THE EMOTIONAL STATES ASSOCIATED WITH REPRODUCTIVE DECISION MAKING IN WOMEN WITH A *BRCA* PATHOGENIC VARIANT

by

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The Emotional States Associated with Reproductive Decision-making in Women with a *BRCA* Pathogenic Variant

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Background: Women who inherit a *BRCA* pathogenic variant are 6 times more likely to develop breast cancer and 4 times more likely to develop ovarian cancer over the course of their lifetime. These are devastating statistics for women who are told this, as carrying this mutation can have a significant impact on family planning decisions in these women who are of reproductive age. Since the primary preventative measures include risk-reducing surgery that can render women infertile, the psychological and physiological consequences can be overwhelming since cancer risk reduction must be balanced with family planning. The aim of this study was to explore the role of emotional states on reproductive decision-making in women with a known *BRCA* pathogenic variant.

Methods: This exploratory, descriptive study included women with a *BRCA* pathogenic variant recruited from a familial cancer registry. Data were collected via a validated questionnaire to measure emotional states, familial cancer registry records and medical records. Logistic regression was performed to assess the relationship between emotional states, *BRCA* pathogenic variant status and individual factors on reproductive decision-making. Descriptive statistics were used to characterize the sample of women.

Results: 85 women completed data collection. There were no significant interactions between emotional states and reproductive decision-making. Age at genetic testing and number of children were significant for predicting being finished having children. Women who had a female relative with ovarian cancer reported higher loss/benefit scores.

Conclusions: Women who are older, and already have children are more likely to be finished having children. Having a relative with ovarian cancer is associated with higher scores of loss/benefit when assessing probability of being finished having children. Future research should identify women newly tested and follow them longitudinally to understand how emotional states change over time and identify vulnerable phases in the reproductive decision-making trajectory.

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Preface

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1.0 Proposal and Introduction

Women who live in the United States have a 12% risk of developing breast cancer and a 2% risk of developing ovarian cancer during their lifetime. For women who carry a pathogenic *BRCA*1 or *BRCA*2 variant, one that affects approximately one in 200-400 women living in the United States, this risk increases (Kuchenbaecker et al., 2017a; Manickam et al., 2018). For breast cancer, lifetime risk ranges from 55-70% for *BRCA*1 carriers by the age of 70 and between 45-70% in *BRCA*2 carriers. For lifetime risk of ovarian cancer, the risk ranges from 40-45% for *BRCA*1 and 15-20% for *BRCA*2 (Kotsopoulos, 2018; Kuchenbaecker et al., 2017a). In addition to the increased personal risk, women with a *BRCA* pathogenic variant have a 50% chance of passing the pathogenic variant to their offspring (U. S. Preventive Services Task Force, 2019).

Overall survival for *BRCA* associated breast and ovarian cancer is similar than that of women with breast or ovarian cancer who do not carry a *BRCA* pathogenic variant (Lieberman et al., 2019). However, due to the increased risk of cancer in these individuals, primary risk reduction strategies are often recommended, especially in those at increased risk for ovarian cancer. Risk-reducing surgical options may include bilateral mastectomy and bilateral salpingo-oopherectomy (U. S. Preventive Services Task Force, 2019). For a young woman who is not ready to make family planning decisions, these surgical procedures can be significantly life altering, especially in bilateral salpingo-oophorectomy, which renders a woman infertile (U. S. Preventive Services Task Force, 2019).

Much research has focused on the myriad of issues associated with women who have tested positively for a *BRCA* pathogenic variant. In the past ten years, requests for pathogenic variant testing have increased twofold to threefold (Evans et al., 2015; Juthe et al., 2015). Studies have

identified factors influencing the decision to have *BRCA* testing including age, and the number of living children. (Battistuzzi et al., 2019; Claes et al., 2004; Halbert et al., 2011; Hesse-Biber et al., 2016; Lynch et al., 2006; Nelson et al., 2005; Pasacreta, 2003). Women with a *BRCA* pathogenic variant who have been diagnosed with cancer have experienced an increase in symptoms of distress, anxiety and depression in the first few months after genetic test disclosure (Beran et al., 2008; Bosch et al., 2012; Claes et al., 2004; Graves et al., 2012; Halbert et al., 2011; Schwartz et al., 2002; Smith et al., 2008; van Dijk et al., 2006). Other research has focused on the decision to have risk-reducing surgery. These studies also found this decision to be influenced by age, in addition to the desire for children, gender of living children and a family history of cancer (Battistuzzi et al., 2019; Gavaruzzi et al., 2017; Hesse-Biber, & An, 2016).

