2014

The Paternal Age Effect: A Preliminary Study of Current Challenges for Prenatal Genetics Care

Andrew Tyler Gunter
University of South Carolina - Columbia

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by

Andrew T. Gunter

Bachelor of Science
Clemson University, 2011

Bachelor of Arts
Clemson University, 2011

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in

Genetic Counseling

School of Medicine

University of South Carolina

2014

Accepted by:

Peggy Walker, Director of Thesis

Isaac M. Lipkus, Reader

Helga V. Toriello, Reader

Lacy Ford, Vice Provost and Dean of Graduate Studies

Dedication

This study is dedicated to fathers everywhere. May they love and lead their families well.

Acknowledgements

I first give thanks to my God and Savior, Jesus Christ. As I start my career, my prayer is that I will use these gifts and training for his glory and to make him known.

I cannot express enough gratitude to my adviser, Peggy, and to my exceptional committee members, Isaac and Helga, for their time, guidance, and expertise throughout this project.

To the faculty of the Genetic Counseling program at USC, thank you for your investment in the future of genetic counseling and for your enthusiasm as you have taught me and earnestly sought to see your passions become my own. To my extraordinary classmates who inspire me each day, thank you for driving me to grow my skills and for your encouragement. I know that each of you will be an asset to your practices and an incredible colleague in the field.

Many thanks to my family and friends who have been so encouraging as I begin my career. Thank you for your prayers, phone calls, emails, hospitality, and time over the past two years.

Finally, I especially want to thank my parents for exemplifying sacrificial love and support for my entire life and for instilling in me the centrality of faith in all that we do. I love you both so much, and I do not say it often enough!

Abstract

Advanced paternal age (APA) is related to various genetic conditions, behavioral disorders, and adverse pregnancy outcomes. Since the publication of ACMG's practice guidelines on APA in 2008, much has been learned about the causes of paternal age effect (PAE) mutations and their clinical implications. However, no guidelines exist to refer these high-risk pregnancies to prenatal genetics care, nor are effective screening techniques presently available. As such, many patients are not fully-informed about the risks to their pregnancies due to possible APA effects, and neither are are the men who have fathered these pregnancies.

Our findings support that limited APA principles are being disseminated into the general population. Additionally, prenatal patients of advanced maternal age (AMA) and their partners favor the fathers of pregnancies as important decision makers, second only to the mothers. Based on current knowledge of APA risks and molecular mechanisms, as well as our study findings, we support a collaborative effort to address the shortcomings of current prenatal genetic counseling procedure in its discussions of APA. The approach to rectify this discrepancy in prenatal genetic counseling should include a revisit of the 2008 ACMG guidelines concerning APA as well as research efforts directed toward the future goal of providing inclusive genetic counseling for men of APA and the pregnancies they father.

Keywords: advanced paternal age, paternal age effect, advanced maternal age, decision making, prenatal genetic counseling

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List of Abbreviations

ACMG.....American College of Medical Genetics and Genomics

ACOG .....American Congress of Obstetricians and Gynecologists

AMA ..... Advanced Maternal Age

APA.....Advanced Paternal Age

CF..... Cystic Fibrosis

CVS..... Chorionic Villus Sampling

EI..... Early Intervention

GWAS..... Genome-wide Association Studies

NIPS..... Noninvasive Prenatal Screening

OI .....Osteogenesis Imperfecta

PAE.....(The) Paternal Age Effect

RAS.....(from rat sarcoma)

RTK.....Receptor Tyrosine Kinase

SNP ..... Single Nucleotide Polymorphism

Chapter 1: Background

A 2013 study conducted in Taiwan documented the clinical care for a family who was referred to prenatal genetic counseling due to maternal age and because of a previous child diagnosed with osteogenesis imperfecta (OI) (Chen et al., 2013). Following her diagnosis, a frameshift mutation was identified in the daughter, an insertion in the fifty-second exon of *COL1A1*. The expectant parents were ages thirty-seven years (patient) and forty-four years (partner). The curious aspect of this case is that the diagnosis of autosomal dominant OI type III seen in the couple's eighteen-month-old daughter had recurred in the patient's current pregnancy. Neither parent was affected, nor was the couple's three-year old son or the patient's two older children from a previous relationship. Based on the prenatal diagnosis, the couple decided to terminate the pregnancy at twenty-three weeks gestation. Upon analysis for gonadal mosaicism, a causative germline mutation was identified in the paternal line (Chen et al., 2013).

This incidence of recurrent OI type III warrants several questions. First, what mechanism(s) explain the repetition of a *de novo* mutation in the paternal germline? Second, what influence might the father's age at conception have on recurrence of a dominant disorder? Other studies have documented increased incidence of male gonadal mosaicism associated with increased age in other dominant disorders as well, including Hutchinson-Gilford progeria syndrome (D'Apice, Tenconi, Mammi, van den Ende, & Novelli, 2003; Eriksson et al., 2003) and achondroplasia (Giudicelli et al., 2008). Third,

what factors contribute to a couple's decision to continue or not with the pregnancy? Finally, how might genetic counseling be beneficial to couples in this type of situation, and what information should be relayed to them?

The case above is but one example of increased occurrence of dominant disorders in individuals whose fathers were aged forty years or older at the time of conception, which is termed advanced paternal age (APA). According to the Centers for Disease Control and Prevention, 3,952,841 births were registered in the United States in 2012. Of these births, babies were born to fathers of APA at a rate of approximately 39/1000 (Martin, Hamilton, Osterman, Curtin, & Mathews, 2013). This included a 2% increase for fathers aged 40-44 over births in 2011 and a 4% increase for fathers aged 45-49 over births in 2011; births to fathers aged 50 and above remained comparable to those in 2011 (Martin et al., 2013).

Multiple studies have shown higher risks for behavioral and genetic disorders, chromosomal conditions, and congenital birth defects in pregnancies with fathers of APA than with younger fathers (Wiener-Megnazi, Auslender, & Dirnfeld, 2012; McGrath et al., 2014). Wilhelm Weinberg may have been the first to document in 1912 his suspicion about the relationship between paternal age and the risk for a dominant disorder, specifically achondroplasia. His clinical notes were confirmed decades later by L.S. Penrose (Thacker, 2004).

Saha and colleagues found children of APA fathers to be at an increased risk for impairments in cognitive development when assessed at multiple ages during childhood, when compared with children whose mothers were of advanced maternal age (AMA), defined as age thirty-five years or older at the time of conception (Saha et al., 2009).

Others have shown an increased risk for behavioral disorders such as autism spectrum disorder (Durkin et al., 2008; Puleo et al., 2012) and schizophrenia (Sipos et al., 2004). A cohort study of individuals born over a six-year period in the 1980s showed that children born to fathers aged forty years and older were at a 5.75 times increased odds ratio to develop autism spectrum disorder (Reichenberg et al., 2006).

As for paternal age and pregnancy outcome, the American College of Medical Genetics and Genomics (ACMG) guidelines estimate that genetic mutations contributing to disease onset for eighty-six examined congenital anomalies occur 20% more frequently in APA pregnancies than in pregnancies that have younger fathers (Toriello & Meck, 2008). Green et al. found increased risk for certain types of multifactorial birth defects in children of APA fathers (Green et al., 2010). The anomalies that showed significant linear correlation with APA were cleft palate, diaphragmatic hernia, obstruction of the right ventricular outflow tract, and pulmonary valve stenosis (Green et al., 2010). In a study in British Columbia, McIntosh, Olshan, and Baird (1995) found increased risk for open neural tube defects, congenital cataracts, pyloric stenosis, and upper limb reductions in newborns of fathers with APA. They reported higher incidence of Down syndrome as well, occurring more than twice as frequently in fathers who were fifty years or older at the time of conception than in fathers who were in their mid- to late twenties (McIntosh, Olshan, & Baird, 1995). In all of these studies, the separate influence of AMA was carefully controlled.

Research has shown an increase in pregnancy loss for fathers who fall into the advanced age category. A two-year cohort in Denmark gave a cautious estimate that the risk of miscarriage begins to increase steadily starting at a paternal age of forty-five

years, with a two-fold risk for fathers who are age fifty and above (Nybo Andersen, Hansen, Andersen, & Davey Smith, 2004). A 2005 study also showed a strong correlation between APA fathers and miscarriage due to chromosomal abnormality, with a significant risk increase for first trimester losses (Slama et al., 2005). The causes of chromosomal aberrations in the paternal germline include increased nondisjunction, acentric chromosomal fragments, and complex radial figures possibly resulting from chromatin damage (Sartorelli, Mazzcatto, & de Pina-Neto, 2001).

Goriely and Wilkie published an analysis in 2012 of the evolving understanding of the correlation between paternal age and genetic disorders, which is termed the "paternal age effect," or PAE (Goriely & Wilkie, 2012). In their considerations, a disorder is determined to have a PAE if it matches three criteria: (a) there is an extreme bias in paternal origin for mutations; (b) the age of fathers of affected children is on average more than two years older than the general population's typical fathering age; and (c) a high *de novo* mutation rate for specific mutations in the paternal germline has been established (Goriely & Wilkie, 2012). By their criteria, nine conditions caused by point mutations in various genes were analyzed: four craniosynostosis disorders (Apert, Crouzon, Pfeiffer, and Muenke syndromes); two skeletal dysplasias (achondroplasia and thanatophoric dysplasia); two neuro-cardio-facial-cutaneous syndromes (Costello and Noonan syndromes); and multiple endocrine neoplasia types 2A and 2B.

