Graduate Studies

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Abstract

Purpose: This study explored opinions and attitudes of genetic counselors regarding three controversial applications of preimplantation genetic diagnosis (PGD): PGD for early-onset Alzheimer, use of embryos that are *BRCA* positive after PGD revealed no disease-free embryos to be available, and PGD to select against a variant of unknown significance (VUS) for Marfan syndrome. **Methods:** Genetic counselors were contacted through the National Society of Genetic Counselors (NSGC) electronic mailing list. Inclusion criteria required that a participant was currently practicing as a genetic counselor, was a member of the NSGC, and has counseled patients about PGD. Twenty-nine participants volunteered to participate and 24 recorded interviews were transcribed for data analysis. The survey consisted of 34 questions including demographic questions, qualitative questions about each of the three case scenarios, and general questions about PGD. Qualitative analysis was performed using a conventional content analysis approach as described by Hsieh (2005). **Results**: Themes common to all three scenarios included: necessity of appropriate/thorough counseling, the importance of the genetic indications, patient perceptions, and respect for patient autonomy in decision making. Multiple themes were also described for each unique case scenario. The majority (65%,15/23) of participants felt PGD for an adult-onset disorder was least controversial, and PGD for a VUS was most controversial. **Conclusion**: Participants felt that PGD was appropriate for

life limiting conditions, cases where there was an established diagnosis with a known pathogenic mutation, and when symptom severity and disease burden were significant. Participants agreed that appropriate/thorough counseling was necessary, patient perceptions of 'serious' disease were critical, and patient autonomy were key factors when dealing with controversial applications of PGD. Ultimately, genetic counseling is recommended and patients need to understand the benefits, disadvantages, and the potential outcomes of PGD in order to make the decision that is most appropriate for their families.

Keywords: Preimplantation genetic diagnosis (PGD), controversial, genetic counselors' opinions.

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List of Abbreviations

ASRM……American Society of Reproductive Medicine

CVS……..…Chorionic Villus Sampling

HFEA……Human Fertilization and Embryology Authority

NGS…….Next Generation Sequencing

NSGC…….National Society of Genetic Counselors

PGD……Preimplantation Genetic Diagnosis

VUS……..Variant of unknown significance

WGS……Whole Genome Sequencing

Chapter 1. Background

First used in the 1990s to successfully prevent X-linked disease, preimplantation genetic diagnosis (PGD) is a technique designed to prevent genetic disorders from being inherited by future generations. Individuals who carry a known genetic mutation or chromosome rearrangement can use PGD to identify embryos at risk of inheriting a genetic condition. For couples at increased risk of having affected offspring, PGD is an alternative to prenatal diagnosis, via amniocentesis or chorionic villus sampling (CVS), in which selective termination is often used to avoid affected offspring (Chang et al., 2011).

Since the 1990s, significant improvements have been made in the biopsy and molecular diagnosis techniques used for PGD, which have allowed for an increasing number of genetic disorders to be tested. Indications for PGD include aneuploidy screening, structural chromosome rearrangements, hereditary diseases, human leukocyte antigen typing, and maternal-fetal blood incompatibility (Chang et al., 2011). Disorders include, but are not limited to, Huntington's disease, Marfan syndrome, hereditary cancer syndromes, cystic fibrosis, and hundreds more (Brezina, Brezina, & Kearns, 2012).

For couples at risk for a genetic condition, there are several reproductive options. Couples could choose to remain child free or adopt in lieu of having a biological child. For those that decide to pursue a pregnancy, there are several options available to prevent the birth of an affected child. One of these options is the use of donated gametes. For

example, intrauterine insemination or in vitro fertilization (IVF) using an unaffected sperm donor could be used in the case of X-linked or autosomal recessive conditions to greatly reduce the risk. The use of donated oocytes from a healthy female can be used in conjunction with IVF to prevent autosomal recessive, X-linked, and mitochondrial conditions (Vergeer, Van Balen, & Ketting, 1998). Other couples may choose to proceed with a natural pregnancy and may or may not use prenatal diagnosis by amniocentesis or CVS (Vergeer et al., 1998; Harper and Sengupta, 2012).

Amniocentesis is typically performed between 15 and 20 weeks gestation and results are received seven to 14 days later. Since the timing of an amniocentesis only allows for second trimester termination, CVS is an alternative diagnostic procedure that can be done between approximately 10 and 12 weeks gestation and enables the option of first-trimester termination (Goldberg, Martin, Lebo, & Pedersen, 1993).

Preimplantation genetic diagnosis is a reproductive option that allows couples, in many cases, to avoid pregnancy termination. Because the PGD technique requires *a priori* knowledge of the genetic condition, couples who choose PGD typically have had a previous diagnosis of a specific disorder, either in an affected child or in one of the members of the couple. Alternatively, some couples may not have any history of a disorder but may be aware of a positive carrier status through routine genetic carrier screening. However, PGD is not a simple process. In addition to undergoing the physical and emotional challenges of IVF, couples often need to have unique, specific molecular tests designed and validated to carry-out the genetic testing (Coutelle et al., 1989).

1.1 Preimplantation Genetic Diagnosis (PGD) and In Vitro Fertilization (IVF)

Preimplantation genetic diagnosis is performed in conjunction with IVF. Approximately four to six percent of IVF cycles in the United States utilize PGD and nearly 74% of fertility clinics offer PGD (Baruch, Kaufman, & Hudson, 2008). For IVF, ovaries are stimulated using a combination of injectable hormones to produce a higher than usual number of mature follicles. Under ultrasound guidance, oocytes are retrieved from the ovaries by follicular fluid aspiration and fertilized in the laboratory to create embryos (Coutelle et al., 1989). The oocytes and embryos can be tested at various stages of development by biopsying cells through various micromanipulation procedures (Goldberg et al., 1993).

Preimplantation genetic diagnosis involves the biopsy of polar bodies, blastomeres, or trophectoderm from developing oocytes and embryos. Polar body biopsy is useful for screening oocytes for maternal genetic abnormalities only, since no paternal genetic contribution is present. In Germany and Italy, with strict regulations on embryo biopsy, polar body biopsy is preferred because it occurs before fertilization is complete (Brezina et al., 2012). After fertilization, the resulting embryo goes through several stages of development. Three days after the fertilization procedure, embryos reach the cleavage stage of development, and are approximately four to eight cells in size. Cleavage stage biopsy involves removing one or two cells called blastomeres, and was the most common biopsy method used in PGD for many years (Brezina et al., 2012). Five days after the fertilization procedure, the embryo has reached the blastocyst stage and is composed of two cell types: the inner cell mass and the trophectoderm. The inner

cell mass is a collection of cells that eventually becomes the fetus. Trophectoderm cells are fated to become the placenta. Biopsy at the blastocyst stage consists of removing several trophectoderm cells. Several studies suggest more accurate PGD results with this type of biopsy as opposed to cleavage stage biopsy (Brezina et al., 2012).

Genetic abnormalities are identified by a variety of methods such as: polymerase chain reaction (PCR), microarrays and fluorescence in situ hybridization (FISH) (Practice Committee of the American Society for Reproductive Medicine, 2004; Brezina et al., 2012). Embryos that are unaffected can then be transferred to the woman's uterus five or six days after egg retrieval, or are cryopreserved for future use (Practice Committee of the American Society for Reproductive Medicine, 2004). The goal of PGD is to only transfer embryos that are most likely to be unaffected by a genetic condition (Ehrich & Williams, 2010).

Although PGD reduces risk, it is not considered an alternative to prenatal genetic diagnosis. Prenatal genetic diagnosis, through CVS or amniocentesis, is recommended to confirm the PGD results, given the limitations resulting from testing the minute amount of DNA from an embryonic cell (Practice Committee of the American Society for Reproductive Medicine, 2004). However, PGD is an attractive means of excluding embryos with genetic abnormalities and its use is becoming increasingly common.

1.2 Benefits and Limitations

The benefits of this technology include the avoidance of a genetic abnormality or inherited disease, as well as, the lessened chance of a couple being faced with the decision of pregnancy termination (Fragouli, 2007). However, there are risks associated

with PGD. Embryo biopsies may damage or destroy embryos, requiring that embryologists and laboratory technicians performing embryo biopsy are highly skilled (Baruch et al., 2008). Removal of a cell from an embryo may also decrease implantation rates (Baruch et al., 2008). According to Baruch, "in all cases of PGD, it is critical to know whether the positive effect of selecting "normal" embryos or those with the desired trait is worth the risks and potentially detrimental effect of removing a cell for analysis" (Baruch et al., 2009, p. 250).

With newer advancements in genetic diagnostic technology, the uses of PGD have expanded dramatically, and some of these newer uses are controversial. Many individuals in the research, bioethics, and medical communities are concerned that non-health-related traits or "positive traits" such as intelligence or athleticism could be selected for in the future. Yet not all disease or non-health-related traits have an identified gene (Baruch et al., 2008). Often, "positive traits" are associated with multiple genetic and environmental factors and cannot be identified through current genetic testing technologies. Therefore, at the current time, parents are unable to select every characteristic or trait of their future child(ren). Preimplantation genetic diagnosis is also unable to create new traits that do not otherwise exist in the parents. PGD does not involve "genetic manipulation or "engineering" of the embryo itself" (Baruch et al., 2009, p. 250).

1.3 Current Applications of PGD

There are numerous reasons why couples may choose PGD testing. These reasons include, but are not limited to: sex selection, a previously affected pregnancy/

child, human leukocyte antigen (HLA) matching, one member of a couple is affected with a genetic condition or carries a balanced chromosomal rearrangement, advanced maternal age, and to increase the effectiveness of IVF by ruling out chromosomal causes of miscarriage and failed embryo implantation (Chang et al., 2011).

Initially, PGD was only used to identify embryos at risk for childhood-onset, single gene disorders. Single gene disorders are caused by mutations in a specific gene; examples include cystic fibrosis, sickle cell disease, hemophilia and Marfan syndrome. In principle, PGD, is able to identify the same single gene disorders tested for by prenatal diagnosis (Chang et al., 2011). In order for PGD to be performed for single gene disorders, a known disease-causing mutation must have been identified in the family (Handyside, Lesko, Tarin, Winston, & Hughes, 1992).

In the early 1990s, researchers attempted, for the first time, to identify embryos with cystic fibrosis using PGD (Handyside et at., 1992). Cystic fibrosis is an autosomal recessive condition common in the Caucasian population, with an incidence of one in 2500 live births and a carrier frequency of one in 25. A mutation in the cystic fibrosis transmembrane regulator (*CFTR*) gene causes defective chloride ion transport, which leads to multiple medical complications affecting several organs including the lungs and pancreas (Cant, Pollock, & Ford, 2014). In the study by Handyside et. al. (1992), three couples, all carrying the common delta F508 mutation in the *CFTR* gene, requested PGD to prevent the birth of children with cystic fibrosis. Each couple had at least one previously affected child with cystic fibrosis and wished to avoid another affected child or pregnancy termination after prenatal diagnosis. Couples were counseled about the

risks of the procedures and understood that, at the time, this was still an experimental treatment (Handyside et at., 1992). Using polymerase chain reaction (PCR), researchers amplified the *CFTR* gene from single cells removed from the couples' embryos and identified non-carrier, carrier, and affected embryos. In one couple, a non-carrier embryo and a carrier embryo were both transferred on the same day of DNA analysis. A pregnancy resulted and a female child was born, free of the parental mutations and therefore unaffected by cystic fibrosis. Another couple also transferred both a carrier embryo and a non-carrier embryo; however, no pregnancy resulted. A third couple did not undergo embryo transfer as none of their embryos were identified as free of the mutation (Handyside et at., 1992).

Some couples may choose to pursue PGD to select embryos that are a human leukocyte antigen (HLA) match for a sibling in need of a bone marrow transplant. An HLA matched embryo allows for allogeneic haematopoietic stem cell (HSC) transplantation through cord blood or bone marrow donation from a healthy sibling to one who is ill (Pennings, Schots, & Liebaers, 2002). In some conditions, a stem cell transplant from an HLA matched sibling is often the only cure (Pennings et al., 2002).

In 2001, the first case of PGD for an HLA matched sibling was successful for Fanconi anemia. Fanconi anemia is an autosomal recessive condition that causes a multitude of congenital anomalies and developmental issues, and most affected individuals have a significantly shortened life span due to bone marrow failure and a significantly increased risk of developing leukemia (Kupfer, 2013). Although many anomalies in Fanconi anemia may persist, the bone marrow failure and high risk for

leukemia may be successfully treated with a cord blood or bone marrow transplant. The success rate of a bone marrow transplant to treat Fanconi anemia is significantly greater when the donor is an HLA matched sibling to the recipient. When testing an embryo for HLA matching, testing for a single gene disorder can also be done at the same time to ensure that the embryo is also free of the genetic condition (Milachich et al., 2013). In this first case, researchers were able to successfully identify and transfer embryos that were unaffected with Fanconi Anemia and were also an HLA match to the affected sibling (Verlinsky, Rechitsky, Schoolcraft, Strom, & Kuliev, 2001). A healthy, HLA matched baby was born to this couple, and a successful bone marrow transplant was later performed on the affected child using umbilical cord blood collected from the newborn at the time of delivery. Preimplantation genetic diagnosis has been used effectively for this purpose in similar situations, such as β-thalassemia, and severe combined immunodeficiency (SCID) (Milachich et al., 2013).