Although women want to be logical in their decision-making, emotions may complicate this process. By definition, emotions are complex, multi-dimensional judgments that reflect a great deal of information about one's relationship to social and physical surroundings. One's own internal thoughts regarding these relationships are also reflected (Lambie & Marcel, 2002; Smith & Ellsworth, 1985). Strong evidence supports the association of emotions and the decision to be tested for a *BRCA* pathogenic variant (Dean et al., 2017a; Rini et al., 2009; Werner-Lin, 2008). However, the role that emotions play in the reproductive decision-making process of women with a *BRCA* pathogenic variant is unknown. Qualitative studies have examined the complex decisions influencing finding a partner and the timing of having children (Dean, 2016; Dean, & Rauscher, 2017a; Dean et al., 2017b; Donnelly et al., 2013b; Rauscher et al., 2017). However, no studies were identified that focused on the emotional aspect of reproductive decision-making.

Lazarus and Folkman's Transactional Model of Stress provides the foundation to better understand the effects of emotion on healthcare decision-making (Bagneux et al., 2012; Lerner et

al., 2005; Lerner et al., 2001; Lerner et al., 2014; Lerner et al., 1999). This model includes three basic dimensions, or emotional states; threat, challenge, and loss/benefit (Folkman et al., 1985). These emotional states are accompanied by core appraisal themes, which influence the likelihood of specific courses of action (Frijda, 2002; Lazarus, 1991; LeBlond, 2008). Threat is referred to as the anticipation of psychological or physical damage or loss; challenge results from demands that a person feels confident about mastering and loss/benefit refers to psychological loss or gain that has yet to occur.

The Agency for Healthcare Research and Quality (AHRQ) has been authorized by the U.S. Congress to convene the United States Preventive Services Task Force (USPSTF) and to provide ongoing scientific, administrative, and dissemination support to the Task Force. The Task Force works to improve the health of all Americans by making evidence-based recommendations about clinical preventive services such as screenings, counseling services, and preventive medications (U. S. Preventive Services Task Force, 2019). In their Final Evidence Synthesis for *BRCA* Related Cancer in Women, the Task Force reports that younger women are subjected to additional harms related to the impact of risk-reducing surgery on reproductive life decisions (U. S. Preventive Services Task Force, 2019). These harms include an increase in anxiety, depression, distress and uncertainty. It is safe to conclude that these harms can lead to various emotional states in women who are already distressed. This study will focus on how the three emotional states of threat, challenge, and loss/benefit are associated with patient decision-making and eventual clinical outcomes, such as the decision to undergo risk-reducing surgery.

The purpose of this study is to explore the role of emotional states on reproductive decision-making in women with a known *BRCA* pathogenic variant.

1.1 Aims

Specific Aim 1: Describe the distribution of a *BRCA* pathogenic variant among women who are in the Cancer Family Registry (CFR).

The sample of women in the CFR will be described, including the distribution of *BRCA*1 and *BRCA*2 pathogenic variants.

Specific Aim 2: Explore the association between emotional states and reproductive decision-making.

The primary emotional states of threat, challenge and loss/benefit, as defined by the Transactional Model of Stress, will be assessed using the Appraisal of Life Events scale questionnaire in women who are *BRCA* positive and have made or are making reproductive decisions.

Specific Aim 3: Explore the association between individual factors (age, race, ethnicity, marital status, number of children and family history of breast and ovarian cancer) and reproductive decision-making.

Individual factors (age at diagnosis, race, ethnicity, marital status, number of children and family history of breast and ovarian cancer) will be assessed to explore their influence on reproductive decision-making. Individual factors will be assessed using a combination of self-report and information from the medical record.

Specific Aim 4: Explore how *BRCA* pathogenic variant status (*BRCA*1 vs *BRCA*2) moderates the relationship between emotional states and reproductive decision-making.

BRCA pathogenic variant status, measured from the CFR, will be assessed to explore its moderation on the relationship between emotional states and reproductive decision-making.

Specific Aim 5: Explore how individual factors moderate the relationship between emotional states and reproductive decision-making.

Individual factors will be assessed to explore their moderation between emotional states and reproductive decision-making.

The results of this pilot study will provide critical information regarding emotions and reproductive decision-making to inform further research which may lead to successful interventions to support women with a *BRCA* pathogenic variant.