Goriely and Wilkie's analysis related these PAE disorders to a molecular phenomenon in the paternal germline. For the nine conditions described above, they noted that mutations in the causative genes have also been related to tumor formation in somatic tissues. Mutations in some of these genes are linked to the formation of

spermatocytic seminomas in the spermatogonial stem cell line, which are precursors for sperm formation (Goriely & Wilkie, 2012). In particular, spermatocytic seminomas are more commonly found in the testes of older men. The authors therefore theorized that mutations in these genes undergo positive selection in the paternal germline over time in a process akin to oncogenesis, promoting their increased prevalence in the sperm of older men, which would correlate to the higher incidences of these disorders in pregnancies with APA fathers (Goriely & Wilkie, 2012). This concept, which has been termed selfish spermatogonial selection (Goriely, McGrath, Hultman, Wilkie, & Malaspina, 2013), is supported in numerous observations by various investigators (Kong et al., 2012; Lim et al., 2012; Qin et al., 2007).

Goriely and colleagues (2013) described a common molecular denominator on a cellular level for selfish spermatogonial selection. PAE genes are clustered within a single pathway: the receptor tyrosine kinase/*RAS* (*RTK*/*RAS*) signaling cascade (Goriely et al., 2013). This pathway is responsible for controlling proliferation and differentiation during spermatogenesis. Because of the strong pathogenic selection these mutations cause within testes and the lethal or deleterious effects of many *de novo* mutations on the *RTK*/*RAS* pathway, many PAE-associated mutations are unlikely to have a long-term disease burden on the general population (Goriely et al., 2013). However, they propose that many selfish mutations with a weaker selective advantage are predicted to cause less severe phenotypes (e.g., variants with low/varying penetrance or susceptibility). The difference with these mutations is that these milder PAE mutations are a potential contributing source for heritable variations and could increase the genetic burden of common diseases in the general population (Goriely et al., 2013).

Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) around these genes which are thought to increase risk for multifactorial disorders, ranging from cancer to behavioral disorders such as schizophrenia (Goriely & Wilkie, 2012). In addition, Perrin and co-authors proposed epigenetic regulation as another probable cause for the relationship between paternal age and schizophrenia (Perrin, Brown, & Malaspina, 2007). Environmentally-induced variation in paternal epigenetic factors may have transgenerational consequences as well (Curley, Mashoodh, & Champagne, 2011).

With current working knowledge of potential explanations for PAE disorders, one may consider the appropriate methods by which counseling for APA risks could be developed and applied clinically in the prenatal setting. As a point of comparison, the prenatal care offered for AMA pregnancies reveals potential parallels for prenatal screening and diagnosis in APA pregnancies. There are four major areas of contrast between the care for AMA pregnancies and the care for APA pregnancies in prenatal genetics: established referral procedures, counseling protocols to incorporate comprehensive risk education, a counseling model to educate all parties contributing to pregnancy risk, and the understanding of who remains the primary figure in fully-informed pregnancy decision making for genetic testing.

The strengths of today's prenatal care includes screening and diagnostic testing for possible chromosomal and genetic conditions, typically including genetic counseling to inform the patient about the pregnancy's risks for certain conditions. This has resulted from professional societal guidelines such as the American Congress of Obstetricians and Gynecologists (ACOG) practice guidelines outlining recommendations for prenatal

screening and testing (ACOG, 2007). From guidelines such as these, prenatal genetic counseling has grown to offer information on specific risks related to AMA, including options for screening and testing. The education that is available to prenatal patients of AMA through the genetic counseling process is aimed at fully informing the patient so that she can make an autonomous decision about which screening and/or testing is appropriate for her individual pregnancy. In contrast, these driving forces are not typically in place for fathers of APA for their partners to be counseled and fully informed about today's knowledge of the risks of PAE and implications of the multiple conditions that may result.

When women of AMA are counseled during pregnancy about their age-related risks for genetic disease, it is most often in reference to the risk of aneuploidy, defined as abnormal chromosome number. Aneuploidy conditions may be the result of an error in meiosis known as nondisjunction, where the chromosomes fail to separate equally during gamete formation, leading to abnormal chromosome numbers in gametes. If these gametes result in successful fertilization, the developing embryo will have an aneuploidy condition. Increased risk of aneuploidy conditions associated with AMA include Trisomy 21 (Down syndrome), Trisomy 18, Trisomy 13, and sex chromosome aneuploidies such as Klinefelter syndrome (47,XXY), and Triple X syndrome (47,XXX). While nondisjunction can occur in both sperm and eggs, the process has been more commonly associated with female gamete formation (Chiang, Schultz, & Lampson, 2012; Hassold & Hunt, 2001), with the risk for meiotic error increasing as a pregnant mother's age increases.

As a result of potential aneuploidy conditions, a numerical cutoff risk (approximately 1 in 300) has been established by medical professionals to designate pregnancies at higher risk for chromosome abnormalities. This cutoff is based on the approximate risk for miscarriage due to complications from the amniocentesis procedure, which is the key technique to diagnose aneuploidy conditions prenatally. Studies have shown that this cutoff risk is also the estimated frequency of aneuploidy conditions in children of women who were 35 years of age at the time of delivery (Morris, Wald, Mutton, & Alberman, 2003), described commonly as advanced maternal age (AMA), with increasing maternal age correlating with higher risk for chromosomal conditions.

The standard of care for AMA patients for many years has included referral to a genetic counselor who educates them about their risks and informs them about various screening and testing options (Rubin, Malin, & Maidman, 1983), which then leads to individual decision-making about pregnancy testing and management. Because of the availability of effective screening and diagnostic options for aneuploidy testing, these referrals are made with high confidence in the quality of care given to patients. In 2007, the American Congress of Obstetricians and Gynecologists (ACOG) issued a revised Practice Bulletin (#77) stating that all women of any age should be offered both prenatal screening and prenatal diagnostic testing for aneuploidy (ACOG, 2007).

Diagnostic testing is performed through chorionic villus sampling (CVS) or through amniocentesis; both are more than 99% accurate for detecting chromosome aneuploidy and can be used to test for other potential genetic conditions, as well. These types of prenatal diagnostic testing carry an inherent risk of miscarriage. Therefore, patients often choose screening tests for information about their levels of increased

chance of aneuploidy before considering an invasive procedure (e.g., CVS or amniocentesis) for prenatal diagnosis. Screening options include measurements of biomarker levels in maternal serum, as well as ultrasound imaging. Most recently, noninvasive prenatal screening (NIPS) of cell free placental DNA in the mother's blood has been shown to have levels of sensitivity and specificity approaching those achieved by diagnostic testing for chromosome aneuploidy (Devers et al., 2013). After educating a patient on AMA risks and also on available testing options, the counselor facilitates the patient's decision making regarding her pregnancy care.

In stark contrast, the management of APA pregnancies differs critically from the care of AMA pregnancies in several ways. First, no established professional guideline exists for APA pregnancies to be referred to genetic counselors specifically for APA. The ACOG committee opinion on APA was withdrawn in 2008. A single ACMG guideline outlines what prenatal counselors should discuss with patients when APA is a potential risk factor and specifically notes the increased risks for certain dominant traits as well as for some birth defects and behavioral disorders. The use of ultrasound to monitor for problems with fetal development is recommended (Toriello & Meck, 2008).

Specifically because no guideline exists recommending that APA be a referral indication for genetic counseling and possible indication for screening for prenatal disorders, many APA pregnancies are likely not being properly counseled or evaluated for PAE. This overriding challenge for referral of APA pregnancies prevents the information from being widely known and acted upon through prenatal screening and/or diagnostic testing. In fact, the frequency at which patients in the APA category are being "missed" is difficult to pinpoint. However, a reasonable estimation of these cases can be

made based on the frequency of APA births. According to the work of Martin and colleagues (2013), the birth statistics in the United States for 2012 demonstrate that APA births occur at approximately 39/1000 live births, and AMA live births occur at an approximate rate of 148/1000 (Martin et al., 2013). This roughly equates to one APA birth for every four AMA births. While these numbers are not representative of AMA and APA pregnancies that did not carry to term, a reasonable expectation would be that total APA and AMA pregnancies occur at a comparable rate. Therefore, APA pregnancies would account for approximately 20% of age-related indications for prenatal genetic counseling if established referral protocols were in place. However, without these necessary guidelines, a significant proportion of high risk pregnancies are likely not receiving full risk information during prenatal genetics care.

A second challenge arises from the logistics involved in PAE sessions, specifically the complexity of information and time constraints, which may place a limitation upon genetic counseling for cases of APA. In addition, because of the limited feasibility in current screening and testing methods for the numerous conditions that are associated with APA, a potential issue arises in that the counselors discussing these risks with patients and their partners may feel they are violating the health care creed of *primum non nocere* (first, do no harm) by causing undue anxiety for counselees, especially given the limited feasibility in screening and testing methods for these conditions. This professional reservation, in turn, may influence how patients are educated and, ultimately, lack of accurate information could impact patient autonomy in decision making.

This hesitation on the part of genetic counselors has also been observed in the realm of genetic counseling for psychiatric illness. The wide array of risk estimates partnered with the unavailability of testing options for behavioral disorders produces among counselors the tendency to assume that these ranges are not useful and should not be discussed thoroughly. This assumption is then projected onto clients that they, too, would find risk ranges meaningless, when in fact they desire whatever information genetic counselors can provide (J. Austin, personal communication, April 11, 2014; Monaco, Conway, Valverde, & Austin, 2010; Hippman et al., 2012).

Prenatal testing options for genetic conditions related to PAE will likely become available to patients in the near future with advancements in sequencing and screening techniques, but this does not speak to how patients and their partners are currently being counseled. Hence, an issue worthy of exploration is to inquire of current patients about the level of detail parents may desire about APA information and health consequences of PAE, including options available for screening, diagnosis, and treating such conditions.

A third consideration for genetic counselors is how the current AMA-based counseling model does not incorporate the equipping of APA men with their genetic risk education for their future planning. This in turn affects the facilitation of autonomous decision making, a central tenet to counseling technique.