Another frequent indication for PGD is a balanced chromosomal rearrangement in one parent, such as an inversion or translocation (Alfarawati, Fragouli, Cools, & Wells, 2011). Balanced chromosomal rearrangements are the basis of recurrent miscarriages in five to 10 percent of couples (Vanneste et al., 2011). Individuals who carry a balanced chromosome rearrangement are typically healthy but can produce unbalanced gametes. Embryos with unbalanced rearrangements often fail to implant or result in miscarriage, and therefore, couples in which one partner carries a balanced rearrangement are at increased risk for infertility and/or recurrent miscarriage. If a live birth with an unbalanced rearrangement does occur, there are often birth defects, developmental

delays, and/or intellectual disabilities (Chang et al., 2011). Alternatively, those who inherit balanced rearrangements from a parent, with no extra or missing genetic information, are not usually at increased risk for spontaneous abortion or developmental problems (Chang et al., 2011). For carriers of balanced rearrangements, PGD to select against embryos carrying unbalanced chromosome rearrangements can reduce spontaneous abortion, minimize the risk of offspring inheriting a chromosome imbalance, and increase pregnancy rates (Vanneste et al., 2011).

Preimplantation genetic diagnosis can also be used to select against conditions that usually do not manifest until adulthood, such as Huntington's disease or early-onset Alzheimer's disease. Huntington's disease is an autosomal dominant neurodegenerative disorder affecting muscle control, cognitive functions, behavior and personality (Lee, Hwang, Hun, Kowall, & Ryu, 2013). The majority of cases experience symptoms between the ages of 30 and 50 years old. Alzheimer's disease is another adult-onset, irreversible, progressive brain disease. Most cases of Alzheimer's disease occur after the age of 60, but there is also an early onset, monogenic form (Verlinsky et al., 2002).

The first use of PGD for early-onset Alzheimer's disease occurred in the early 2000s. Three genes associated with this form of Alzheimer's disease are presenilin one (*PSEN1*), presenilin two (*PSEN2*), and amyloid precursor protein (*APP*) (Verlinsky et al., 2002). Mutations in these genes predispose a person to developing Alzheimer's disease. Penetrance has not been established for all three genes, but mutations in the *APP* gene are known to be almost completely penetrant (Verlinsky et al., 2002). In one case, a 30-year old female requested PGD because she carried a familial mutation in the *APP* gene.

Embryos without the familial mutation were identified and transferred. A pregnancy was successfully established and verification of an unaffected fetus was obtained through CVS. This case demonstrates the feasibility of using PGD for adult-onset predisposition genes, for conditions like Alzheimer's disease (Verlinsky et al., 2002).

1.4 Practice Guidelines in the Utilization of PGD

Preimplantation genetic diagnosis has several uses that push bioethical boundaries and thus are considered controversial. For this reason, in many countries, there are professional organizations that provide guidance regarding the use of PGD. These ethics committees include the Human Fertilization and Embryology Authority (HFEA) in the United Kingdom, and the American Society for Reproductive Medicine (ASRM) in the United States. Both committees have published guidelines regarding use of PGD. It is important to distinguish that the HFEA influences laws governing the use of PGD, versus ASRM which develops guidelines for healthcare providers. There are no laws governing PGD in the United States, which is different from the United Kingdom. American physicians can choose to implement or ignore guidelines, whereas British physicians are mandated by laws developed from HFEA regulations.

In the United Kingdom, the HFEA is the governing authority regarding the use of gametes and embryos in research and fertility treatment. The HFEA determines the conditions for which PGD can be used and grants licenses for each condition (Ormondroyd et al., 2012). According to the HFEA website, as of 2012, the HFEA allows for PGD to be performed for more than 350 genetic conditions. Decisions regarding which conditions are allowed are guided by three ethical principles (Williams,

Ehrich, Farsides, & Scott, 2007). First, the individual seeking PGD must feel that a condition is serious enough to cause them concern. Second, there should be a significant risk that an embryo will have a serious genetic condition. Third, indications for PGD should be similar to current practices in prenatal diagnosis (Williams et al., 2007). When deciding which diseases can be tested by PGD, the HFEA also considers the suffering experienced by the affected individual and if there are effective treatments available. In 2006, HFEA supported "widening the scope for PGD to include susceptibility to late onset, lower penetrance conditions" (Williams et al., 2007, p. 1095).

In the United States, the American Society of Reproductive Medicine (ASRM), has published several committee opinions regarding the use of PGD. The ASRM recommends that couples considering PGD should receive genetic counseling. Genetic counselors who handle PGD cases must relay to each couple information relating to risks associated with IVF, risks associated with biopsy and culture of embryos, inheritance, quality of life, possibility of misdiagnosis, prenatal diagnostic testing, the possibility that all embryos are affected, and alternative methods of avoiding disease (Practice Committee of the American Society for Reproductive Medicine, 2008).

Regarding PGD for adult-onset conditions, ASRM concludes that PGD is ethically justified when a condition is serious and there are no safe and effective treatments available. As a matter of reproductive liberty, ASRM also advocates for the ability to use PGD for less serious or lower penetrance conditions. In the case of a single gene disorder, ASRM states that PGD is a significant advance over prenatal diagnosis and pregnancy termination (Ethics Committee of American Society for Reproductive

Medicine, 2013). With regards to sex selection, ASRM concludes that PGD should only be allowed to prevent sex-linked genetic conditions from being transmitted and not as a means of family balancing (Ethics Committee of American Society for Reproductive Medicine, 2013).

Although ASRM has published many committee opinions regarding the use of PGD, there are several recently evolved uses of PGD that have yet to be addressed with practice guidelines. These include: PGD for a variant of unknown significance and use of embryos with genetic disease after PGD revealed no disease-free embryos to be available.

1.5 Controversial Applications of PGD

1.5.1 Adult-onset Disorders. PGD for couples whose offspring are at risk for adult-onset conditions has raised concerns as these conditions do not occur until later in life. Approximately 28% of fertility clinics that responded to a 2005 survey reported that they have provided PGD to avoid serious adult-onset diseases (Baruch et al., 2008). Many factors determine what conditions are "serious" including severity of symptoms, penetrance, potential for treatment, disease progression, heritability, and age of onset (Krahn, 2009).

The use of PGD to avoid offspring who have inherited mutations that predispose to diseases and are incompletely penetrant is also controversial. For example, mutations in the *BRCA1* and *BRCA2* genes can confer predisposition to certain cancers but do not guarantee that cancer will occur (Ormondroyd et al., 2012). In women, mutations in these genes confer a lifetime risk of up to 87% for developing breast cancer and up to a

44% lifetime risk of developing ovarian cancer. Men who carry mutations in these genes have an increased risk of breast and prostate cancer. Prior to 2006, HFEA only licensed conditions that had close to 100% penetrance, meaning individuals who had a mutation were nearly 100% likely to develop the disorder. In 2006, the HFEA expanded its list of approved PGD uses to include cancer predisposition genes, including *BRCA1* and *BRCA2* (Ormondroyd et al., 2012). According to the HFEA, "in principle, it is appropriate that PGD be available for serious, lower penetrance, later-onset genetic conditions such as inherited breast, bowel, and ovarian cancer" (Krahn, 2009, p. 189). Although some adult-onset conditions, such as breast cancer, can be successfully treated and are not necessarily fatal, the HFEA identifies them as "serious genetic conditions because they cause suffering and are life threatening," and determines that "PGD should be available to test for these cancers" (Krahn, 2009, p. 189).

1.5.2 Variant of Unknown Significance. A more recent development in the use of PGD comes from patient requests for selection against a genetic variant of unknown significance (VUS). A VUS is a deletion, duplication, or nucleotide sequence change that has not been previously defined as deleterious and can be either inherited or *de novo*. A genetic change categorized as a VUS has not been defined as clinically significant or predictive of an individual's phenotype. For individuals that have inherited a VUS, clinical significance and recurrence risk are often difficult to elucidate because of unknown factors such as variable expressivity and incomplete penetrance (Reiff et al., 2012).

This is another controversial issue faced by the PGD community, as it is not definitively known if a VUS is disease causing. There is little published information about the experience of PGD laboratories in terms of testing for these variants. However, according to a genetic counselor at Reproductive Genetics Institute (RGI) in Chicago, there are increasing requests for selection against a VUS in both situations where the VUS is believed (but not proven) to be disease causing, or where there is a significant degree of uncertainty surrounding a particular genetic disease (Besser, 2013). One such disease is Marfan syndrome.

The first reported clinical use of PGD to avoid the inheritance of Marfan syndrome occurred in the mid 1990s (Harton et al., 1996). Marfan syndrome is an autosomal dominant connective tissue disorder, which mainly affects the skeleton, eyes and cardiovascular system (Coron et al., 2012). There is a wide range of phenotypic variability, and while some individuals have severe involvement of multiple organ systems, mildly affected individuals can remain undiagnosed for their entire lives without major health concerns (Harton et al., 1996). Preimplantation genetic diagnosis is usually feasible if a known pathogenic mutation in the *FBN1* gene is identified. However, most mutations in the *FBN1* gene are private, and therefore molecular sequencing of this gene often identifies a VUS. Given the uncertainty surrounding a VUS and whether it is truly causing a patient's clinical diagnosis of Marfan syndrome, it is often difficult to counsel patients about what this result can mean for future children. Performing PGD for a VUS for Marfan syndrome does not guarantee that a child will not have Marfan syndrome, since it is possible that another pathogenic mutation exists but is unidentifiable with

current technologies. Therefore, the appropriateness of PGD or prenatal diagnosis for a VUS is questionable, and with the increasing availability of multigene sequencing panels and whole exome/genome sequencing, is likely to become a frequent and significant issue in the field.

1.5.3 Use of embryos with genetic disease after PGD revealed no disease-free embryos to be available. Another controversial use of PGD is use of embryos with genetic disease after PGD reveals no disease-free embryos. Some couples deliberately select for a child with a genetic condition typically because at least one member of the couple has that disorder, like deafness or dwarfism (Baruch, 2009). For example, a woman with achondroplasia may choose to implant embryos with the disorder because her small physical stature would affect her ability to carry an average size baby. Several PGD laboratories have stated that individuals seeking to use PGD to intentionally select for diseases or disabilities would not be offered PGD (Baruch, 2009). However, it is possible that during the PGD process, no healthy embryos are available for transfer. In this situation, patients want a healthy child but do not have healthy embryos for transfer. Couples must then choose whether or not to start over or use one of the affected embryos.

1.6 Ethical Considerations For The Use of PGD

Although a valuable and useful technique, PGD has ethical challenges associated with its uses. Currently, there is much debate regarding the appropriate parameters for the use of PGD (David, Weitzman, Herve, & Fellous, 2012). There is also discussion regarding whether PGD is "an obligation or good practice" (David et al., 2012, p. 625).

Some argue that "it is time to recognize that impairments occur along a continuum" (Miller & Levine, 2013, p. 100). On one end of this continuum there are conditions such as congenital deafness, which may not have a significant impact on health or life expectancy. On the other end of the spectrum, conditions like Tay-Sachs disease cause significant suffering and a shortened lifespan. It is argued that "value judgments regarding the quality of life of a person with a given disability must be made by the individual who lives with the disability, not by the researcher or clinician" (Miller & Levine, 2013, p100). Many individuals with disabilities and/or genetic conditions have found their lives to be fulfilling and valuable. The disability community has expressed concern about the intention and outcomes of genetic research; specifically, whether advances in genetic diagnostic technologies are intended to eliminate disability from the population. Specifically, PGD is seen negatively by some members of the disability community, as its intention is to prevent the birth of individuals with disability (Miller & Levine, 2013). Some equate this concern to the notion that there will be lower tolerance for individuals with disabilities, as well as increased injustice, stigmatization, and discrimination (Vergeer et al., 1998; Petersen, 2005). For these reasons, some people in the disability community are wary of PGD and see it as a misuse of genetic technology.

Others would argue that selection of embryos with a genetic condition is not the intended use of PGD, and that this technology is only intended to prevent the transmission of genetic diseases to future generations. While PGD was not designed to select for children with diseases or disabilities, a survey performed in 2005 by Baruch et

al. found that three percent of fertility clinics reported having used PGD to select for a particular disease or disability. In all cases, the conditions selected for were forms of deafness or dwarfism (Baruch et al., 2008).

There are arguments that parents have the moral and ethical responsibility to select embryos that have the "best chance in life," and therefore, embryos with a known genetic condition should not be selected for implantation. Other factors to take into account when examining the ethics of reproductive decision-making include procreative autonomy and non-directive counseling (Savulescu, 2001).

The basis of procreative autonomy is that couples are free to decide what kind of children to have, as well as when and how to have these children, even if that means they are selecting for a disability. According to the principle of non-directive counseling, medical personnel should provide patients with information about risks and options to reduce these risks. Specific advice or direction should not be given to patients. This principle argues, for example, that if a couple knowingly chooses to transfer an embryo that is affected with a genetic disease, then the medical professional should not express agreement or disagreement about this decision (Savulescu, 2001).