A third challenge for genetic counselors is how to best educate the AMA/APA parent(s) to ensure that that she/he/they are fully informed about these potential conditions in order for the patient/partners to make a fully informed decision about screening and testing during pregnancy. The responsibility of the counselor is to ensure that the patient leaves the session well-informed to make the best personal decisions

regarding her pregnancy care (Weil, 2000, p. 145). This is of particular importance to the male parent also, in that he should become aware of any possible risks to a pregnancy due to his age, given that he may be fathering children in the future with the same or another partner.

Much can be learned for educating the APA parent(s) from the current high standards of AMA counseling. While the standard AMA genetic counseling session follows a fairly standard agenda of issues to be covered, minimal information has been reported about how effective the counseling is in educating the AMA patient. After many years, the public is generally aware that older age of a pregnant female parent can confer a higher risk of aneuploidy in the fetus. Finding out about general knowledge of APA and especially of PAE and health implications to the offspring in a survey setting of AMA patients could serve as a preliminary baseline of information about the general patient's knowledge of PAE.

As an additional consideration for fully-informing prenatal patients, various individuals' understanding of numbers and how to apply them (i.e., numeracy) can impact their healthcare decisions, including within genetic counseling. If a patient has low numeracy, she is less likely to choose the most effective treatment and accurately assess the level of benefit of treatment (Lipkus & Peters, 2009; Sheridan, Pignone, & Lewis, 2003). For example, the genetic counselor must explain the various testing options with detection rates, accuracy measures, limitations, and associated benefits and risks (Pergament & Pergament, 2012). This aspect of counseling requires the counselor to evaluate patient health literacy and numeracy in order to convey genetic risk in a way that is best understood by each patient (Lea, Kaphingst, Bowen, Lipkus, & Hadley,

2011). Therefore, when considering concepts like PAE, identification of the preferred numerical risk representations of women and men in relation to healthcare may improve patient understanding in prenatal settings and promote better decision making in some patients/couples, as well as reduce the chance for undue anxiety. The benefit of this type of information for patients may be ascertained through the risk information they desire to be given and by the ways in which they make decisions regarding pregnancy care. Therefore, assessing patients' understanding of health risks associated with advanced parental age may prove helpful to enhance risk comprehension and maximize retention post-counseling in discussions of APA-related conditions. This evaluation could include determining knowledge of basic genetic principles regarding advanced parental age, as well as by identifying the numerical risk formats that are most preferred by patients and partners.

Additionally, the possible desire of patients and their partners to have risk assessment based on their status as a couple or upon each individual's contribution is unknown. Understanding the impact of PAE risk on decision-making processes may demonstrate the desire of patients and partners to be counseled by healthcare professionals concerning both AMA and APA risks.

The risk in making decisions for a not fully informed patient may include unpreparedness to handle challenges that come with having an affected child. As an example, Jiminez and colleagues found that parents with low health education and understanding experienced more confusion over early intervention (EI) referrals for their affected children (Jimenez, Barg, Guevara, Gerdes, & Fiks, 2013). In addition, many of these parents felt that physicians did not adequately explain the purpose and methods of

EI (Jimenez et al., 2013). Therefore, the fully-informed prenatal patient relies upon the knowledge and practices of her healthcare providers. Additionally, if patient education is essential to equipping parents to plan and care for their families, which is addressed by the core definition of genetic counseling, this suggests that the role of genetic counselors is to help patients/parents adapt to the diagnosis of a genetic condition (Resta et al., 2006). Based upon current practices for APA pregnancy care and their insufficiency to address the current understanding of PAE risks and mechanisms, this core principle to the discipline of genetic counseling is violated.

Another consideration for the impact of relaying PAE risk assessments to a fully-informed patient is the decision-making process of the patient, often with the input of her partner. Several psychosocial facets of relationships influence the way individuals perceive and interpret risks and testing options (Weil, 2000, p.39-46). In regards to the decision-making processes of patients and partners together, though, a literature review yields little information about role of couple dynamics in healthcare decision making, particularly in relation to prenatal care. However, some study findings may have implications for counseling couples in prenatal settings. In 1996, Cairns, Shackley, and Hundley published an article examining women's preferences for carrier screening for cystic fibrosis (CF) and found that, depending on how screening options are presented to patients, their screening preferences may change. Their results suggest that patients desire to know their partners' genetic risk contributions to pregnancy, and that patients' primary preference, if they choose to have prenatal screening, may be to have genetic screening performed in tandem with their partners (Cairns, Shackley, & Hundley, 1996). Therefore, the preferred simultaneous screening to assess the couple's risk for an affected

child may also be found favorable to patients in other prenatal care scenarios, as well, such as in the provision of age-related risk assessments.

In a recent study, Shiloh et al. assessed adult participants' attitudes about multiplex genetic testing for their personal health risks. The study's reported goal was to learn how preexisting attitudes about common adult-onset diseases would influence an individual's desire to undergo genetic testing for those diseases (Shiloh, Wade, Roberts, Hensley Alford, & Biesecker, 2013). Of the 294 adult participants, 140 opted to have multiplex testing completed for eight common adult-onset diseases. However, 78% of those who chose testing elected not to receive information regarding at least one of the diseases included in the panel (Shiloh et al., 2013). If the results of this study were to be found applicable to prenatal decision making, then prenatal patients who were offered a multiplex test for conditions associated with PAE may best be offered the option to select which genetic susceptibilities are reported to them for consideration in decision making.

Recently this opt-out approach has been applied to NIPS procedures. In October 2013, Sequenom® Laboratories added to their MaterniT21™ Plus test a series of chromosome abnormalities with an opt-out option for reported results. Now, in addition to their aneuploidy analyses of chromosomes 13, 18, 21, X, and Y (which are reported to all patients), Sequenom® offers the reporting of aneuploidies for chromosomes 16 and 22, as well as several microdeletion syndromes: 22q11.2 deletion syndrome, Angelman and Prader-Willi syndromes, Cri-du-chat syndrome, and 1p36 deletion syndrome (Sequnom® Laboratories, 2014). These added conditions are rarer than the aneuploidy conditions and have various intellectual, behavioral, and physical ramifications. For this panel expansion, the laboratory has afforded patients the option to choose not to have the

additional results reported (Sequenom® Laboratories, 2014). Additional rare conditions are expected to be added to this screening periodically in the coming months.

In summary, the effect of APA on genetic risks in pregnancy presents several challenges for genetic counseling, some of which are similar to those which were addressed in order to provide the best care for AMA pregnancies:

a. The absence of professional societal guidelines that direct the referral of APA pregnancies as an indication for prenatal screening and testing, including genetic counseling;
b. The equipping of genetic counselors with current information and education to effectively counsel these parents;
c. The necessity of patient education about APA and PAE such that they understand the possible implications and potential risks to their pregnancy in order to make fully informed decisions about screening, testing, and pregnancy management; and
d. The ways in which patient decision making may or may not change in a setting where additional risks and different medical concerns due to the effects of APA are fully discussed.

First, differences have evolved in the way parental age is addressed with each gender group. The care for expectant women of AMA has long been studied with reliable screening and diagnostic techniques available. In addition, specific guidelines for referral and practice have been established to assist couples as they make decisions regarding the care for their pregnancies. For APA pregnancies, however, a recommendation for referral to genetics for the advising of increased genetic risks due to

APA is not supported by multiple medical societies. Additionally, when APA pregnancies are seen for genetic risk assessment, ACMG's guidelines published in 2008 may not provide a sufficient strategy for counseling since much has been discovered about PAE in more recent years. Also, no effective screening technique for PAE-related conditions currently exists beyond the minimal potential benefit through ultrasonography. Therefore, counselors do not have tools in place to provide patients reassurance of a lowered risk assessment or confirmation of an empiric risk estimate.

Another consideration lies in understanding what education about PAE, if any, prenatal patients and their partners wish to have. The benefit of this type of information for patients may be ascertained through the risk information they desire to be given and by the ways in which they make decisions regarding pregnancy care. Therefore, assessing patients' understanding of health risks associated with advanced parental age may prove helpful to enhance risk comprehension and maximize retention post-counseling in discussions of APA-related conditions. This evaluation could include determining knowledge of basic genetic principles regarding advanced parental age, as well as by identifying the numerical formats that are most preferred by patients and partners.

Additionally, the possible desire of patients and their partners to have risk assessment based on their status as a couple or upon each individual's contribution is unknown. Understanding the impact of PAE risk on decision-making processes may demonstrate the desire of patients and partners to be counseled by healthcare professionals concerning both AMA and APA risks. The definition of a fully-informed patient changes when considering the practice of counseling a couple on APA risks. In

turn, the facilitation of autonomous decision making is complicated by the incorporation of the father's opinions regarding his risk contribution and the testing options that may become available.

Because of the limited information concerning the implementation of genetic counseling for PAE in relation to prenatal patient care, we have designed this study with the intent to establish a foundation for addressing clinical concerns of prenatal risks from APA. We hope to gain initial insight into how patients and their partners prefer to be educated about prenatal risks associated with increased parental age, with a specific focus on APA concerns, and seek their opinions about how they think they would react to future pregnancy scenarios that are consistent with some APA conditions.

We hypothesize that our study will show that patients favor receiving more thorough genetic counseling regarding APA risks, despite the current limitations of effective screening tools available for conditions associated with APA. We will collect responses about communications concerning risk assessment and their preferences. From the data we generate, we hope to ascertain if we should offer more information about the prenatal risks due to APA and how we might educate prenatal patients and their partners concerning the known contributions of APA to genetic disease risks. We hope to open discussion about incorporating APA education into a new "standard" of care for prenatal parents by genetic counselors and other healthcare professionals and to promote collaborative thinking and research to address current and upcoming issues with APA. Our desire is that the findings of this study will foster the production of informed and malleable clinical guidelines for inclusive genetic counseling on APA.

Chapter 2:

The Paternal Age Effect: A Preliminary Study of Current Challenges for Prenatal Genetics Care [1]

2.1 Abstract

Advanced paternal age (APA) is related to various genetic conditions, behavioral disorders, and adverse pregnancy outcomes. Since the publication of ACMG's practice guidelines on APA in 2008, much has been learned about the causes of paternal age effect (PAE) mutations and their clinical implications. However, no guidelines exist to refer these high-risk pregnancies to prenatal genetics care, nor are effective screening techniques presently available. As such, many patients are not fully-informed about the risks to their pregnancies due to possible APA effects, and neither are the men who have fathered these pregnancies.

Our findings support that limited APA principles are being disseminated into the general population. Additionally, prenatal patients of advanced maternal age (AMA) and their partners favor the fathers of pregnancies as important decision makers, second only to the mothers. Based on current knowledge of APA risks and molecular mechanisms, as well as our study findings, we support a collaborative effort to address the shortcomings of current prenatal genetic counseling procedure in its discussions of APA. The approach to rectify this discrepancy in prenatal genetic counseling should include a revisit of the

[1] Gunter AT, Walker P, Lipkus IM, and Toriello HV. To be submitted to *Journal of Genetic Counseling*.

2008 ACMG guidelines concerning APA as well as research efforts directed toward the future goal of providing inclusive genetic counseling for men of APA and the pregnancies they father.

Keywords: advanced paternal age, paternal age effect, advanced maternal age, decision making, prenatal genetic counseling

2.2 Introduction

The effect of APA on genetic risks in pregnancy presents several challenges for genetic counseling. The first challenge is the different medical concerns due to the effects of AMA and APA. In AMA, aneuploidy conditions are most common, whereas the types of genetic conditions associated with APA are primarily due to single gene changes and chromosome aberrations (Sartorelli et al., 2001). APA conditions are also more varied in their clinical courses and include behavioral disorders, genetic disorders, chromosomal conditions, and congenital birth defects (McGrath et al., 2014; Wiener-Megnazi et al., 2012; Reichenberg et al., 2006; Green et al., 2010). In addition to the different types of disorders more prevalent in APA pregnancies, the mechanisms that promote the increased frequencies of genetic conditions differ between women and men: the increased risk of nondisjunction in the eggs of aging women (Chiang et al., 2012; Hassold & Hunt, 2001) versus the increased risk for *de novo* germline mutations, coupled with positive selection, in aging men (Kong et al., 2012; Lim et al., 2012; Qin et al., 2007). Additionally, evidence suggests that disorders associated with APA may increase the genetic burden of disease in the population over time (Goriely et al., 2013).

Second, differences have evolved in the way parental age is addressed by gender group. The care for expectant women of AMA has long been studied with reliable

screening and diagnostic techniques available (Devers et al., 2013). In addition, specific guidelines for referral and practice have been established to assist couples as they make decisions regarding care for their pregnancies (Rubin et al., 1983; ACOG, 2007). For APA pregnancies, however, a recommendation for referral to prenatal genetics services for the advising of increased genetic risks due to APA is not supported by multiple medical societies. Additionally, when APA pregnancies are seen for genetic risk assessment, ACMG's guidelines published in 2008 may not provide a sufficient strategy for counseling because of newer discoveries about PAE in recent years. Also, no effective screening technique for PAE-related conditions currently exists beyond the minimal potential benefit through ultrasonography. Therefore, healthcare providers do not have tools in place to provide patients reassurance of a lowered risk assessment or confirmation of an empiric risk estimate.

A third challenge lies in understanding what education about PAE, if any, prenatal patients and their partners desire. The benefit for patients in receiving education on APA-related risks may be ascertained through the risk information they desire and by the decision-making strategies they employ in regards to pregnancy care.

As another consideration, for effective genetic education, determining how concepts can best be relayed to counselees is an important factor in equipping them for making decisions. Therefore, assessing patients' understanding of health risks associated with advanced parental age may prove helpful to enhance risk comprehension and maximize retention post-counseling in discussions of APA-related conditions (Lea et al., 2011). This evaluation could include determining knowledge of basic genetic principles

regarding advanced parental age, as well as by identifying the numerical formats that are most preferred by patients and partners.

Additionally, the possible desire of patients and their partners to have risk assessment based on their status as a couple or upon each individual's contribution is unknown. Understanding the impact of PAE risk on decision-making processes may demonstrate the desire of patients and partners to be counseled by healthcare professionals concerning both AMA and APA risks.

In summary, the effect of APA on genetic risks in pregnancy presents several complications for current counseling models in prenatal genetics, some of which are similar to those which were addressed in order to provide the best care for AMA pregnancies:

a. The absence of professional societal guidelines that direct the referral of APA pregnancies as an indication for prenatal screening and testing, including genetic counseling;
b. The equipping of genetic counselors with current information and education about APA-related conditions and mechanisms of PAE to effectively counsel these parents;
c. The necessity of patient education about APA and PAE such that they understand the possible implications and potential risks to their pregnancy in order to make fully informed decisions about screening, testing, and pregnancy management; and

d. The ways in which patient decision making may or may not change in a setting where additional risks and different medical concerns due to the effects of APA are fully discussed.

Because of the limited information concerning the implementation of genetic counseling for PAE in relation to prenatal patient care, our group designed this study to establish a foundation for addressing clinical concerns of prenatal risks from APA. We hoped to gain initial insight into the desire patients and their partners to be educated about prenatal risks associated increased parental age, with a specific focus on APA concerns.

We hypothesized that patients favor receiving more thorough genetic counseling regarding APA risks, despite the current limitations of effective screening tools available for conditions associated with APA. Some couples may also desire that their risk be communicated as a single estimate based on the couple's combined risk contributions. Findings can help illuminate if more information about the prenatal risks due to APA should be offered, the appropriate content of the information (e.g., how we might educate prenatal patients and their partners about known contributions of APA to genetic disease risks), and plausible specific genetic counseling practice recommendations that can guide genetic counseling services to prenatal patients and their partners of APA. We intend to foster collaborative thinking and research to address current and upcoming issues with APA. Our desire is that the findings of this study will promote the production of informed and malleable clinical guidelines for inclusive genetic counseling on APA.

2.3 Materials and Methods

2.3.1 Participants

This study was targeted to adult women and men in high risk pregnancy scenarios, where at least one parent is of advanced parental age (35 years for women and 40 years for men). The following inclusion criteria were used:

a. Women presenting for prenatal genetic counseling who were 35 years or older and/or whose partner was 40 years or older;
b. Men who were 40 years or older, presenting with their partners for prenatal genetic counseling and/or whose partners were 35 years or older;
c. English speakers, due to limitations of written materials; and
d. Recognized competence to read and understand the written materials.

The following exclusion criteria were included for this study:

a. Individuals who were not proficient in English to an 8th grade reading level;
b. Individuals who did not meet the age specifications above;
c. Individuals whose reading comprehension was insufficient to understand the survey information;
d. Individuals whom the Genetic Counselor considered to be emotionally unable to participate based on extraordinary referral reasons (e.g., fetal demise or severe fetal prognosis by ultrasound);
e. Individuals who were referred for preconception counseling (i.e., are not currently pregnant); and
f. Individuals who were counseled by the primary investigator.

A survey was distributed through a prenatal genetics clinic in Columbia, SC, to eligible patients and their partners who met the aforementioned study criteria. The survey was offered at the end of the genetic counseling session, and participants were able to complete the survey in the waiting room or at home after the session. Surveys were distributed over a four-month period from September 2013 through January 2014. Surveys were received from participants until mid-February 2014.

The survey consisted of a series of statements for each participant's consideration to assess their understanding of risk contribution by each gender to future offspring, as well as their opinions on pregnancy decision making within the couple dynamic. Participants were also asked to consider scenarios for a hypothetical future pregnancy where prenatal screenings are available for conditions associated with APA. Participants were asked to indicate their theoretical desire to undergo various screening techniques in order to provide risk information to them.

Answers were based on a Likert scale of agreement or disagreement with each statement (1 = Strongly Disagree and 5 = Strongly Agree). Additionally, each subject was presented with several representations of the same numerical value based upon the common practices of the clinic and also on the findings of Grimes and Snively (1999). Each participant was asked to identify the numerical representation she/he felt was most easily understood when used to relay risk estimates. For the questions regarding future screening techniques, participants were asked to comment on their motivations for preferring one method over another.

2.3.2 Statistical Analysis and Methods

Microsoft Office Excel 2013 software was used to identify frequencies and percentages in responses. For quantitative analysis, Statistical Package for Social Sciences (SPSS), version 22.0, was used after the data was transferred from Excel spreadsheets to SPSS. Correlation studies using Spearman's Rho analysis compared demographic variables to the Likert-scale responses available for the five conditions presented in the scenarios.

In addition, Fisher's exact test was employed to determine if a dependency existed between independent and dependent variables. For the survey portions regarding advanced parental age concepts, numerical preferences, and decision-making preferences, Fisher's test compared participants' responses to their demographic information, such as their parental status (having children or not), for possible statistically significant associations. Respondents' answers to the Likert-scale questions regarding a future at-risk pregnancy were analyzed quantitatively for frequency, calculated as percentage of total responses, regarding their decision to test or not to test for the proposed conditions. Written responses to these same questions were then analyzed qualitatively using grounded theory methods for identifying possible common themes about respondents' reasons for making their individual decisions.

This study was approved by the Institutional Review Board of the Office of Research Compliance, University of South Carolina, Columbia, in August, 2013.

2.4 Results

2.4.1 Participants

Fifty-eight surveys were distributed to eligible subjects. Twenty-three of the distributed surveys were completed and returned to the primary investigator for a response rate of 40%. Study participants (N = 23) were organized by age, gender, ethnicity, marital status, highest level of education, and status of having children prior to their current pregnancy. These demographics can be found in Table 2.1. The ages of participants ranged from 29-45 years old with an average age of 38 years (*SD* = 3.67). All participants had obtained at least a high school-level education, and a majority (65%) had had some college education or more. Individuals who indicated they had children outside of their current pregnancy were asked to report how many they had. Reported numbers ranged from one child to six children, and these participants had 2-3 children on average, including their current pregnancy. We note that of the 23 total respondents, only two were male.