Some bioethicists argue that children have a right to an "open future" and if their parents choose to "unreasonably limit the life plans available to their child, the child suffers a moral harm" (Smolensky, 2008, p. 3). However, what if prospective parents feel as though they have no other choice because all of their embryos are affected with a genetic condition? According to some, there is a difference between choosing an embryo with a genetic predisposition when you have the option of another healthy embryo with

the “best” chance, and choosing an embryo with a genetic predisposition only because there are no “healthy” embryos. The question becomes, should couples be able to use an affected embryo if no healthy ones are available?

The goal of PGD is to produce healthy offspring by not implanting embryos that are affected with a known disease. In the United States, the use of PGD is often determined by the IVF clinics and PGD laboratories. Although there are professional guidelines to assist with decision-making, these guidelines do not address all possible scenarios that may arise. As there are no regulations regarding the use of PGD, many genetic counselors and other IVF/PGD providers continue to face the ethical dilemmas described.

1.7 Need for Current Study

The purpose of this study is to explore the opinions and attitudes of genetic counselors who work with patients throughout the PGD process. Another purpose is to determine common themes identified by genetic counselors regarding three controversial PGD case scenarios: PGD to select against an adult-onset condition, use of embryos with genetic disease after PGD revealed no disease-free embryos to be available, and PGD to select against a variant of unknown significance (VUS). The information gained from this study will add perspectives from genetic counselors who work with PGD patients to the discussion concerning controversial applications of the technology. Interviews will provide a more detailed description of ethical challenges experienced by genetic counselors and help professional organizations properly guide the use of PGD.

Chapter 2: Walking the Edge with Controversial Use of Preimplantation Genetic Diagnosis (PGD): Opinions and Attitudes of Genetic Counselors[1]

2.1 Abstract

Purpose: This study explored opinions and attitudes of genetic counselors regarding three controversial applications of preimplantation genetic diagnosis (PGD): PGD for early-onset Alzheimer, use of embryos that are *BRCA* positive after PGD revealed no disease-free embryos to be available, and PGD to select against a variant of unknown significance (VUS) for Marfan syndrome. **Methods:** Genetic counselors were contacted through the National Society of Genetic Counselors (NSGC) electronic mailing list. Inclusion criteria required that a participant was currently practicing as a genetic counselor, was a member of the NSGC, and has counseled patients about PGD. Twenty-nine participants volunteered to participate and 24 recorded interviews were transcribed for data analysis. The survey consisted of 34 questions including demographic questions, qualitative questions about each of the three case scenarios, and general questions about PGD. Qualitative analysis was performed using a conventional content analysis approach as described by Hsieh (2005). **Results**: Themes common to all three scenarios included: necessity of appropriate/thorough counseling, the importance of the genetic indications, patient perceptions, and respect for patient autonomy in decision making. Multiple themes were also described for each unique case scenario. The majority (65%,15/23) of

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participants felt PGD for an adult-onset disorder was least controversial, and PGD for a VUS was most controversial. **Conclusion**: Participants felt that PGD was appropriate for life limiting conditions, cases where there was an established diagnosis with a known pathogenic mutation, and when symptom severity and disease burden were significant. Participants agreed that appropriate/thorough counseling was necessary, patient perceptions of 'serious' disease were critical, and patient autonomy were key factors when dealing with controversial applications of PGD. Ultimately, genetic counseling is recommended and patients need to understand the benefits, disadvantages, and the potential outcomes of PGD in order to make the decision that is most appropriate for their families.

Keywords: Preimplantation genetic diagnosis (PGD), controversial, genetic counselors' opinions.

2.2 Introduction

Since the 1990s, preimplantation genetic diagnosis (PGD) has been used to prevent genetic disorders from being inherited by future generations. Individuals who carry a known genetic mutation or chromosome rearrangement can use PGD to identify embryos at risk of inheriting a genetic condition. Indications for PGD include, but are not limited to: sex selection, a previously affected pregnancy/child, one member of a couple is affected with a genetic condition or both carry an autosomal recessive mutation, and to increase the effectiveness of IVF by ruling out aneuploidy, chromosomal causes of miscarriage and failed embryo implantation (Hershberger & Pierce, 2010; Chang et al., 2011). However, given the advancements in genetic testing and expansion of knowledge

in the field of genetics, PGD has been used for other indications, some of which are controversial.

Professional guidelines from the American Society of Reproductive Medicine (ASRM) and the Human Fertilization and Embryology Authority (HFEA) explicate appropriate utilization, yet these guidelines do not address all possible scenarios that may arise. Therefore, many genetic counselors and other IVF/PGD providers continue to face ethical dilemmas.

Here we discuss the opinions of genetic counselors regarding three controversial uses of PGD: (1) PGD for early-onset Alzheimer, (2) transferring male embryos which carry a *BRCA1* mutation when no unaffected embryos are produced, and (3) PGD for a variant of uncertain significance (VUS) for Marfan syndrome.

2.3 Materials and Methods

2.3.1 Participants. After receiving Institutional Review Board approval from the Office of Research Compliance, University of South Carolina, Columbia, SC, an invitational letter (Appendix A) was sent through the National Society of Genetic Counselors (NSGC) electronic mailing list to genetic counselors, inviting their participation in our study. The inclusion criteria required that a participant was currently practicing as a genetic counselor, had counseled patients regarding the use of PGD, and was a member of the NSGC. The Assisted Reproductive Technologies and Infertility Special Interest Group (ART/Infertility SIG) of the NSGC also forwarded an invitational letter to its members.

2.3.2 Research Methods. Individuals who responded to the invitational letter were asked for their verbal consent (Appendix B) before accruing into the study and proceeding with the survey (Appendix C). Consenting participants were interviewed by telephone and all interviews were recorded to maintain the veracity of the data. The survey consisted of 34 questions and required 25 to 45 minutes to complete (see Appendix C). Six demographic questions were followed by qualitative, semi-structured, open ended questions about each of the three case scenarios (21 questions), and general questions about the use of PGD (7 questions). No identifying information was collected. The survey questions were used to assess participants' opinions and attitudes about each case scenario and their opinions on controversial uses of PGD technology.

2.3.3 Statistical Analysis. The audio recorded interviews were transcribed and verified for accuracy by the principal investigator (first author). Qualitative analysis was performed using a conventional content analysis approach as described by Hsieh & Shannon (2005). This approach allows for the identification and coding of data that reflects the participants' views and opinions of the scenarios presented. During the analytic process, patterns emerged from the codes and were classified into categories. The categories formed the basis for emergent themes and sub-themes. An advantage of conventional content analysis is that it gains "direct information from study participants without imposing preconceived categories or theoretical perspectives" (Hsieh & Shannon, 2005, p. 1279-1280). Thus, this analytic method was selected for our study because it identifies themes that are intended to help understand participants' unique

perspectives. Consistent with content analysis, frequency counts were performed, when appropriate, during data analysis.

2.4 Results

Twenty-nine participants volunteered for the study; two participants were excluded as they did not meet inclusion criteria. Three audio recordings were unusable; therefore, a total of 24 recorded interviews were transcribed and used for data analysis.

2.4.1 Demographic Data. Table 2.1 shows the distribution of participants' gender, age, years of practice as a genetic counselor, number of years they have counseled for PGD, number of PGD cases seen per month, setting of practice, and region of practice. The large majority of participants were women, 96% (23/24). Most participants were between the ages of 25 and 30 years of age, 42% (10/24), and had less than one year to five years of experience practicing as a genetic counselor (54%, 13/24). Fifty-four percent (13/24) had been counseling for PGD for zero to five years and 42% (10/24) typically counsel for PGD one to five times a month. Six of the 24 participants counsel greater than 20 PGD cases a month. The largest group of participants indicated that they were working in settings other than reproductive endocrinology clinics or PGD laboratories, 54% (13/24). These settings included maternal fetal medicine clinics, pediatric clinics, and adult clinics. Twenty-five percent (6/24) indicated they worked in a PGD laboratory setting and 21% (5/24) indicated they worked in a reproductive endocrinology setting.

Table 2.1
Demographics

Demographic	% of Participants	Number of Participants
Gender		
Male	4.2%	1
Female	95.8%	23
Age		
< 25	4.2%	1
25-30	41.7%	10
31-35	16.7%	4
36-40	12.5%	3
41-50	16.7%	4
> 51	8.3%	2
Number of years in practice as a genetic counselor		
0-5	54.2%	13
6-10	12.5%	3
11-15	16.7%	4
16-20	4.2%	1
21-25	8.3%	2
>25	4.2%	1
Number of years participants have counseled for PGD		
< 1	8.3%	2
1-5	54.2%	13
6-10	20.8%	5
11-15	12.5%	3
16-20	4.2%	1
Number of all PGD cases seen per month		
< 1	16.7%	4
1-5	41.7%	10
6-10	8.3%	2
11-15	4.2%	1
16-20	4.2%	1
21-30	8.3%	2
> 30	8.3%	2
> 50	8.3%	2
Setting of Practice		
PGD Laboratory Setting	25%	6
Reproductive endocrinology	20.8%	5
Other	54.2%	13
Region of Practice		
Region 1	20.8%	5
Region 2	25%	6
Region 3	4.2%	1
Region 4	25%	6
Region 5	8.3%	2
Region 6	16.7%	4

2.4.2 Conventional content analysis. Conventional content analysis was used to analyze data obtained from recorded interviews. Themes and key words were identified from answers given by each of the 24 participants and quotes were used to illustrate and support the identified themes. Frequency counts were also used for certain questions.

2.4.3 PGD for an adult-onset condition. For PGD for early-onset Alzheimer's disease, participants were first asked if this scenario raised any concerns for them, and if so, what concerns were raised. Of the 24 participants, 58% (14/24) stated that PGD for this reason raised no concerns and 43% (6/14) of those participants were not concerned because of patient autonomy. From those 14 participants, 21% (3/14) stated they were comfortable offering PGD for any adult-onset condition including early-onset Alzheimer. Forty-six percent (11/24) of participants raised several concerns. Several themes emerged, including: effects on counselors' comfort, psychosocial topics, and autonomy of the child and spouse.

2.4.3.1 Effects on counselors' comfort levels.

Necessity of appropriate/thorough counseling

Several commonly shared concerns regarding PGD for adult-onset conditions were noted. For 17% (4/24) of the counselors interviewed, the specific mutation in the discussed scenario predisposed, but did not guarantee, a person to have early onset disease. Therefore, penetrance of the condition affected counselors' comfort levels of using PGD:

"I think one of my main concerns is whether it is one of those conditions for which having the mutation is a given to getting the diagnosis or it is a pre-disposing factor so those conditions that PGD would be used to detect predisposition I think are a little harder to swallow ethically than those which the mutations kind of equals the disease state at some point" (S)

"I think that if it were a highly penetrant mutation, my concerns would be lessened…" (B).

Having a known mutation influenced 13% (3/24) of participants' comfort level for offering PGD:

"It doesn't raise any significant concerns for when there is a clear genetic cause that leads to an increased risk for an adult-onset condition such as early onset Alzheimer…" (K)

"I think people should be able to do this for any reason that they choose as long as there is evidence to support that it should be done…" (F).

If patients choose to pursue PGD for an adult-onset condition, 29% (7/24) of participants agreed that it is the patient's right:

"I don't feel that it is my place as a counselor to tell that couple that they couldn't use it…" (W)

"I just try and let my patients make the choice that's right for them" (C).

Three participants (13%, 3/24) wanted patients to understand that otherwise healthy embryos could be discarded and potentially their could be future treatments:

"Part of the genetic counseling for PGD is making sure that the couple is aware of the implications of discarding otherwise healthy embryos" (N)

"A potential concern would be the possibility of anything adult-onset, is will treatment become available by the time a potentially affected child would be born and have and be at risk for this" (Q).

2.4.3.2 Psychosocial Topics. Twenty-one percent (5/24) of participants considered the patient's perception of which conditions were "serious enough," concerning, or burdensome as important and 20% (1/5) of these participants considered PGD an opportunity to spare the child:

"Ultimately is that something that the patient wanted to do and felt that it was important enough…I would continue to counsel them appropriately" (B)

"What I always try to tell my patients to think about is how burdensome has this disease been in your own life…for some patients it feels like a huge huge burden to know that this is coming later down the road and for them the idea of being able to spare that for their child is a really big gift" (C)

"I think that if it's concerning for the couple and they want to choose to avoid a pregnancy that is at risk for early-onset Alzheimer then they can…" (E).

Concern for the family

Eight percent (2/24) of participants were concerned that PGD for this reason, undervalued the life of the patient and other affected family members:

"Just because they'll have Alzheimer let's say at 55, doesn't mean that they might not win a Nobel Prize at 40…" (N)

"I would be concerned that the parent is undervaluing their life or the life of their family that had been affected with the disorder" (A).

Eight percent (2/24) of participants stated children would not exhibit symptoms for many years and if a laboratory error occurred and an affected embryo were transferred, the child's autonomy would be violated. In total, 13% (3/24) of participants were concerned about the potential child's autonomy:

"The pre-child, the un-conceived child… can't consent to that testing…we don't have a fetus yet and the whole point is to avoid having a fetus who would have the gene…it is kind of semantic on one level but I see it on both as if there is not yet a person who would not need to consent…" (U).

Participants were next asked how they felt about PGD to identify embryos at risk for early-onset Alzheimer's disease. The two themes that emerged were: comfortable and patient autonomy.

2.4.3.3 Comfortable. The majority of participants (83%, 20/24), were comfortable with PGD for this use; however, 60% (12/20) still had concerns, including: necessity of appropriate/thorough counseling, penetrance, patient's perceptions, and propriety of this use of PGD. Thirty-five percent (7/20) of the comfortable participants agreed this was an appropriate use of the technology: *"If it is something that is important to the patient then I think that's a valid use of the technology" (C).*

2.4.3.4 Patient autonomy. Eight percent (2/24) of participants were not comfortable using PGD in this situation but would support the family regardless. Fifty percent (1/2) of those participants were concerned that a *PSEN1* mutation was not 100% penetrant and

this was not an ideal use of the technology (2/24), however, they would support the patient as long as appropriate counseling occurred (3/24):

> *"I feel kind of unhappy about that…I think a lot of what it comes down to is the level of education provided to the couple I think. And I feel pretty strongly in general that if they really have a good handle on what the limitations of the testing are and they understand …that it would be a predisposition, it would not be a given, and they still maintain that they are still really interested in pursuing it then I would be more comfortable" (S)*
>
> *"The biggest concern with that [BRCA mutations] could be discarding an embryo that while it carries the mutation a person may never have actually had cancer" (Q).*

Fifty percent (12/24) agreed they would support the patient's decision and 33% (4/12) stated the patient should determine if the condition is "serious enough":

> *"For someone that watched a family member die from early-onset Alzheimer I can see why they would want to prevent having a child with it…so that they can give their child a better life. You know I feel like that is a completely unselfish reason to do PGD because it is not helping them at all because they probably will not live to see their child diagnosed with it. They are ensuring that their child will not get early onset Alzheimer" (B)*
>
> *"That particular family knows the disease better than anybody else. And if they feel that the disease is, you know, it is bad enough to warrant PGD and embryo testing then you know that is their decision" (D)*

"I do not have a problem…because I care more about what the patient thinks than what I think. And I think that the patient's concerns given her life experience, given her family experience that she is deciding for her own children, I am on board" (H).

Eight percent (2/24) of participants believed that even though this is an option for patients, it was not necessarily the most ideal use of PGD: *"I feel that while it might not be the ideal use of PGD it's certainly not the worst use of PGD" (M).*

Participants were asked about previous experiences counseling PGD cases for adult-onset conditions. Twenty-five percent (6/24) have never counseled patients about PGD for adult-onset disorders, versus 75% (18/24) had previous experience with such cases. Of the participants with experience (75%, 18/24), 56% (10/18) have had cases of Huntington's disease and 5 of those 10 participants (50%), have also counseled for cancer predisposition syndromes (i.e. Lynch syndrome, FAP, and BRCA1/2). In total, 67% (12/18) have counseled for cancer predisposition syndromes, 50% (6/12) of those that have counseled for cancer syndromes have not counseled other adult onset disorders. One participant (6%, 1/18) counseled a single patient about PGD for Alzheimer's disease.

Regarding participants' experiences counseling about PGD for adult-onset disorders, participants were asked about their concerns. Of the 18 participants with experience, 33% (6/18) had no concerns and 67% (12/18) had concerns. From this data we established the following themes: non-disclosure/ exclusion testing and necessity of appropriate/thorough counseling.

2.4.3.5 Non-disclosure/ Exclusion testing. Fifty percent (5/10) of the individuals who have counseled about PGD for Huntington's disease were concerned about non-disclosure testing and 60% (3/5) of those participants were concerned patients might accidentally learn their mutation status:

> *"My biggest concern was for the non-disclosure Huntington patients. Patients who themselves did not want to know their status but still wanted to do PGD to make sure their kids didn't have it. And I felt there was a lot of psychosocial things that could be explored with those patients" (A)*
>
> *"My primary concern is that we were going to blow it somehow and we were going to give her, you know her results" (F)*
>
> *"There is still a test result out there and even though the lab and whoever is involved would do anything it can to make sure that information is not released, certainly there are instances where mistakes can happen" (T).*

Twenty-five percent (3/12) of participants were uncomfortable with discarding healthy embryos after exclusion testing for Huntington's disease or carriers of cancer predisposition gene mutations: *"You might be discarding embryos that are completely unaffected" (T).*

2.4.3.6 Necessity of appropriate/thorough counseling. Adult-onset conditions are complex and psychosocially challenging for couples and counselors. Sixty-seven percent (8/12) of participants felt appropriate counseling was crucial when dealing with such cases:

"As long as the family or the couple is appropriately counseled about, the benefits and limitations of the technology and really understands the ins and outs and understands they are not using embryos that other than developing Alzheimer at an earlier than expected age but can have an otherwise, healthy life as long as they understand all of those aspects then I think they have the decision to make the reproductive choice that makes the most sense to them" (Q).

Seventeen percent (2/12) of participants said PGD prevents suffering for future generations; although one of the two participants stated patients need to understand that risk to a potential child is not completely eliminated, as well as the potential for treatments to become available in the future:

"So I think in those cases [cancer predisposition syndromes] we felt like it was definitely a good reason to prevent suffering in a person down the road" (S)

"She was not interested in having her children necessarily be…having to go through that knowing that they already would probably have to deal with her health issues" (V)

"We talked about the concerns that it's not going to eliminate the risk of cancer and there could be…they could have a PTEN mutation and we didn't test for that" (V).

"I think that one [BRCA] is a little bit trickier for people because unlike Huntington's there are actually things you can do to help prevent or reduce the risk of cancer…because that is something that there is at least some action that you can take I think that one is a little bit harder for people to understand" (T).

Lastly, participants were asked how comfortable they were offering PGD for any adult-onset condition. On a scale of one to five, where one was not comfortable at all and five was very comfortable, the majority of participants, rated themselves as a four (38%, 9/24) or five (33% (8/24) (see Figure 2.1).

2.4.4 Use of embryos with genetic disease after PGD revealed no disease-free embryos to be available. Participants were asked if they had any concerns regarding the transfer of a male embryo that carries a *BRCA1* mutation when no unaffected embryos were produced. Themes that emerged from discussion were: necessity of appropriate/ thorough counseling, patient autonomy, and implications of gender selection.

2.4.4.1 Patient autonomy. Forty-two percent (10/24) understood couples' reasoning for transferring a male carrier because the risk of cancer is less in a male. Forty-two percent (10/24) agreed that it is the patient's choice and 60% (6/10) of those 10 felt that couples were making a well informed decision. One individual (4%, 1/24) was worried about the autonomy of the child since his genetic status would be known from birth:

> *"They have completely eliminated that person's decisions of whether or not to do testing as an adult. So I would be curious, I would want to explore with the parents about are they planning on telling their son this information and I do not know what the right answer to that questions is….you are also leaving that son with having to make the same decisions when he becomes of child bearing age" (V).*

2.4.4.2 Necessity of appropriate/thorough counseling. Twenty-five percent (6/24) of participants had no major concerns and 50% (3/6) of those stated couples were choosing the "less risky" sex. Twenty-nine percent (7/24) of participants were concerned the potential male child's future children are now at risk of inheriting the mutation and 86% (6/7) of those seven participants agreed couples need appropriate counseling to be fully informed of the long term ramifications of transferring a male with a *BRCA1* mutation. In total, 58% (14/24) stated that appropriate genetic counseling was important:

> *"What if that poor man has daughters someday…a lot of things that they need to think about and those cases I would really really hope there is a genetic counselor helping them make the decision to implant that embryo. While a reproductive endocrinologist is very interested in getting them pregnant with a healthy baby, perhaps they are not equipped to really help the couple see long term ramifications of that decision" (A).*

Thirty-eight percent (9/24) responded couples may not understand a male's cancer risk is not zero and could still develop cancer in his lifetime:

> *"I think the most important thing in this situation is to make sure that they realize that a male embryo is not without risk…that there is increased risk for certain types of cancer…and to make sure they realize that it is not a totally risk free option" (R)*
>
> *"Just because it is a male, it does not mean that he would have no risk of any type of cancer" (S).*

2.4.4.3 Gender selection. In total, 13% (3/24) felt this was more about gender selection than choosing a male embryo with "less risk" of cancer and one participant (33%, 1/3) responded that for females with a *BRCA1* gene mutation, there is increased surveillance and medical management options available:

> *"Breast cancer is somewhat preventable with increased surveillance and choosing a male while it reduces his personal risk of breast cancer, you know it is still not changing the risk for his children, his future offspring. Breast cancer is kind of a tough one because it is very manageable. And it feels like gender selection" (B).*

Participants were asked how they felt, in general, about patients using affected embryos when no unaffected embryos were produced. Common topics that emerged were comfort, propriety of the use of this technology, and patient autonomy. Twenty-nine percent (7/24) were comfortable with patients transferring affected embryos when no unaffected embryos are produced and 100% of the seven participants agreed that it was the patient's choice, which they would support. In total, 75% (18/24) of participants would support the patient's decision to transfer an affected embryo. Thirty-three percent (8/24) did not think this was an appropriate use of PGD technology, however, 38% (3/8) would support the patient regardless.

Participants were asked if they had previous experience transferring affected embryos when no disease free embryos are available after PGD. Twenty-five percent (6/24) had encountered cases where couples transferred affected embryos after PGD, 75% (18/24) had not. When asked which conditions couples have transferred affected

embryos for, two of these six participants stated the conditions were cancer predisposition syndromes and one of these participants reported a case of Charcot-Marie Tooth disease. Two participants reported cystic fibrosis cases and one reported a case for aneuploidy.

These six participants were asked if they had any concerns regarding cases where couples transferred affected embryos after PGD. One participant (17%, 1/6) stated that she had no concerns and the other 83% (5/6) had concerns. The main concerns that emerged were confusion and frustration.

2.4.4.4 Confusion and frustration. Participants with concerns about patients transferring affected embryos used key words/phrases such as "why", "I don't understand", "it's confusing." For 80% (4/5) that had concerns, a main concern was the health of the child. Sixty percent (3/5) felt this was not the intended use of the technology and two of those three participants were frustrated and confused by patients wanting to transfer affected embryos. In total, 60% (3/5) expressed frustration/confusion:

> *"I wanted to say to the family, "then why did you do the test,"…It is confusing…I think there is some frustration and then I think in my mind I am also saying to myself this could be a sick child. You have done all of this, and you are going to have a sick child, but then that is their decision" (A).*

One participant worked with a couple that transferred a non-viable aneuploid embryo after the physician stated the test may be inaccurate. This participant expressed her frustration and anger in the following statement:

> *"The whole point of people doing this they want to improve their pregnancy rate, they want to improve the implantation rate and they want to reduce the chance of*

loss so you are talking about aneuploidy cases so they do not want to have a baby with a chromosome problem, they are not having a loss or a child born with something like Down syndrome. So to me it seems a little almost disingenuous for the physician to say well it may not be accurate let us just transfer" (I).

This same participant stated it would only take one wrongful life lawsuit before reproductive endocrinologists would change their clinic policies:

"I am sure all it will take is just one lawsuit where someone will get pregnant and it will be a funky mosaic…and the patient is going to say, you know what I, I don't understand, now I am sitting here, I am in this horrible situation, my baby, my pregnancy is this and that and the other is probably going to say something like that and a lawsuit before physicians, IVF physicians will think a little bit more about whether they transfer these abnormals" (I).

In total, 100% (5/5) of the participants with concerns agreed that ultimately it was the patient's choice to transfer affected embryos and regardless of their own personal beliefs, counselors would support patient autonomy.

Lastly, participants were asked how comfortable they were offering PGD to a patient that would use affected embryos for any condition. On a scale of one to five, where one was not comfortable at all and five was very comfortable, the majority of participants, 71% (17/24), rated themselves as a three or less (see Figure 2.1).

2.4.5 PGD for a VUS for Marfan syndrome. Participants were presented with the unique case scenario of using PGD for a VUS for Marfan syndrome and asked if this scenario raised any concerns for them and, if so, what concerns. Thirteen percent (3/24)

of participants reported no concerns and 88% (21/24) raised multiple concerns. A significant amount of participants shared many common concerns, from which, emerged several themes: uncertainty, directiveness of counseling provided, and lack of risk reduction. For the "uncertainty" theme, two sub themes emerged: necessity of sufficient evidence and is PGD necessary.

2.4.5.1 Uncertainty.

Necessity of sufficient evidence

Ninety-one percent (19/21) of participants were concerned that we cannot be 100% certain a VUS is disease causing and 68% (13/19) of these individuals strongly encouraged family studies and felt more information/sufficient evidence was needed regarding the pathogenicity of the variant in question in order to feel more comfortable using PGD for a VUS. In total, 71% (15/ 21) stated sufficient evidence from family studies was needed:

> *"We actually request family studies…we actually thoroughly discuss with the couple doing PGD for this if it is not the cause you are not reducing risk" (I)*
>
> *"Because of the ambiguity…I would have a very lengthy discussion about…the fact that it is a VUS, it is not a known deleterious mutation, we could be deciding not to transfer embryos based on…incomplete information…I would also strongly suggest family studies…there would be a lot of counseling that would go with it" (K).*

A main concern for 10% (2/21) of participants was the exclusion of healthy embryos in the event that the VUS was, in fact, a benign polymorphism:

"I think the concern that you would be discarding embryos that are not actually affected…that is probably the biggest one" (R).