2.4.2 Comprehension of Advanced Parental Age Concepts and Numbers

Questions concerning participant understanding of age-related genetic risks revolved around three foci: how well participants retained information received through AMA risk counseling, participants' understanding of pregnancy risks associated with APA, and participants' preferences for risk communication based on a limited set of numerical options.

For AMA-associated risks, most subjects (65%) agreed with the statement that a baby's risk to have Down syndrome is increased only by parents' genetic information and not by parental environment. Most respondents (87%) indicated understanding that a

Table 2.1

Participant Demographics

Age	n	%	**Ethnicity**	n	%
25-30	1	4	Asian	1	4
31-35	4	17	Black	9	39
36-40	11	49	Hispanic	1	4
41-45	7	30	White	10	44
			Other	2	9
Education			**Marital Status**		
HS diploma/GED	8	35	Single/Never Married	5	22
Some College	3	13	Married	13	57
Bachelor's	5	22	With a Partner	4	17
Beyond Bachelor's	7	30	Divorced	1	4
Have children outside current pregnancy			**Gender**		
Yes	17	74	Female	21	91
No	6	26	Male	2	9
Average number children	2.6				

mother who is 35 years or older at pregnancy has a higher chance to have a baby with Down syndrome than a younger mother.

For APA-associated pregnancy risks, about one third (35%) of respondents indicated agreement with the statement that a father older than 40 years at conception has a higher risk of having a baby with Down syndrome. Figure 2.1 represents subjects' understanding for the chances for Down syndrome in relation to genetics versus environment, AMA, and APA. Forty-four percent of participants showed uncertainty with the statement that older paternal age carries a lower risk of fathering a child who will develop autism, suggesting that they do not know this information, while 57% disagreed with the same statement, suggesting more were correct than the percentage who did not know the correct answer.

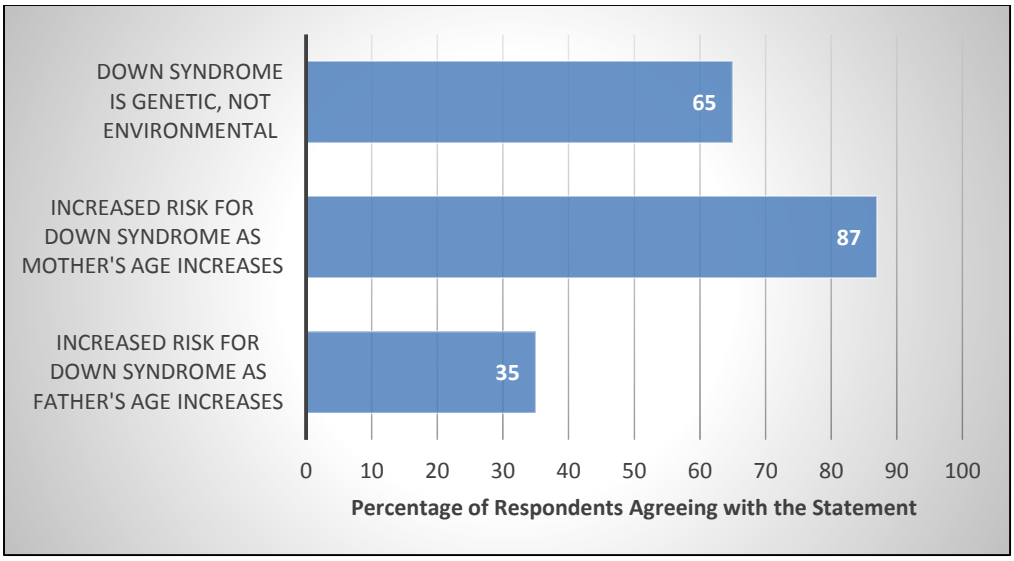

Figure 2.1 Respondents' knowledge regarding Down syndrome risk factors.

Two questions reflected respondents' preferred numerical format of conveying risk information: a) Selection of a simple risk descriptor [options: 10%, 1/10, 1 chance in 10, or 10 chances out of 100]; and b) Comparative description of the chance for event occurrence and event nonoccurrence (e.g. 10% chance of having the condition, and 90% chance of NOT having the condition). Most respondents (78%) desired a percentage (e.g., 10%) or a ratio (e.g., "1 chance in 10" for a condition to manifest). When asked how they would prefer a medical professional to report chances for a serious condition such as a heart condition, most (87%) preferred a ratio or a percentage for the event occurrence or nonoccurrence (e.g., "10% chance of having the condition, and 90% chance of NOT having the condition"). The dependence between respondents' preferences in the first question was statistically significant in determining their preferences in the second question (Fisher's exact test, $p = .006$), which indicates that respondents are likely to remain consistent in their preferred numerical format.

Participants were also asked to indicate which of their previous responses would be their choice overall (i.e., choosing a simply-stated percentage versus a percentage for the condition and a percentage not to have the condition). Roughly 70% of respondents indicated preference for being told both sides of a risk assessment.

2.4.3 Decision-Making Preferences During Pregnancy

Participants indicated their level of agreement with which individual should make decisions regarding genetic testing during pregnancy: the patient, her partner, the doctor, or the genetic counselor (see Figure 2.2). Twelve participants (52%) believed that the mother should make final decisions regarding any genetic testing during pregnancy, based upon four Likert-scale questions. Fourteen participants (61%) disagreed that the

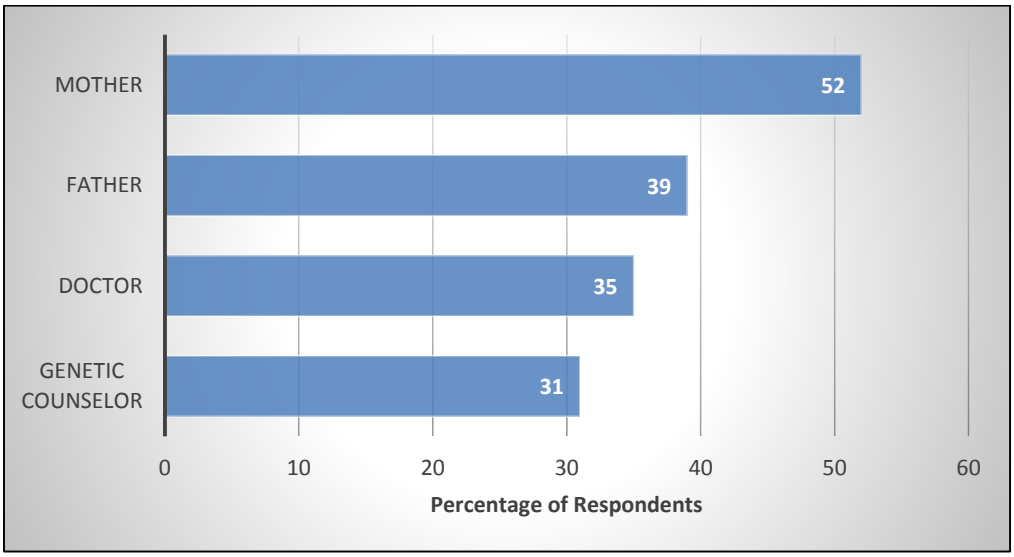

Figure 2.2 Participants' favor towards each respective individual as the decision-maker for genetic testing during pregnancy.

father should be the primary decision-maker for prenatal testing. About two-thirds of respondents disagreed with the physician making the decisions (65%) and with the option for the genetic counselor to make decisions about prenatal genetic testing (69%).

Participants' agreement with the mother as being primary decision maker for prenatal genetic testing and disagreement with the father as primary decision maker using Likert scale responses was shown to be statistically significantly correlated by Spearman's Rho analysis, $r(21) = .422$, $p = .045$. The distribution of participants' responses can be found in Figure 2.3a. In comparison, however, there was not a statistically significant correlation by Spearman's Rho analysis between participants preferring the mother as primary decision-maker for genetic testing compared with a genetic counselor as primary decision-maker, $r(21) = .056$, $p = .800$. The distribution of those responses can be found in Figure 2.3b.

When considering decision-making as a couple for prenatal genetic testing, 20 of 23 participants (87%) agreed with the statement that final decisions regarding prenatal genetic testing should be based on the parents agreeing together on one testing option. In addition, 21 of 23 participants (91%) believed that they would have the same opinions as their partners regarding testing options. Participants' responses were not statistically significantly dependent on marital status (Fisher's exact test, $p = .308$).

When asked who should make a final decision for prenatal genetic testing in the event of a patient and her partner being unable to agree on an option, participants ranked their preferences from among the patient, her physician, her partner, and her genetic counselor (see Figure 2.4). Twelve of 21 respondents (57%) ranked the patient first in making the final decision when the two are in disagreement, and Spearman's rho analysis showed a statistically significant correlation between ranking of the mother's and father's decisions, $r(17) = .589$, $p = .008$. The correlation between ranking of the father's choice over the physician's choice was negative and was also significant, $r(17) = -.730$, $p < .001$.