Is this necessary?

Forty-three percent (9/21) questioned if PGD was necessary and 78% (7/9) said it was not a proper use of the technology:

"I feel uncomfortable with the use of PGD for a VUS…We do not even know whether it is the cause, does not seem like a great idea to me…" (S)

"Just a straight up variant of unknown significance, then I do not really think that PGD has a big, large role to play in that" (P).

2.4.5.2 More directive counseling style. Eighty-one percent (17/21) responded that PGD requests for a VUS would require more extensive counseling sessions and were more likely to use directive counseling in this situation:

"I would have lots and lots and lots of talk about how unsure this is and this probably the scenario that I would be most likely to be directive that it is not a good idea to use PGD" (H).

2.4.5.3 Not reducing risk. Fifty-two percent (11/21) believed that PGD for a VUS for Marfan did not reduce risk and a future child still could inherit Marfan syndrome and should still be assessed for a connective tissue disorder:

"I would want to make sure that they fully understand that implanting embryos without the VUS still has some significant risk to create a child with Marfan syndrome" (L)

"I think in the case of with something like Marfan syndrome we would potentially recommend that they have a child evaluated for Marfan and know that it is something running in the family…kind of have them watched a bit more closely" (S).

However, 4% (8/21) of participants that had concerns stated that it was not their place to inform a patient that they could not use PGD for a VUS:

"I am never going to be in a position where I am absolutely going to tell a patient no I am not going to offer PGD because that is not my job…my job is to make sure they are informed" (L).

Participants were next asked how they felt about using PGD for a VUS for Marfan in particular. Thirteen percent (3/24) were comfortable, and 38% (9/24) were uncomfortable:

"Genetics is such a moving target in some ways especially when it comes to sequencing that it just makes me really uncomfortable to use something that you do not know for sure is definitively causative or linked with the disease" (N).

From the other 11 participants, two common themes were established: proper use of the technology and evidence-based medicine.

2.4.5.4 Proper use of the technology. Twenty-seven percent (3/11) questioned if this was a proper use of the technology and whether or not it is a waste of resources, including time, and money:

" I hate to bring anything back to money because you cannot put a price on your child's health and wellbeing but I feel like it would just be kind of a waste of resources unless we have reason to believe that the VUS is disease causing" (B)

"It is kind of giving false hope to the parents" (J)

"I think it is just not enough, that is not an appropriate use of the technology, because we are not sure that we are preventing the disease and thinking that we are when maybe we are not can have dangerous consequences" (C).

2.4.5.5 Evidence-based medicine. The other 73% (8/11) felt that their comfort level would depend on the information/ data (i.e. family studies, research, laboratory classification etc.) available and counseling:

"It just depends on how much investigative work has gone on prior to considering PGD" (D)

"It would be concerning to me that we would be doing something without really having the science behind us, we would not really know if we are selecting for or against anything" (W).

When asked if participants had previous experience managing cases involving PGD for a VUS, 46% (11/24) had and 54% (13/24) had not. The 11 participants with previous experience indicated a variety of disorders for which they have counseled for a VUS. These conditions included muscular dystrophy (1/11), polycystic kidney disease (1/11), Fanconi anemia (1/11), cystic fibrosis (2/11), epidermolysis bullosa (1/11), hypertrophic cardiomyopathy (1/11), Treacher Collins syndrome (1/11), Cohen syndrome (1/11), and 2/11 indicated counseling for multiple conditions involving a VUS.

Participants who have counseled PGD cases for a VUS were asked what concerns they had regarding their experiences. All 11 participants had concerns and, again, common themes emerged. These themes were: necessity of appropriate/thorough counseling and risks. A sub-theme of appropriate counseling was "will this truly help the patient?".

2.4.5.6 Necessity of appropriate/thorough counseling. All participants stressed that patients need to be appropriately counseled for fully informed decision making and that counseling must included a special consent process regarding the uncertainties of PGD for a VUS:

"It would require some really, really careful consenting" (V).

Forty-six percent (5/11) stated that sufficient evidence indicating the VUS was disease causing was needed and that family studies should be performed to help determine pathogenicity.

Will this truly help the patient?

Fifty-five percent (6/11) felt there were numerous uncertainties and 50% (3/6) of these individuals questioned if the technology would truly be beneficial to the patient:

"The main thing is counseling them appropriately that this may not be the cause and that doing testing for this may, one it may not be needed and two not reduce the risk whatsoever" (I).

2.4.5.7 Risks. Eighteen percent (2/11) of participants were concerned healthy embryos would be discarded:

"This could rule out embryos that are in fact healthy" (T).

Lastly, participants were asked how comfortable they were offering PGD for a VUS for any condition. On a scale of one to five, where one was not comfortable at all and five was very comfortable, the majority of participants 63% (15/24), rated themselves as a two or less and four percent (1/24) were very comfortable (see Figure 2.1).

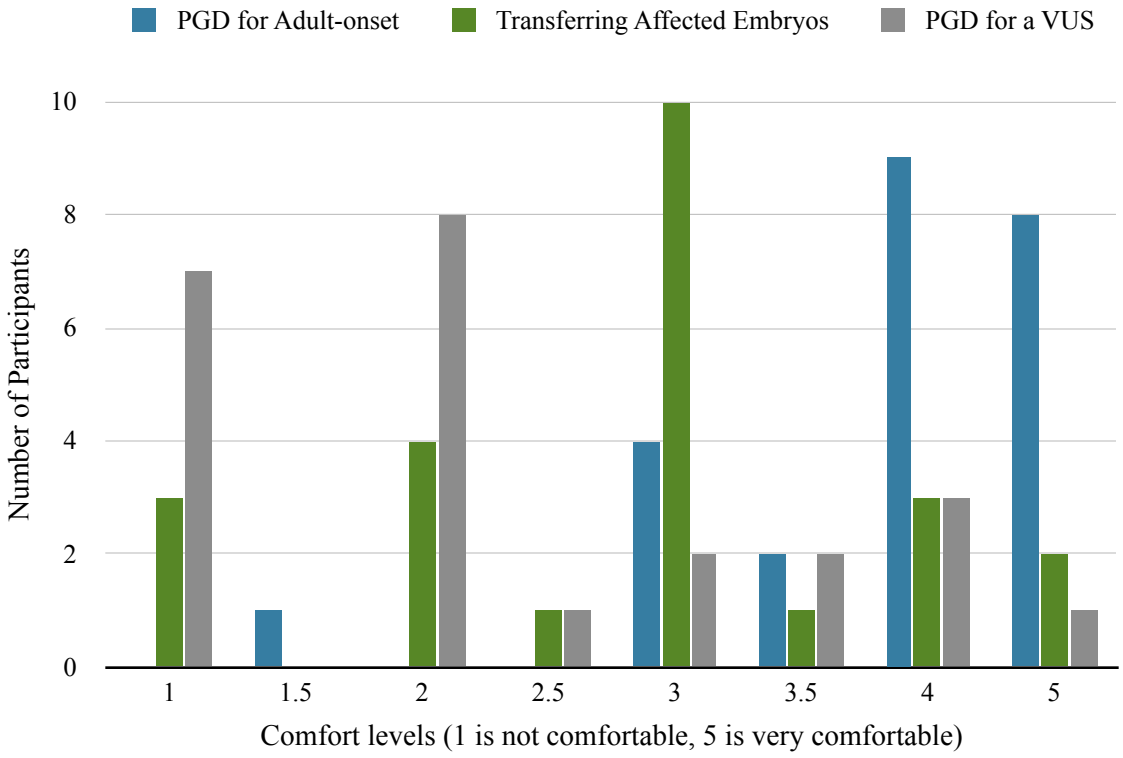

Figure 2.1
On a scale of one to five (one being not comfortable at all, five being very comfortable) participants' comfort levels regarding PGD for any adult-onset condition, transferring affected embryos when no disease free embryos are available, and PGD for a VUS.

2.4.6 General Questions. General questions asked during interviews included ranking the three case scenarios from least controversial to most controversial, what PGD should and should not be used for, key factors in determining the appropriate use of PGD, what the future holds for the use of PGD, and what concerns participants about the potential

uses. Lastly, participants were asked if there were any other controversial uses of PGD they would like to discuss.

Participants were first asked to rank the three case scenarios, PGD for an adult-onset disorder, transferring affected embryos when no disease free embryos are produced, and PGD for a VUS, from least controversial to most controversial. Results were established from 23 participants as one participant felt she could not rank the scenarios in any order. Overall, the majority (65%,15/23) of participants felt that PGD for an adult-onset disorder was the least controversial, and PGD for a VUS was the most controversial (see Figure 2.2).

Of the six participants who counsel greater than 20 PGD cases per month, and work in a PGD laboratory or Reproductive Endocrinology clinic, 50% (3/6) stated that transferring affected embryos was most controversial and these same participants felt that PGD for a VUS was moderately controversial. In total, 8/23 participants stated that PGD for a VUS was moderately controversial (6/8) or least controversial (2/8).

When asked what PGD should be used for, several themes emerged from the discussions. Themes included: having a healthy child, what the patient perceives as severe/burdensome, conditions that are life limiting or cause a diminished quality of life, gender selection for X-linked conditions, and establishing clear risk of a genetic disorder.

2.4.6.1 Having a healthy child. Twenty-five percent (6/24) of participants said that PGD should be used for *"anything and everything" (L)* to have a healthy child:

> *"I think that PGD should be used for all of these things for helping people have the highest likelihood to have a healthy child" (E).*

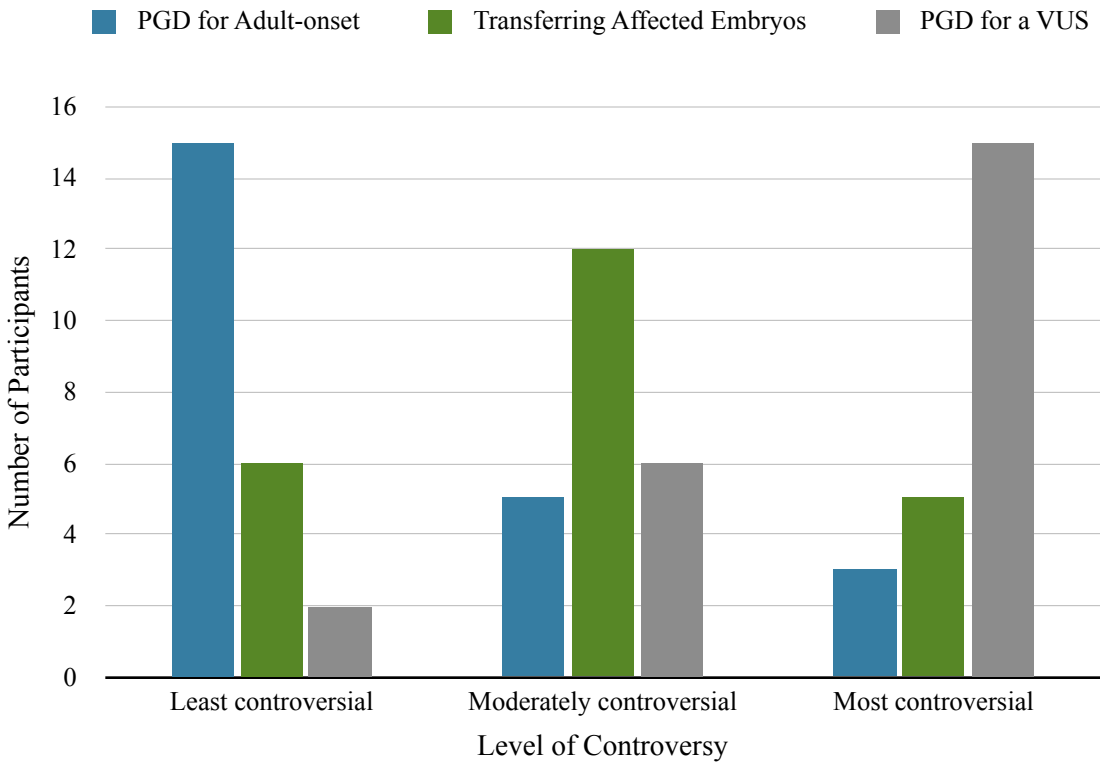

Figure 2.2.
Participants' ranking of the three case scenarios from least controversial to most controversial.

Chromosome abnormalities were identified as another legitimate use of PGD by 25% (6/24):

> *"Most embryos have chromosome issues so the most important thing at this point is viability, PGD really helps us pick the embryos that are most likely to result in viability" (F).*

2.4.6.2 What the patient perceives as severe/burdensome. Forty-two percent (10/24) agreed that PGD is appropriate for couples where the disease causes significant burden to the family:

"PGD should be used for…a serious, life threatening conditions…I think that the definition of severe that is a very broad term and I think it needs to be interpreted in the context of that particular family" (D).

2.4.6.3 Conditions that are life limiting or cause a diminished quality of life. Fifty percent (12/24) responded that PGD should be used to avoid diseases that are life limiting or resulted in a diminished quality of life:

"I think PGD should be used to prevent suffering of a future child" (B)

"It really should be for medical purposes to avoid suffering, to avoid disease… doesn't necessarily have to be childhood onset, doesn't necessarily have to be fatal but that is sort of where the avoiding suffering comes in" (N).

2.4.6.4 Clear risk of a genetic disorder. Forty-two percent (10/24) said PGD should be used in cases where clear risk for a genetic disorder is established. Eight percent (2/24) felt it should be used for highly penetrant conditions:

"It should be used to test embryos for a clear risk for a significant medical issue" (K)

"It should be used in cases where there is a clear risk for a known genetic condition being passed on in a family" (T).

Gender for X-linked conditions

Gender selection solely for X-linked conditions was accepted by 21% (5/24) of participants.

Participants stated that PGD should not be used for gender selection (i.e family balancing, or just general gender preference), conditions that are not life limiting, and selecting for a genetic condition.

2.4.6.5 Gender selection. The majority (71%, 17/24) agreed PGD should not be used for sex selection:

> *"Barebones gender is not a disease and I tend to want to do this to help avoid disease" (I)*
>
> *"I would say sex selection, but even there I have to grapple with that it is that in my heart of hearts I believe that every baby born should be loved and so I believe that if a couple perceives that they would love a baby more because it is a girl or the baby is a boy, I should not stand in the way of creating that family" (G).*

2.4.6.6 Conditions that are not life limiting. Fifty-four percent (13/24) thought PGD for conditions that are not life limiting, including but not limited to positive trait selection, was not an appropriate use of the technology:

> *"PGD should not be used to select for healthy traits, so I do not think it should be used for physical features…I enjoy human variation, I think that we all have a lot to offer" (A)*
>
> *"If somebody wants to prevent polydactyly, I think that would probably be a silly use of PGD… you know anything that is not really life limiting" (B)*
>
> *"It is a good tool to prevent a significant condition from being passed on but not necessarily something to be used to screen out a trait that a couple prefers not to have" (S)*

"Male patterned baldness, if they wanted to use it for something insignificant then I would be like this is such a waste of resources, it is not like impacting quality of life" (X).

Ambiguous genetic information

For 33% (8/24), PGD for ambiguous genetic information such as a VUS, single nucleotide polymorphisms (SNPs), and predisposition genes are other inappropriate uses of the technology:

"SNPs that we do not know, you know like stuff on 23andMe you know the test that have very low relative risk odd scores or low odd risks. They probably do not have much of a place in this" (F)

"I just get uncomfortable when I start thinking about the next generation sequencing and all the SNP chips and all that kind of stuff out there because you and I both know and my argument here is prenatally we don't even know what the hell the SNPs mean so now you are going to do it on an embryo" (I).

"Aside from VUSs…I think there are a lot of genes out there and predisposition type things that just are not ready for prime time in general…for example APOE and the Alzheimer increased risk, I think there are things out there so ambiguous…" (L).

2.4.6.7 Selection for a condition. Eight percent (2/24) said selecting for a genetic condition, like deafness, was also inappropriate.

For key factors in determining the appropriate use of PGD, four common themes emerged. These themes were: diminished quality of life and life span, patient's life experiences, established diagnosis, and patient education.

2.4.6.8 Diminished quality of life and life span. Fifty-eight percent (14/24) responded that diseases that result in a diminished quality of life and therefore are medically significant were key in determining if PGD was appropriate:

> *"I think it should be symptom severity. If you are talking about someone not being able to have a normal life or potentially having a chance of a shortened lifespan then that is a reasonable thing to talk about" (A)*
>
> *"Overall the impact on life or quality of life or what the disease burden is" (Q).*

2.4.6.9 The life experiences of the patient. For 38% (9/24), the patient's life experiences influenced whether or not PGD should be used:

> *"It is their experience that matters, it is not my opinion that matters…For some of them they really do feel a serious burden and a large desire to avoid passing it on to children and so it became very easy to just make sure that every patient knew about their options and to let them then direct me regarding how much they wanted to know about it" (C).*

2.4.6.10 There is an established diagnosis in the family. Thirty-three percent (8/24) agreed that PGD was appropriate for an established diagnosis and known mutation:

> *"I think the biggest thing is to make sure that you are operating, that you are working with things you know, that you can confirm the mutation" (W).*

2.4.6.11 Patient education. Lastly, 42% (10/24) determined that PGD was appropriate if the patient was well educated:

> "*I think the most important thing is education, I think that our biggest job is to make sure that patients understand the process, the goal of the testing and you know possible hang ups and what the potential outcomes are and beyond that I think that you know your biggest job is to provide education on it and it is the patient's job to figure out what options are going to be best for them" (H).*

Participants were next asked what the future holds for the use of PGD and if they had any concerns regarding its potential uses. Themes that were established included: testing for things that are not medically significant, expansion of genetic testing of embryos, accessibility, misconceptions about PGD, lack of genetic counselors in fertility clinics, and advancements in PGD technologies. A sub-theme of testing for non-medically significant traits was eugenics.

2.4.6.12 Expansion of genetic testing of embryos. Fifty-eight percent (14/24) believe expansion of genetic screening of embryos, through next generation sequencing and whole exome sequencing, is inevitable and 57% (8/14) of these participants were concerned:

> *"You know what is funny about that to me?…That we will not be able to put back any embryos" (G)*
>
> *"You are not going to have any "normal" embryos" (I)*
>
> *"If we start testing for "everything", and association risk and what not, we are not going to have any embryos to transfer because we are all at risk for*

something, we all carry things, we all, we are human beings, we are susceptible to disease, sometimes pretty severe disease, so I, we need to keep it in check to a certain degree (K).

2.4.6.13 Testing for traits that are not medically significant. Thirty-eight percent (9/24) felt eventually more ambiguous, mundane, non-medically significant traits would be commonly tested for and all nine of these participants along with seven other participants, 67% (16/24), were worried about this occurring:

"If we start to do PGD you know for what we might term less severe conditions or just multifactorial conditions we are going to reduce a lot of the variation in our society and I would hate to see a society of perfect people where the few people who are not perfect are left out" (B)

"With the use of exome sequencing it is going to be a lot more common for people to do PGD for non-medical reasons…What could be the evolutionary long term…what are going to be the down stream affects of …other mutations that when we do that become more evident…are we going to find out that when we select for those genes that there are unintended consequences…is it going to lower the diversity in the population" (M).

Eugenics

Forty-four percent (7/16) of this group of participants are concerned this would lead us down the path of eugenics and a "GATTACA" like future and 29% (2/7) were worried people may someday be required to do PGD:

"I do not want to live in GATTACA you know I do not want to live in a society where people have to use PGD to reproduce, I do not want to live in a society where we will not let people have kids on their own, I do not want us to have to test every embryo and make everybody do that to have a child that that sounds crazy but…that does scare me" (F).

However, 8% (2/24) of participants were not concerned about the potential uses, such as positive trait selection, because genetics are extremely complicated:

"I do not have any concerns…that is how much I believe in how stupid we are. And that is how much I believe in the complexity of life and that is how much I believe that yes so when things happen in a lab they are incredibly artificial. And once again, I might be naive, is that health care professionals have their own internal checks and balances that we will never run on luck. And we will never do things that are unethical and immoral" (G).

2.4.6.14 Accessibility. With regards to accessibility, affordability, and improved techniques, 42% (10/24) of participants hoped or believed more people will have access in the future:

"Unfortunately it remains unavailable due to cost for a lot of my patients, so that is a concern that I have, I wish it were more available for those patients and I do not know that if it is ever going to become too available because lots of patients are not going to be ever willing to go through the process of IVF which is what is required for PGD" (L).

However, 17% (4/24) are worried about possible class discrimination with only the wealthy being able to afford PGD:

"People just you know they feel that everything they want and they want it now immediately or ten minutes ago, because it is expensive, it is very expensive and a lot for people to go through, it is definitely its own niche [of people]" (R).

2.4.6.15 Misconceptions about PGD. Seventeen percent (4/24) were concerned about the public's/patient's misconceptions:

" I often get questions from families "well what can we test for?" Sometimes jokingly but sometimes partially serious they ask "do we have the ability to test for intelligence?" and things like that…I think the general public has misconceptions about what we actually can and cannot do" (Q)

"In Hollywood right now it [genetics] is evil, it is the bad guy. Every zombie movie is because of a genetically engineered virus and I always like to see how science fiction kind of predicts society's biggest fears and most of them happen to be genetics right now and it is fun to talk to people and say you know what honestly, that [designer babies] is not to far in the future, but no in medical genetics that not really the focus" (U).

2.4.6.16 Lack of genetic counselors in the reproductive endocrinology field. Because there are not enough genetic counselors in fertility clinics, 25% (6/24) were concerned that reproductive endocrinologists will inappropriately use PGD:

"I am more concerned about the REIs, but I think most PGD labs…understand why PGD was developed and would not be comfortable offering that to families

and I would hope that REIs would not feel comfortable offering it to their patients" (D)

"There is going to be an extremely large need for genetic counselors and very thorough consenting and very thorough data analysis, I do not think we have the man power for that so my fear is that things are going to fall in the hands of the reproductive endocrinologist and things are going to be done irresponsibly" (V).

2.4.6.17 PGD is advancing. Finally, 8% (2/24) were adamant most people do not realize how fast this field is advancing:

"People do not really know what is happening in the field, it is moving very quickly, we tend to focus on things that are hypothetical, they are actually happening…We like to think about "hey you know should we pick BRCA that sounds fine"…it is not a scenario anymore, it is actually happening, we need to be ready for it and I don't think we are" (F).

Lastly, participants were asked if there were additional controversial aspects of PGD. Forty-six percent (11/24) of the participants felt the study scenarios captured the essence of controversial indication for PGD and the slippery slope that genetic counselors find themselves traveling. The other 54% (13/24) of participants mentioned subjects such as non-disclosure testing (8%, 1/13), *BRCA* positive patients being put on injectable hormones (8%, 1/13), preimplantation genetic screening (8%, 1/13), HLA matching (8%, 1/13), the lack of guidelines (15%, 2/13), and gender selection (8%, 1/13) as other controversies they have personally faced.

2.5 Discussion

This study is one of the first to assess the opinions of genetic counselors regarding controversial applications of PGD. Although practice guidelines put forth by the American Society of Reproductive Medicine (ASRM) address specific topics of PGD, such as adult-onset conditions, there are still gaps in the information regarding applications that are controversial. This study looked at three such applications including: PGD for adult onset predisposition to disease, use of embryos with genetic disease after PGD revealed no disease-free embryos to be available, and PGD for a VUS. Genetic counselors who have counseled PGD cases were questioned about these three applications, and from these discussions themes were established from their opinions, thoughts and concerns.

From the discussions we determined that certain factors influence counselors' comfort of PGD being used for adult-onset conditions, transferring affected embryos when no disease free embryos are available, and testing for a VUS. Themes common to all three scenarios included: the need for appropriate/thorough counseling, the importance of the genetic indication, patient perceptions, and respect for patient autonomy in decision making.

2.5.1 Need for appropriate/thorough counseling. Appropriate counseling included review of the benefits and limitations of PGD, education about the disease, and addressing psychosocial elements. In order for patients to be fully informed, several topics should be covered. For adult-onset disorders, many genes, including *PSEN1* and *BRCA* mutations, are considered predisposition genes that are not 100% penetrant.

Mutations in predisposition genes cause increased susceptibility to developing a particular disease but do not guarantee that symptoms will occur in the person's lifetime (Ormondroyd et al., 2012). For some counselors, PGD for predisposition genes or genes that exhibit reduced penetrance is more difficult to accept as there is not a 100% risk to the individual. Part of this concern is that we could potentially be discarding embryos that are otherwise healthy and these potential children could have led fulfilling lives. Therefore, for some counselors, the penetrance of the condition can affect how comfortable they are using PGD. Another key discussion to have with patients is about the potential of disease treatments or potential cures in the future.

While the risk of cancer developing in a *BRCA* positive male is significantly less than a female's risk, it is not negligible. Also, a *BRCA* positive male's future children are at 50% chance of inheriting the same mutation. The potential male child resulting from the transfer of a known *BRCA* positive embryo may someday be put in the position of deciding to use PGD for his own children. Although this type of scenario has the potential for causing "uneasy" feelings in genetic counselors, most participants in this study understood the patient's reasoning for selecting a male embryo. Per Savulescu (2001), if a couple knowingly chooses to transfer an embryo that is affected with a genetic disease, then the medical professional should not express agreement or disagreement about this decision.

Counseling for PGD should include discussion of all possible outcomes, so that on the day of embryo transfer, couples are not forced to make immediate, emotionally laden decisions. This includes the possibility that all embryos may be affected.

Therefore, genetic counselors need to assist patients in considering a course of action for each potential outcome. Patients also need to understand a potential child's risk of developing the disorder in question and the long term ramifications of such a decision.