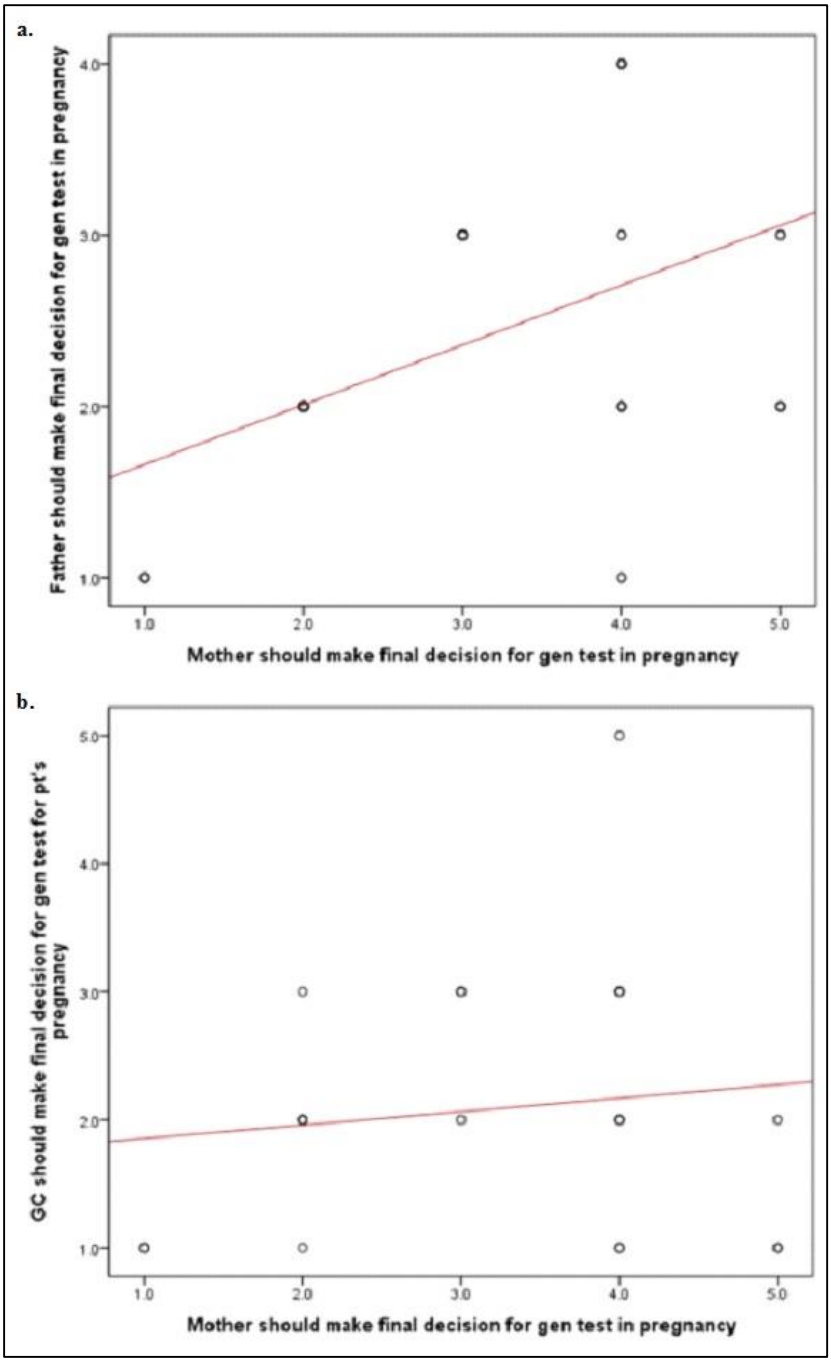

Figure 2.3 Distribution of participants' responses to preferring maternal decision making for genetic testing versus paternal decision making (a) and preferring maternal decision making versus genetic counselor decision making (b).

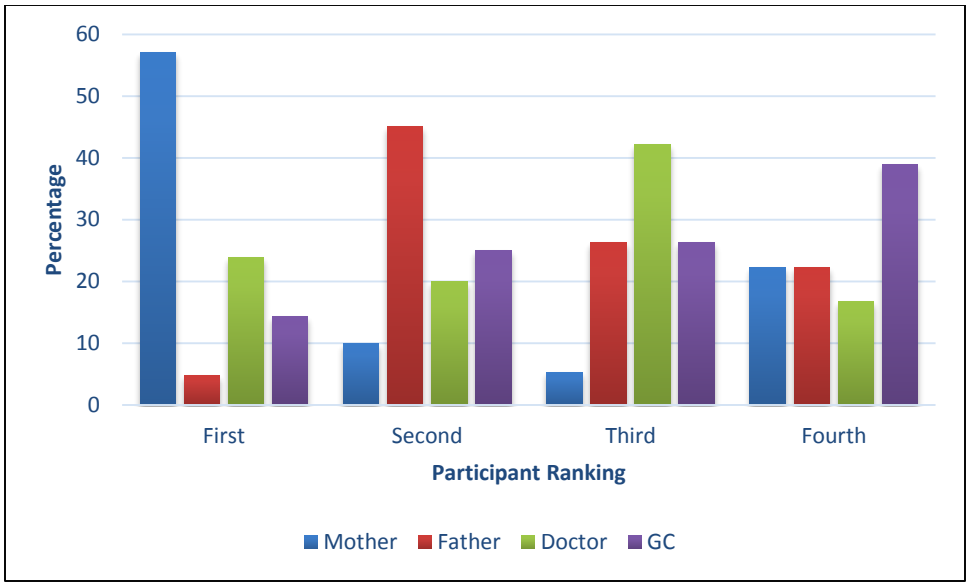

Figure 2.4 Participant priority rankings for the right to make genetic testing decisions in the event that a patient and her partner do not agree on an option together.

There was also a statistically significant and negative correlation in the rankings between father's choice and genetic counselor's choice, $r(17) = -.466$, $p = .044$, but not between rankings of physician's choice and genetic counselor's choice, $r(18) = .371$, $p = .107$.

2.4.4 Genetic Education Preferences Related to Parental Age Risks

Participants were asked about their desire to know all parental age-related risks. For each question, approximately 70% favored education about all risks associated with advanced parental age. The responses to these three questions were combined into a composite score (Crohnbach's $\alpha = .995$) for statistical comparisons. Participants were also asked to indicate a preference for risk assessment based upon each parent's individual contribution to age-related risk or for a single combined risk estimate for the couple. Neither option was strongly favored over the other, as 44% preferred two separate risk numbers, 48% preferred a combined risk estimate for the couple, and two participants indicated a preference for both.

2.4.5 Considerations for Potential Future Testing Options

Participants were given three scenarios for possible future pregnancies, asking them to indicate if they would want screening in each scenario. For a potential maternal blood test for genes associated with a higher risk of a child to develop autism, most respondents (74%) indicated they would want this type of information in a future pregnancy. Only one respondent indicated she definitely would not want this type of testing. For a possible scanning test that could be offered in a future pregnancy to assess higher risk for juvenile-onset seizures, 14 of 23 participants (61%) favored this type of screening. For a maternal blood test that could detect potential learning problems for an expected child, slightly over half of respondents (54%) favored this type of screening for a future pregnancy. Figure 2.5 captures subjects' favorability for each type of testing proposed.

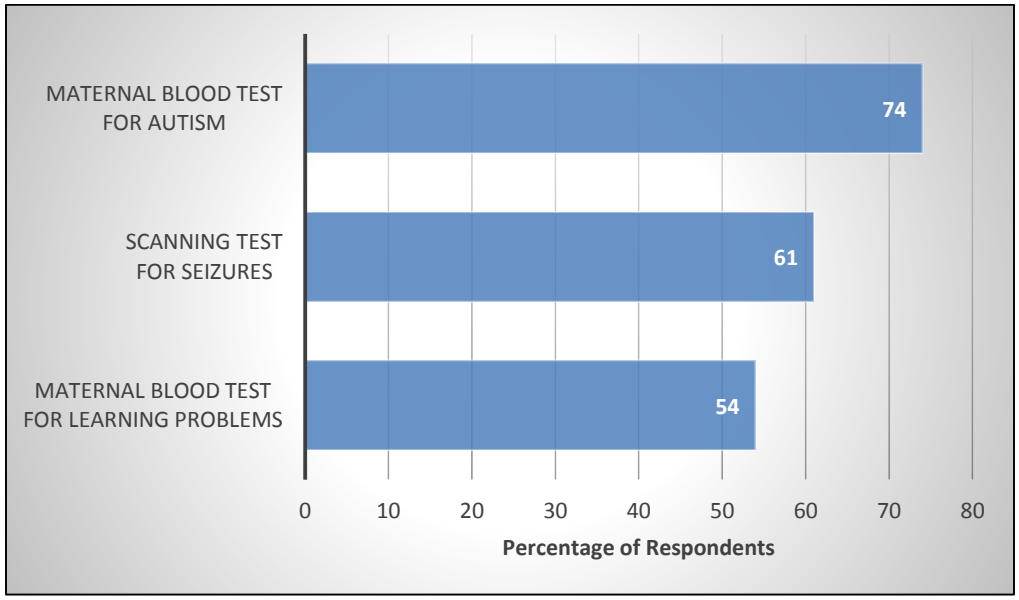

Figure 2.5 Respondents' favorability toward prenatal or screening for conditions associated with APA.

When offered ultrasound screening for features of genetic conditions associated with parental age, 13 of 22 participants (59%) indicated a desire to know all possible risks for their child prior to having the ultrasound conducted. The remaining nine participants (41%) indicated a desire to only know specific risks to the baby after ultrasound findings were reported. Participants' preferences for receiving education about genetic risks associated with parental age was not significantly associated with their favorability toward any of the testing options proposed in the hypothetical future pregnancy scenarios (Fisher's exact test, $p > .410$ for each proposed testing option) or with their parental status prior to their current pregnancy (Fisher's exact test, $p = .333$).

Two investigators coded the responses of participants concerning their motivations for favoring/disfavoring the various screening/testing tools proposed for future pregnancies. Both coders came to the same conclusion that motivating factors for respondents included the desire for risk-associated information, the potential influence this information would have on decision making, and the effect on how the patient and/or her partner could prepare for their child.

Eight respondents described their priority to receive risk-related information regarding pregnancy. Their motivations included the following: "[It] would be better to know than to not know;" "Knowing the test is available and not taking it is not an option for me. I <u>always</u> want to know;" and "If I am at higher risk I want to know more details if possible."