Given the increased use of genetic testing through next generation sequencing panels, microarray, and whole exome/genome studies, requests to use PGD to test for a VUS is likely to increase. As a VUS has not been defined as clinically significant or predictive of an individual's phenotype, the appropriateness of PGD for a VUS is debatable. The presented scenario of PGD for a VUS for Marfan syndrome raised multiple concerns for the majority of participants in this study, and participants expressed concern about PGD for a VUS for any genetic condition. Because a VUS is not definitively disease causing, transferring embryos that lack the VUS does not guarantee that the potential child will not have the disease (Reiff et al., 2012). In addition, discarded embryos that carry the VUS could be disease free. Most participants expressed that sufficient evidence is needed to support that the VUS was disease causing including research, laboratory classification, and family studies to determine if the VUS tracks with affected family members.

According to the principle of non-directive counseling, medical personnel should provide patients with information about risks and options to reduce these risks (Savulescu, 2001). Although non-directive counseling is a central tenet of the genetic counseling profession, a more directive counseling style may need to be considered in both the situations of PGD for a VUS and when considering transferring affected embryos when no disease free embryos are available. Patients need to be extensively

counseled that selecting against a VUS may not be reducing the risk of passing on the condition in question, and children born after PGD should still be evaluated by a geneticist for the disease. On a more practical note, unless there is evidence in support of the pathogenicity of the variant, some believe PGD for a VUS is not an appropriate use of the technology and may be a misuse of patient's time and money, as well as medical resources. However, some people believe that PGD should be used to reduce uncertainty, and therefore PGD for a VUS would be appropriate since that would accomplish this goal.

2.5.2 Patient Perceptions. Counselors felt it was important to discuss how burdensome a disease has been in the patient's life. Many factors are considered in determining which conditions are labeled as "serious" including penetrance, potential for treatment, progression, age of onset, and severity of symptoms (Krahn, 2009). However, it is important to remember that every patient's perception of what is "serious" or "burdensome" is different (Miller & Levine, 2013). Genetic counselors should specifically address the unaffected spouse and discuss how he/she feels about caring for a new baby and the spouse, both with a genetic condition, some that are potentially life threatening.

2.5.3 Patient Autonomy. For many counselors, regardless of their own personal feelings, patient autonomy was of utmost importance. Ultimately, patient's choices will affect their own lives, and it is not the position of a provider to say whether they can or cannot use PGD. Genetic counselors have a responsibility however, to ensure patients are appropriately counseled and fully informed about the benefits and limitations of PGD.

Most genetic counselors believe patients have procreative autonomy. The basis of procreative autonomy is that couples are free to decide what kind of children to have, as well as when and how to have these children (Savulescu, 2001).

2.5.4 General Questions

2.5.4.1 Least controversial and most controversial scenarios. Overall, the majority of participants stated PGD for a VUS was the most controversial scenario of the three scenarios presented, while PGD for adult-onset conditions was the least controversial. This finding was most likely due to the uncertainty of a VUS being disease causing. Having an established diagnosis with a known disease causing mutation made participants more comfortable offering PGD.

Testing for an adult-onset condition, with an identifiable mutation, was easier for participants to accept, possibly because it is no longer considered a "novel" idea and has been done more frequently. With expansion in genetic testing, more "novel" ideas, like PGD for a VUS, and PGD for ambiguous genetic information will create unease among professionals. In the beginning, new concepts are prone to be controversial and cause discomfort.

A counselor's experience with PGD may have influenced their opinions. Six genetic counselors reported having counseled 20 or more PGD cases per month. Four of these genetic counselors work in a PGD laboratory setting and the other two work in Reproductive Endocrinology clinics. We determined that the majority of this subset of participants that felt transferring affected embryos was most controversial, worked in a PGD laboratory or Reproductive Endocrinology clinic. A potential explanation could be

that genetic counselors in these two settings feel that the intended use of the technology is to transfer unaffected embryos. Of the participants that stated PGD for a VUS was moderately or least controversial, half of them worked in these two settings. This could be because they have more experience addressing VUS cases and the issues are less novel.

2.5.4.2 Counselors opinions regarding what PGD should and should not be used.

Participants stated that PGD should be used for the purpose of having healthy children. The ultimate goal of PGD is to produce healthy children and avoid suffering. In order for this to be possible, participants felt that there needs to be a clearly established risk of an inherited genetic disorder within a family.

Half of the participants also felt PGD was appropriate for conditions that are life limiting or cause reduced quality of life. It is important to consider a patient's perception of which conditions are serious or burdensome enough to warrant the use of PGD. Most providers cannot fully understand or appreciate the experiences of individuals whose families are stricken with genetic conditions. For some, having a child with a *BRCA* mutation may be acceptable because there is treatment, increased surveillance and medical management options. For another whose family has been devastated by the disease, they may decide that the disease needs to "end with them" and not be transmitted to future generations.

When considering what PGD should not be used for, participants stated that gender selection, testing for ambiguous genetic information, HLA matching and selecting for (rather than against) a genetic condition were inappropriate. With regard to gender

selection, the majority felt PGD should not be used as gender is not a "disease." However, the caveat here is that for X-linked conditions, gender selection is the easiest method of selecting out embryos and therefore was considered the only appropriate reason for gender selection.

The majority of counselors raised concerns about testing for conditions that are not necessarily life limiting or testing for ambiguous genetic information. For example, positive trait selection is not life limiting. Over half of the participants felt that PGD should not be used to select for "healthy traits" such as hair color, eye color, height, or athleticism. A common reason for this belief was that human variation was appealing to participants. Participants expressed that PGD should be used to prevent significant health problems, but should not necessarily be used to select for traits that a couple prefers to have. Another consideration is that testing for traits that do not impact quality of life is a waste of resources.

Participants indicated that ambiguous genetic information included: VUSs, single nucleotide polymorphisms (SNPs), and predisposition genes. With the development of tests such as that provided by the company 23andMe, in which the genetic information present often has low relative risk scores, people may request PGD for SNPs and predisposition genes. The problem is that with VUSs, SNPs and predisposition genes there is not enough evidence to support using these indications for PGD.

2.5.4.3 Key factors in determining the appropriate use of PGD. There were five common themes that were key in determining appropriate uses of PGD. The majority of participants felt that PGD was an appropriate use if conditions were life limiting and

resulted in a diminished quality of life. Participants were more comfortable when symptom severity and disease burden were significant. The patient's life experiences were a common theme throughout the study and was key in determining the appropriateness of PGD. Ultimately, a patient's experiences superseded counselor opinions. Also, participants were more at ease with offering PGD if there was an established diagnosis with a known pathogenic mutation. Last, participants believed patient education was important in determining if PGD was appropriate. Genetic counselors must ensure that the patient is well educated about the PGD process, the benefits and disadvantages, and the potential outcomes of PGD, and ultimately, patients must decide on the course of action that is most appropriate for their families.

2.5.4.4 The future of PGD and counselors concerns about its potential uses. Overall, the majority of counselors interviewed had concerns about the potential uses of PGD. Participants responded that PGD is likely to eventually be used to test for non-medically significant traits, that there would be expanded testing of embryos, and that accessibility would change. Participants had concerns about these eventual uses but were also concerned about patient/public misconceptions, and the lack of genetic counselors in fertility clinics. However, two participants were not concerned about future uses, such as positive trait selection, because of the complexity of genetics, and how difficult it would be genetically manipulate or engineer individuals.

The majority of genetic counselors interviewed believed that next generation sequencing and whole genome/exome sequencing will be used to screen embryos and half of these participants were concerned about this testing. The concern was that no

"normal" embryos will be available for transfer because every embryo is susceptible to disease. If these extensive tests are used on embryos, the pool of embryos would most likely be eliminated. Additionally, one must consider who will be responsible for deciding which embryo to transfer after WGS or NGS, will it be the parent or the physician?

Participants also felt that eventually PGD is likely to be used to test for more ambiguous, mundane, non-medically significant traits. The majority were concerned about this potential use of PGD. A concern was that there will be unintended consequences when selecting for certain traits, such as reducing genetic variation within the population. Another concern is that this will lead us down the path of eugenics towards a "GATTACA" future. GATTACA is the title of a science fiction movie where society is driven by eugenics and children are artificially created to have the most advantageous traits. Some participants expressed worry that people may someday be required to do PGD, as depicted in this film.

Many participants hoped that PGD will become more accessible, affordable, and technically improved. Unfortunately PGD is currently unavailable to many patients because of its high cost. However, even if PGD does become affordable, many *"patients are not going to be ever willing to go through the process of IVF" (F)*, because of all that it entails. Some participants were concerned about possible class discrimination, where only the wealthy are able to afford PGD.

Another concern for participants was the public's/patient's misconceptions about PGD. In many movies today, genetics is a central theme and this and other popular

media may create misconceptions. People often assume that it is possible to test for every disease, pick and choose physical characteristics, or engineer "designer babies." Efforts to disperse these misconceptions are needed in order for patients and the medical community to understand this is not the primary focus in medical genetics.

A main issue that emerged from participants is that there are not enough genetic counselors involved in the fertility field. Most fertility clinics do not work in association with genetic counselors and several participants in this study expressed worry that reproductive endocrinologists will inappropriately or irresponsibly offer PGD. Genetic counselors could be extremely valuable in these environments, offering guidance for screening and testing of both the couples and their embryos.

2.5.5 Study Limitations. The group of participants was limited to genetic counselor members of the NSGC that have experience counseling PGD cases. The majority of participants were young and inexperienced, which may have affected results. More experienced PGD counselors may be more comfortable with controversial scenarios. Biases may have been created as each scenario is just one example and perhaps participants would have had different responses to different scenarios. Additionally, there is likely a response bias since genetic counselors who do not counsel for PGD might be less likely to offer their participation. It should also be considered that some participants are guided by laboratory policy, and may not have expressed their own opinions and instead expressed the laboratory's opinions. Also, only the opinions and attitudes of genetic counselors were reported in this study. It does not examine the thoughts and

perceptions of the reproductive endocrinologists or other individuals involved in caring for patients who are contemplating PGD, where different perspectives may be present.

2.5.6 Practice Implications. Our findings shed light on genetic counselors' perceptions about current and future uses of PGD. We have identified key areas where tension between advances in PGD and genetic counselors experience significant ethical dilemmas or controversy. Awareness of these key areas will aid genetic counselors in the practice setting and also provide areas for needed research in the future. It will also ensure that genetic counselors who are not currently involved with PGD are cognizant of recent advances in the potential role for genetic counselors in the fertility setting.

2.6 Conclusion

With advancements in genetic diagnostic technology, PGD has expanded to incorporate indications that may be considered controversial. For controversial applications of PGD, five common themes emerged with regards to determining if PGD was appropriate. Participants stated PGD is appropriate for conditions that are life limiting and cause a diminished quality of life. When symptom severity and disease burden were significant, participants were more comfortable. Having an established diagnosis with a known pathogenic mutation, also contributed to counselors' comfort. Patient's life experiences were also key in determining if PGD was appropriate. Participants felt that thorough counseling and education of patients was crucial; however, patient autonomy superseded counselors' concerns. Even though PGD for certain conditions causes discomfort for some counselors, the value of the technology was

recognized by all participants and ultimately, patients need to decide on a course of action that is most appropriate for their families.

As more novel uses of PGD are performed, counselors will need to quickly adapt. Common indications for PGD, like PGD for adult-onset disorders, was initially controversial, however, as more individuals have sought PGD for this reason, genetic counselors have become more at ease with PGD for this use. It is possible that eventually genetic counselors may reach the same level of comfort with using PGD for a VUS and other controversial applications. It is our hope that this study will bring attention to this growing field, and promote education among genetic counselors.

Chapter 3. Conclusion

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References

Alfarawati, S., Fragouli, E., Colls, P., & Wells, D. (2011). First births after preimplantation genetic diagnosis of structural chromosome abnormalities using comparative genomic hybridization and microarray analysis. *Human Reproduction,* 26, (6), 1560-1574.

Baruch, S. (2009). Preimplantation genetic diagnosis and parental preferences: Beyond deadly disease. *Houston Journal of Health Law and Policy,* 8, 245-270.

Baruch, S., Kaufman, D., & Hudson, K. L. (2008). Genetic testing of embryos: practices and perspectives of US in vitro fertilization clinics. *Fertility and Sterility,* 89, (5), 1053-1058.

Besser, A. (2013, February). Personal Communication.

Brezina, P. R., Brezina, D. S., & Kearns, W. G. (2012). Preimplantation genetic testing. *British Medical Journal,* 345, e5908.

Cant, N., Pollock, N., & Ford, R.C. (2014). *CFTR* structure and cystic fibrosis. *International Journal of Biochemistry and Cell Biology* (2014), http://dx.doi.org/10.1016/j.biocel.2014.02.004

Chang, L. J., Chen, S. U., Tsai, Y. Y., Hung, C. C., Fang, M. Y., Su, Y. N., & Yang, Y. S. (2011). An update of preimplantation genetic diagnosis in gene diseases, chromosomal translocation, and aneuploidy screening. *Clinical and Experimental Reproductive Medicine,* 38, (3), 126-134.