For those who described preparedness as a key motivator, responses included thoughts such as "[the ability] to prepare properly for the future and my child's needs" and "…to be informed of any condition that may affect my child, so that I can prepare

myself if it comes to light." When participants described the influence of age-related risk screening as a key component in making decisions, some thoughts that were recorded include: "I prefer to know all the risks my baby might be exposed to before deciding to continue/terminate the pregnancy;" and "…I believe in making informed decisions in life. It is important to know all the facts to make sound decisions."

Other participants noted specific conditions that would determine their desire to proceed with screening or testing. These included the cost of the testing and also the accuracy of the technology to detect a specific condition. Reasons respondents disfavored testing included a lack of family history for the condition, the plan to have no more children after their current pregnancy, and disinterest in a risk percentage (i.e., the preference for definitive results only). One participant noted her motivation for screening as a desire to maintain a sense of control following a previous loss:

> I only chose [the testing option] because I had a stillborn baby last year, and it makes me feel out of control and [have] constant worry, so having lots of tests (which I appreciate) makes me feel in control or able to do something and alleviates my remaining guilt about my baby, even though I'm not supposed to have any. If I'd not had this experience I would not answer yes; I would have no tests and no ultrasound as I did before my [previous] daughter's blissful birth.

2.5 Discussion

2.5.1 Genetic Education on Parental Age Risks

The goal of our study was to establish a foundation for addressing the clinical concerns of prenatal risks from APA. Our first aim was to understand counselees'

understanding pertaining to concepts that are currently discussed in prenatal genetic settings, specifically centered on genetic education and risk assessment. Our results demonstrated that the majority of participants retained basic information discussed during their thorough counseling of AMA-related risks, given that the majority of respondents correctly identified each genetic education concept pertinent to AMA that was proposed in the survey.

We also desired to briefly assess how well APA concepts have permeated the general population's knowledge. Approximately half of respondents indicated an understanding of increased risk for autism with APA, but most did not understand increased risk for Down syndrome with APA. While participants may have guessed on these questions, a possible explanation is that this knowledge is becoming (somewhat) integrated among lay audiences, especially represented in this highly educated sample of respondents (65% with college level education). Therefore, a warranted question is that if the general population is aware of some risks associated with APA, why are these risks not being discussed in clinical genetic settings to enhance understanding and correct misconceptions (e.g., only 35% of respondents comprehended an increased risk for Down syndrome in APA fathers)?

Questions dealing with risk presentation were targeted to understand which representations of numerical values are preferred on an individual basis. Respondents' preferences were assessed more than once, and upon each assessment, percentages and verbal descriptions of rates such as "___ chance(s) out of ten chances" were preferred by a majority. Additionally, the presentation of the chances for a condition's non-occurrence along with the chances for the condition's occurrence was favored, which

further supports the concept of presenting balanced information during genetic counseling sessions. Regarding genetic education preferences, a majority of participants (70%) favored receiving education on all risks surrounding AMA and APA. This is an area that warrants future research to yield more generalized opinions than those represented in this small study focused in a specific geographical area.

2.5.2 Impact on Patient Autonomy in Decision Making

In prenatal genetic care, the mother's decision is considered primary in decision making by her healthcare professionals. The results of this study support that patients and partners agree with this concept. While the majority of participants (91%) were female, upon inspection of the two surveys contributed by male participants, one favored the mother's decision as primary and the father's secondary, and the other considered the patient's and partner's decisions as equally important. Given the effect APA/PAE concepts will have on decision making, the incorporation of these additional risk factors redefines what constitutes a fully informed and autonomous female patient.

In addition, the father of the pregnancy was favored by participants as the second decision-maker in prenatal genetic testing decisions. Because of the high regard that patients and their partners place on the opinions of the father regarding genetic testing, it may be beneficial for genetic counselors to address parental age-related concepts with the father counseled as a "patient" secondary to the mother. This is of particular importance in regards to APA counseling because of the implications for any future pregnancies the father may have, which may be with a different partner. By not adequately counseling these men, healthcare professionals may be doing a disservice by not equipping them with genetic education to help them best plan for their future children.

2.5.3 Considerations for the Future of APA Counseling

More than half of respondents favored potential future testing options to screen for conditions that have been associated with APA. Their reasons for favoring testing reflect the influence this type of information would have on their decision-making processes during pregnancy and their care planning for their child after birth. These results suggest that the development of prenatal screening techniques for conditions associated with APA would be favored among these patients and partners and indicate a potential future direction for these technologies.

Additionally, there may be considerations for the development and application of a couple-centered strategy counseling on age-related genetic risks. Nearly half of respondents were in favor of having risk estimates presented as a combined couple's assessment; over 40% favored being told each parent's age-related contribution to the overall risk. When these findings are partnered with the "new understanding" of what defines a fully-informed APA patient, providing counseling to the patient on her own may prove to be an inadequate service in future prenatal genetic counseling sessions, as men of APA must also be educated about genetic risks associated with their ages. For female patients whose APA partners are not present for genetic counseling, even though he may be referred, a potential counseling model can be adapted from cancer genetic counseling, where the patient leads efforts to disseminate a genetic risk assessment to appropriate parties with the facilitation of the genetic counselor.

2.5.3 Study Limitations

The sample size in this study was small, and with all participants having received counseling in a single geographic region, the opinions and preferences of our participants

are not representative of all advanced parental age couples. All participants were highly educated and are not representative of the general population seen in many prenatal clinics. The limited number of eligible men participating in this study further emphasizes the discrepancy between the genders in who typically attends prenatal genetic counseling sessions. This portrayal of unavailability of fathers to present for prenatal counseling represents an additional challenge in considering male referrals to genetic counseling specifically for APA.

Additionally, the answers provided by participants may not reflect the actions they would take were they in the described situations. A final recognized limitation was that, after reviewing respondents' surveys, some questions may have been worded poorly so that their meaning was misconstrued by subjects. Furthermore, this study was designed as a preliminary approach to address several different aspects of counseling that would contribute to APA pregnancy care, without exploring any area extensively.

2.5.4 Directions for Future Research

Future clinical research needs to make a concerted effort to address the issues discussed in this study. For instance, analysis could be conducted on the impact of health literacy and numeracy on decision making in prenatal genetic counseling sessions. Other research could be conducted to better understand the role of couple dynamics in prenatal decision making and the feasibility of applying a couple's counseling model in scenarios of advanced parental age. Future technological research could focus on the potential development of screening options for conditions related to APA to equip patients with better tools than ultrasound in making decisions about pregnancy care. The aim of research will need to be the collection of reliable information that can used to open the

possibility of the clinical utility of APA counseling. In turn, these efforts will promote the development of effective societal guidelines and the education of genetic counselors, which will translate clinically into fully informed patients and couples who are better able to make truly informed decisions regarding APA risks.

2.5.5 Practice Implications for Genetic Counseling

There is a concerning gap between the knowledge of APA-associated risks and mechanisms and current genetic counseling procedure. In addition, the current AMA-based counseling model is inadequate to fully inform patients regarding the risks under the umbrella of advanced parental age. Our results demonstrate that female patients and their partners expect more from their counselors, and it is time we start meeting their expectations. Genetic counselors must begin strategizing ways to address these shortcomings. We encourage a collaborative effort among representatives of NSGC, ACMG, and ACOG to address the current deficiencies in this aspect of prenatal protocols through the composition of updated guidelines that are informed and are malleable to accommodate future developments in prenatal genetic screening techniques that we may provide higher quality care for men of APA and their partners.

2.6 Conclusions

The purpose of this study was to highlight developments in the understanding of APA-related pregnancy risks, to reflect upon the current shortcomings in prenatal genetic counseling practice regarding APA risks, and to promote the development of updated counseling protocols based upon the educational and decision-making preferences of patients and their partners. Our findings support a necessary address to present procedures within prenatal genetic counseling. We support a revisit of the 2008 ACMG

guidelines concerning APA as well as research efforts directed toward the future goal of providing inclusive genetic counseling not only to benefit women of AMA but also men of APA and the children of these fathers.

Chapter 3: Conclusions

The purpose of this study was to highlight developments in the understanding of APA-related pregnancy risks, to reflect upon the current shortcomings in prenatal genetic counseling practice regarding APA risks, and to promote the development of updated counseling protocols based upon the educational and decision-making preferences of patients and their partners. Our findings support a necessary address to present procedures within prenatal genetic counseling. We support a revisit of the 2008 ACMG guidelines concerning APA as well as research efforts directed toward the future goal of providing inclusive genetic counseling not only to benefit women of AMA but also men of APA and the children of these fathers.

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Appendix A – Participant Materials

Please, do NOT write your name on this survey. There is a section at the end for your contact information if you would like to be included in the drawing. If there is a question you do not wish to answer, please skip it and continue with the rest of the survey.

<u>Part A:</u> This section talks about the ages of parents and possible conditions in pregnancy and in children. Check the box you believe is correct for each sentence.

1. Which parent's genetic information has a stronger effect on the chance of having a baby with Down syndrome?

   □ Mother □ Father □ Equal □ Neither Parent

2. Which parent's environment (factors other than genes) has a stronger effect on the chance of having a baby with Down syndrome?

   □ Mother □ Father □ Equal □ Neither Parent

3. A baby's chance of having Down syndrome is increased only by genetic information from the parents. A parent's environment does not increase the chance of Down syndrome.

   □ Strongly Disagree □ Disagree □ Neither Agree nor Disagree □ Agree □ Strongly Agree

4. When a mother is 35 or older at pregnancy, her chance to have a baby with Down syndrome is higher than a younger mother's chance.

   □ Strongly Disagree □ Disagree □ Neither Agree nor Disagree □ Agree □ Strongly Agree

5. When a father is older than 40 when his partner is pregnant, his chance to have a baby with Down syndrome is higher than a younger father's chance.

   □ Strongly Disagree □ Disagree □ Neither Agree nor Disagree □ Agree □ Strongly Agree

6. The older a mother is, the lower is her chance to have a child with autism.

   □ Strongly Disagree □ Disagree □ Neither Agree nor Disagree □ Agree □ Strongly Agree

7. The older a father is, the lower is his chance to have a child with autism.

□ Strongly Disagree	□ Disagree	□ Neither Agree nor Disagree	□ Agree	□ Strongly Agree

<u>Part B:</u> This section talks about making genetic testing decisions during pregnancy. Genetic testing options include screening tests, such as ultrasound or blood tests, and diagnostic tests, such as amniocentesis or CVS. Check one box for each statement to show if you agree or disagree with each sentence.

1. The mother should make the final decision about genetic testing options for pregnancy.

□ Strongly Disagree	□ Disagree	□ Neither Agree nor Disagree	□ Agree	□ Strongly Agree

2. The father should make the final decision on genetic testing options for pregnancy.

□ Strongly Disagree	□ Disagree	□ Neither Agree nor Disagree	□ Agree	□ Strongly Agree

3. The doctor should make the final decision about genetic testing options for a patient's pregnancy.

□ Strongly Disagree	□ Disagree	□ Neither Agree nor Disagree	□ Agree	□ Strongly Agree

4. The genetic counselor should make the final decision about genetic testing options for a patient's pregnancy.

□ Strongly Disagree	□ Disagree	□ Neither Agree nor Disagree	□ Agree	□ Strongly Agree

5. The parents should make the final decision together on genetic testing options for the pregnancy by agreeing on one option.

□ Strongly Disagree	□ Disagree	□ Neither Agree nor Disagree	□ Agree	□ Strongly Agree

6. Do you think you and your partner would have different opinions on what genetic testing should be done during pregnancy?

□ Yes □ No

7. If you and your partner disagreed on the decision about genetic testing options, who do you think should make the final decision? Please put these in order from the MOST important person to make the final decision (1) to the LEAST important person to make the final decision (4) about genetic testing.

   _____ Doctor
   _____ Mother of the Baby
   _____ Genetic Counselor
   _____ Father of the Baby

<u>Part C:</u> Please answer the next three questions with your opinions about this statement:

Some genetic conditions are related to a parent's age and cannot be tested for during pregnancy at the current time.

1. I would still want to know about any genetic risks for my baby related to parents' ages, even if tests are not available.

   □ Strongly Disagree | □ Disagree | □ Neither Agree nor Disagree | □ Agree | □ Strongly Agree

2. Parents should be informed about all genetic risks related to the mother's age, even if testing is not available for every condition.

   □ Strongly Disagree | □ Disagree | □ Neither Agree nor Disagree | □ Agree | □ Strongly Agree

3. Parents should be informed about all genetic risks related to the father's age, even if testing is not available for every condition.

   □ Strongly Disagree | □ Disagree | □ Neither Agree nor Disagree | □ Agree | □ Strongly Agree

4. Doctors and counselors can tell you about health risks for pregnancy in different ways. One way is to talk about a risk number from the mother and then a risk number from the father. Another way is to combine the couple's estimate of risk together. Which would you rather hear?

   □ Two separate risk numbers based on each parent

   □ One combined risk number for the couple

<u>Part D:</u> This set of questions asks about how you like to hear numbers about health risks.

1. The options below are different ways of stating the same risk number. Imagine you are talking to a doctor about your child's health risks. Which option from the list below do you most easily understand and would want the doctor to use?

   □ 10% chance
   □ 1/10 chance
   □ 1 chance in 10
   □ 10 chances out of 100

2. Imagine there is a chance your child might be born with a serious condition such as a heart condition. How would you want the doctor to present this information to you?

□ 1 chance in 10 of having the condition, and 9 chances out of 10 of NOT having the condition
□ 1/10 chance of having the condition, and 9/10 chance of NOT having the condition
□ 10% chance of having the condition, and 90% chance of NOT having the condition
□ 10 chances out of 100 of having the condition, and 90 chances out of 100 of NOT having the condition

3. Of your answers to these two questions, which do you like better?

□ Answer from Question #1 □ Answer from Question #2

<u>Part E:</u> Read the following situations about possible <u>future</u> genetic testing options for pregnancy. Please explain why you would or would not want to have the testing done.

1. A genetic counselor explains during a future pregnancy that your baby may be at a higher risk for autism due to a parent's age. The counselor tells you about a new blood test for pregnant mothers that can detect genes related to autism. The mother's blood test could be done to find out if the baby will have autism. If you (or your partner) were pregnant and heard this information, would you choose this test in your <u>future</u> pregnancy?

   □ Yes □ No □ I don't know

   Why did you choose that answer?

   _____

   _____

2. Your doctor tells you that the child you are expecting may develop epilepsy (seizures) by the time he or she is a teenager. Your doctor offers a new scanning test that can tell if your child is at a higher risk or a lower risk for seizures. Would you choose this test in your <u>future</u> pregnancy?
   □ Yes □ No □ I don't know

   Why did you choose that answer?

   _____

   _____

3. A genetic counselor tells you about a mother's blood test during pregnancy that can detect certain learning problems that would require special school plans for a child to succeed. If you (or your partner) were pregnant and heard this information, would you choose this test in your future pregnancy?

   □ Yes □ No □ I don't know

   Why did you choose that answer?

   _____

   _____

4. For some genetic conditions, ultrasound imaging during pregnancy might be the only screening test available to you. This may include possible genetic risks in the baby related to the ages of the mother or the father. The genetic counselor tells you in a future pregnancy that all of these conditions can be explained to you before your ultrasound is started. If she counseled you after your ultrasound, she would only explain a specific condition your child is at higher risk for based on the ultrasound. When would you want to hear this information?

   □ I would want to hear about every risk to the baby before the ultrasound is done.

   □ I would only want to hear about a specific risk to the baby after the ultrasound if the doctor sees something of concern on the ultrasound.

   Why would you make that decision?

   _____

   _____

   Other answers or thoughts you might have about this question:

   _____

   _____

   _____

Part F: Please answer the following questions about yourself.

What is your age? _____

What is your gender? □ Male □ Female

What is your highest level of schooling?

□ Did not finish high school
□ Finished high school or GED
□ Some college education
□ Associate's Degree
□ Bachelor's Degree
□ College beyond Bachelor's degree

With which ethnicity do you best identify?

□ Asian
□ Black
□ Hispanic
□ Native American
□ White
□ Other (please specify): _____

What is your marital status?

□ Single/Never Married
□ Married
□ Widowed
□ With a Partner
□ Separated
□ Divorced
□ Remarried

Do you have children outside of any current pregnancy? □ Yes □ No

How many do you have (including any current pregnancy)? _____

If you do not have children today, do you hope to have children someday? □ Yes □ No

---------- **End of Survey** ----------

Thank you very much for taking the time to help with our study. Your answers will help us continue to provide the best care possible for our patients.

When you have completed the survey, please mail it back to us using the postage-paid envelope provided. If you have any questions about the study or the topics in this survey, please email Andrew Gunter (atgunter@gmail.com) or contact my advisor, Peggy Walker, Genetic Counselor, at Peggy.Walker@uscmed.sc.edu

<u>Optional:</u> If you would like to be entered into a drawing for a $25 gift card to a local restaurant or store, please provide the following contact information. Any information will be used only to contact winners of the drawing. This page will be separated from your survey as soon as we open the envelope from you. Contact information will not be connected with your survey answers and will not be used for any other purpose.

Name: _____ (First and Last Names)

Preferred Phone Number: _____

Mailing Address: _____ (Number and Street)

_____ (City, State, ZIP)

Email Address (optional): _____

University of South Carolina School of Medicine
USC Genetic Counseling Program

Dear Potential Participant:

You are invited to take part in a graduate research study focusing on pregnancy risks related to older parents' ages. I am a graduate student in the genetic counseling program at the University of South Carolina School of Medicine. My research looks at what patients and their partners understand about genetics issues and also how a couple makes decisions about pregnancy care. The research involves taking a survey that is included in the packet given to you. Each survey is meant to be filled out individually, either by a patient or her partner.

The survey asks your opinions about how you interpret and use numbers, how you understand some basic genetic principles, and how you make decisions about your pregnancy care. If you do not wish to answer a certain question, please skip that question and continue with the rest of the survey.

All responses from the surveys will be kept anonymous and confidential. **Please do not write your name on the survey.** The results of this study might be published or presented at scientific meetings; however, your answers will not be identified in any way. The survey should take about 15-20 minutes to complete.

As a thank-you for doing our study, you may be entered into a drawing to win a $25 gift card to a local restaurant or store. You are eligible for the prize whether or not you complete the survey. If you would like to be entered for the drawing, please fill out your contact info on the provided last page of packet; packets may be returned before leaving the office or by mailing using the postage-paid envelope in the packet. If your name is chosen, this prize will be sent to you at a later date, after the study is done. Your contact information will not be used for any other purposes besides sending you the gift card if your name is drawn.

Your participation in this research is voluntary. By completing the survey, you are consenting that you have read and understand this information. At any time, you may withdraw from the study by not completing the survey.

Thank you for your time and consideration for taking part in this study. Your answers may help genetic counselors provide the best care for patients and their partners. If you have any questions about this research, you may contact either me or my faculty adviser, Peggy Walker, MS, CGC, at the information below. If you have any questions about your rights as a research member, you may contact the Office of Research Compliance at the University of South Carolina at (803)777-7095.

Sincerely,

Andrew Gunter, BS, BA
Master of Science Candidate
USC School of Medicine
USC Genetic Counseling Program
Two Medical Park, Suite 208

Peggy Walker, MS, CGC
Faculty Adviser
USC School of Medicine
USC Genetic Counseling Program
Two Medical Park, Suite 208

Columbia, SC 29203
atgunter@gmail.com
(803) 341-2808

Columbia, SC 29203
Peggy.Walker@uscmed.sc.edu
(803) 545-5746