Coron, F., Rousseau, T., Jondeau, G., Gautier, E., Binquet, C., Gouya, L.,…Faivre, L. (2012). What do French patients and geneticists think about prenatal and preimplantation diagnoses in Marfan syndrome? *Prenatal Diagnosis,* 32, (13), 1318-1323.

Coutelle, C., Williams, C., Handyside, A., Hardy, K., Winston, R., & Williamson, R. (1989). Genetic Analysis of DNA from single human oocytes: a model for preimplantation diagnosis of cystic fibrosis. *British Medical Journal,* 299, 22-24.

David, B. E., Weitzman, G. A., Herve, C., & Fellous, M. (2012). Genetic counseling for the orthodox Jewish couple undergoing preimplantation genetic diagnosis. *Journal of Genetic Counseling,* 21, (5), 625-630.

Ehrich, K., & Williams, C. (2010). A 'healthy baby': The double imperative of preimplantation genetic diagnosis. *Health (London),* 14, (1), 41-56.

Ethics Committee of American Society for Reproductive Medicine. (2013). Use of preimplantation genetic diagnosis for serious adult onset conditions: a committee opinion. *Fertility and Sterility,* 100, (1), 54-57.

Fragouli, E. (2007). Preimplantation genetic diagnosis: present and future. *Journal of Assisted Reproductive Genetics,* 24, (6), 201-207.

Goldberg, J. D., Martin, C., Lebo, R.V., & Pedersen, R.A. (1993). Preimplantation Diagnosis. *The Western Journal of Medicine,* 159, (3), 301-307.

Handyside, A. H., Lesko, J. G., Tarin, J. J., Winston, R., & Hughes, M. R. (1992). Birth of a normal girl after in vitro fertilization and preimplantation diagnositc testing for cystic fibrosis *The New England Journal of Medicine,* 327, (13), 905-909.

Harper, J. C., & Sengupta, S. B. (2012). Preimplantation genetic diagnosis: state of the art 2011. *Human Genetics,* 131, (2), 175-186.

Harton, G., Tsipouras, P., Sisson, M. E., Starr, K. M., Mahoney, B. S., Fugger, E. F.,… Black, S. H. (1996). Preimplantation genetic testing for Marfan syndrome. *Molecular Human Reproduction,* 2, (9), 713-715.

Hershberger, P., & Pierce, P. (2011). Conceptualizing couples' decision making in PGD: emerging cognitive, emotional, and moral dimensions. *Patient Education and Counseling,* 81, (1), 53-62.

Hsieh, H. F., & Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qualitative Health Research,* 15, (9), 1277-1288.

Krahn, T. (2009). Preimplantation genetic diagnosis: does age of onset matter (anymore)? *Medical Health Care Philosophy,* 12, (2), 187-202.

Kupfer, G.M. (2014) Fanconi Anemia: A Signal Transduction and DNA Repair Pathway. *Yale Journal of Biology and Medicine,* 86, 491-497.

Lee, J., Hwang, Y.J., Hyun, R., Kowall, N.W., & Ryu, H. (2013). Nucleolar dysfunction in Huntington's disease. *Biochimica et Biophysica Acta* (2013), http:dx.doi.org/10.1016/j.bbadis.2013.09.017

Milachich, T., Timeva, T., Ekmekci, C., Beyazyurek, C., Tac, H. A., Shterev, A., & Kahraman, S. (2013). Birth of a healthy infant after preimplantation genetic diagnosis by sequential blastomere and trophectoderm biopsy for beta-thalassemia and HLA genotyping. *European Journal of Obstetrics & Gynecology Reproductive Biology,* 169, (2), 261-267.

Miller, P. S., & Levine, R. L. (2013). Avoiding genetic genocide: understanding good intentions and eugenics in the complex dialogue between the medical and disability communities. *Genetics in Medicine,* 15, (2), 95-102.

Ormondroyd, E., Donnelly, L., Moynihan, C., Savona, C., Bancroft, E., Evans, D. G.,… Watson, M. (2012). Attitudes to reproductive genetic testing in women who had a positive BRCA test before having children: a qualitative analysis. *European Journal of Human Genetics,* 20, (1), 4-10.

Pennings, G., Schots, R., & Liebaers, I. (2002). Ethical considerations on preimplantation genetic diagnosis for HLA typing to match a future child as a donor of haematopoietic stem cells to a sibling. *European Society of Human Reproduction and Embryology,* 17, (3), 534-538.

Petersen, T. S. (2005). Just diagnosis? Preimplantation genetic diagnosis and injustices to disabled people. *Journal of Medical Ethics,* 31, (4), 231-234.

Practice Committee of the American Society for Reproductive Medicine. (2004). Preimplantation genetic diagnosis. *Fertility and Sterility, 82 Suppl 1*, S120-122.

Practice Committee of Society for Assisted Reproductive Medicine (2008). Preimplantation genetic testing: a Practice Committee opinion. *Fertility and Sterility,* 90 (5 Suppl), S136-143.

Reiff, M., Bernhardt, B. A., Mulchandani, S., Soucier, D., Cornell, D., Pyeritz, R. E., & Spinner, N. B. (2012). "What does it mean?": uncertainties in understanding results of chromosomal microarray testing. *Genetics in Medicine,* 14, (2), 250-258.

Savulescu, J. (2001). Procreative beneficence: Why we should select the best children. *Bioethics,* 15, (5/6), 413-426.

Smolensky, K. R. (2008). Creating children with disabilities: Parental tort liability for preimplantation genetic interventions. *Hastings Law Journal*, Vol. 60, 2008. Arizona Legal Studies Discussion Paper no. 08-15.

Vanneste, E., Melotte, C., Voet, T., Robberecht, C., Debrock, S., Pexsters, A., & Vermeesch, J. R. (2011). PGD for a complex chromosomal rearrangement by array comparative genomic hybridization. *Human Reproduction,* 26, (4), 941-949.

Vergeer, M. M., Van Balen, F., & Ketting, E. (1998). Preimplantation genetic diagnosis as an alternative to amniocentesis and chorionic villus sampling: psychosocial and ethical aspects *Patient Education and Counseling,* 35, 5-13.

Verlinsky, Y., Rechitsky, S., Schoolcraft, W., Strom, C., & Kuliev, A. (2001). Preimplantation diagnosis for fanconi anemia combined with HLA matching. *Journal of the American Medical Association,* 285, (24), 3130-3133.

Verlinsky, Y., Rechitsky, S., Verlinsky, O., Masciangelo, C., Lederer, K., & Kuliev, A. (2002). Preimplantation diagnosis for early-onset Alzheimer disease caused by V717L mutation. *Journal of the American Medical Association,* 287, (8), 1018-1021.

Williams, C., Ehrich, K., Farsides, B., & Scott, R. (2007). Facilitating choice, framing choice: staff views on widening the scope of preimplantation genetic diagnosis in the UK. *Social Science & Medicine,* 65, (6), 1094-1105.

Appendix A: Invitation letter to Participants

Invitation to Participate: Genetic Counselors Opinions and Attitudes Towards Uses of PGD

Dear Genetic Counselor,

You are invited to participate in a master of science thesis research study at the University of South Carolina School of Medicine. The objective of this study is to explore the opinions and attitudes of genetic counselors when dealing with controversial uses of preimplantation genetic diagnosis.

Participation in this study is intended to benefit the genetic counseling field by revealing how genetic counselors view various issues. We believe that the study results will demonstrate the opinions and attitudes of counselors regarding use of PGD as no previous studies have focused on this topic. We feel that this study will add information to the discussion concerning applications of PGD technology.

If you decide to participate, you will be asked to complete a qualitative survey over the telephone asking a series of questions about various issues that you may encounter in practice. Your verbal consent will be obtained before the survey begins. The interview should take approximately 30 minutes. You do not have to answer any questions that you do not wish to answer and you can stop taking the survey at any time. The interview will be recorded to ensure accuracy; all identifying information will be deleted after the interview.

If you have any questions, or would like more information, please contact the principal investigator (or my faculty advisor, Janice Edwards), using the contact information below. If you have any questions about your rights as a research participant, you may contact the Office of Research Compliance at the University of South Carolina at 803-777-7095. Thank you for considering participating in this research project. Your input is invaluable, and we appreciate your time!

Kristen Everton
Genetic Counseling Intern
University of South Carolina School of Medicine
Genetic Counseling Program
2 Medical Park, Suite 103
Columbia, SC 29203
phone: (954) 292-0690
Kristen.Everton@uscmed.sc.edu

Janice G. Edwards, MS, CGC
Clinical Professor and Director,
University of South Carolina School of Medicine
Genetic Counseling Program
2 Medical Park, Suite 103
Columbia, SC 29203
(803) 545-5706
janice.Edwards@uscmed.sc.edu

Appendix B: Verbal Consent

You are invited to participate in a master of science thesis research study at the University of South Carolina because of your experience with preimplantation genetic diagnosis (PGD) cases. The purpose of the survey is to explore the opinions and attitudes of genetic counselors when dealing with controversial uses of PGD. This telephone interview will be recorded and all identifying information will be deleted after the interview. Your participation is voluntary and you may skip any questions that you do not feel comfortable answering. You may stop participating at any time. This survey should take approximately thirty minutes. If you have any questions about your rights as a research participant, you may contact the Office of Research Compliance at the University of South Carolina at 803-777-7095. Do you consent to participate in this study?

Yes/No

Appendix C: Survey

I. Introduction/Directions

You are invited to participate in a thesis research study at the University of South Carolina School of Medicine. The objective of this study is to explore the opinions and attitudes of genetic counselors when dealing with controversial uses of preimplantation genetic diagnosis. You will be presented with three case scenarios regarding controversial uses of PGD. For each scenario, you will be asked several open ended questions. At the end, several general questions regarding the use of PGD will also be asked. The survey should take approximately 30 minutes to complete.

II. Demographic Questions
   A. Gender/ Age:
   B. Number of years in practice as a genetic counselor:
   C. Number of months/years you have counseled for PGD:
   D. Number of all PGD cases seen per month:
   E. Location of practice: State
   F. Setting of practice: PGD Laboratory Setting, Reproductive Endocrinology Setting, Other

III. Case Scenarios
   A. PGD for an Adult-Onset Condition: A woman and her husband request PGD for early onset Alzheimer. A disease causing mutation in the PSEN1 gene has been identified. PSEN1 mutations account for 70% of early onset Alzheimer cases. These cases are diagnosed before the age of 65.
      1. Does this scenario for early onset Alzheimer raise any concerns for you and if so, what concerns are raised?
      2. How do you feel about using PGD to identify embryos at risk for early onset Alzheimer?
      3. Have you had any cases that included using PGD for an adult-onset condition?
         a) Describe the case
         b) What was the condition?
         c) Did you have any concerns?
      4. On a scale of 1 to 5 (1 being not comfortable at all, 5 being very comfortable), how comfortable are you offering
         a) PGD for any adult-onset condition?
   B. PGD to Select for a Genetic Condition: A couple requests PGD because of a family history of breast cancer. The mother carries a disease causing mutation in the BRCA1 gene. All of the female embryos and the only male embryo are found to carry the mutation as well. The couple decides to implant the only male embryo.

1. Does this scenario raise any concerns for you and if so, what concerns are raised?How do you feel about your patients using affected embryos when no unaffected embryos are produced?
2. Have you had any cases that you have managed personally that included transferring affected embryos after PGD?
    a) Describe the case
    b) What was the condition?
    c) Did you have any concerns?
3. On a scale of 1 to 5 (1 being not comfortable at all, 5 being very comfortable), how comfortable are you offering PGD to a patient that will
    a) Use affected embryos for any condition

C. PGD for a Variant of Unknown Significance (VUS): A couple requests PGD because the husband has Marfan syndrome. However, no known mutation was identified. Instead, a VUS was found. The couple wants to use PGD to select against the VUS, since there is the possibility that it may be the cause of the husband's Marfan syndrome. Individuals with Marfan can be mildly to severely affected, those that are mildly affected can go undiagnosed for their entire life and have no major health concerns.
    1. Does this scenario raise any concerns for you and if so, what concerns are raised?
    2. How do you feel about using PGD for a VUS for Marfan?
    3. Have you had any cases that you have managed personally that included using PGD for a VUS?
        a) Describe the case
        b) What was the condition?
        c) Did you have any concerns?
    4. On a scale of 1 to 5 (1 being not comfortable at all, 5 being very comfortable), how comfortable are you offering PGD for
        a) A VUS for any condition?

D. General Questions:
    1. Rank the three case scenarios, according to how you personally feel, from least controversial to most controversial.
    2. What do you feel PGD should be used for?
    3. Is there anything you feel PGD should not be used for?
    4. What are some key factors in determining the appropriate use of PGD?
    5. What do you believe the future will hold for the use of PGD?
    6. What concerns you about its potential uses?
    7. Is there anything else you would like me to know about the controversial uses of PGD?

IV. Thank you.

Thank you for your participation in this thesis research study, it has been greatly appreciated. Your input is invaluable. It is my hope that this research will provide

valuable perspectives from genetic counselors who work with PGD to the discussion concerning controversial applications of the technology.