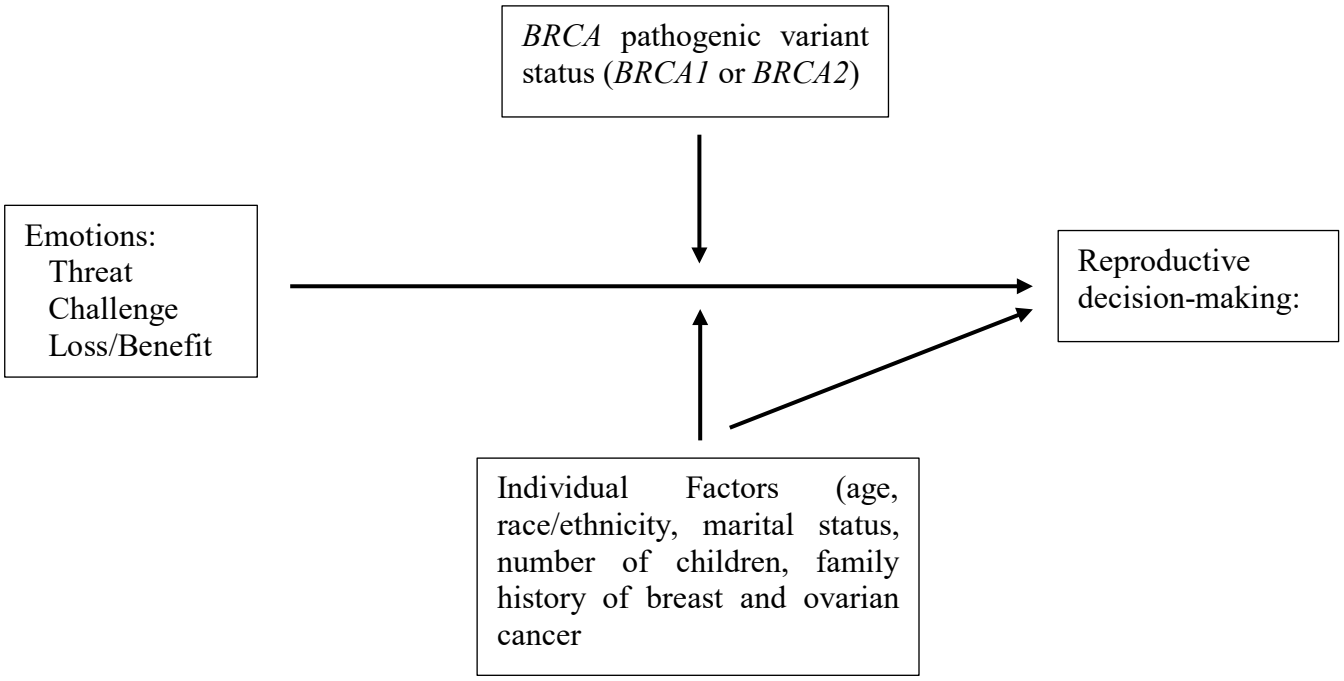

Figure 1 Investigator-developed Conceptual Model

1.2 Background and Significance

1.2.1 Epidemiology of *BRCA*1 and *BRCA*2 Pathogenic variants

Breast cancer genes *BRCA*1 and *BRCA*2 are genes that produce tumor suppressor proteins. The role of these proteins is to repair damaged DNA, thus ensuring the stability and integrity of each cell's genetic material (National Cancer Institute, 2018a). When either of those genes are mutated, the repair work of damaged DNA may not occur. Because of the inability to repair DNA, additional genetic alterations occur, which can lead to cancer. Specific inherited *BRCA* pathogenic variants increase the risk for ovarian and breast cancers. Women who have inherited pathogenic variants in *BRCA1* and *BRCA2* tend to develop breast and ovarian cancers at younger ages than people who do not have these pathogenic variants. These gene pathogenic variants are responsible for 5% to 10% of all breast cancers and 10% to 15% of all ovarian cancers (Heald et al., 2016). The *BRCA*1 gene, discovered in 1994, is located on chromosome 17. More than 1,200 variants have been associated with increased risks of cancer (Nelson et al., 2019b). The *BRCA*2 gene, discovered in 1995, is located on chromosome 13. More than 1,330 variants have been associated with increased risks of cancer (Nelson et al., 2019b).

1.2.2 *BRCA* Pathogenic variant in the General Population

Women who have a *BRCA* gene pathogenic variant have an increased risk of breast and ovarian cancer. The estimates of risk are high: the chance of developing breast cancer by the age of 70 is 55-70% for *BRCA1* carriers and 45-70% for *BRCA2* carriers (Antoniou et al., 2008; Chen et al., 2007; Struewing et al., 1997). Women in the general population have a 7% chance of a

breast cancer diagnosis by the age of 70 (SEER, 2019). To put these risk estimates into perspective, by the age of 70, in a group of 100 women without a *BRCA1* or *BRCA2* pathogenic variant, 7 will be diagnosed with breast cancer and in a group of 100 women with a *BRCA* 1 or *BRCA2* pathogenic variant, 45-65 will be diagnosed with breast cancer. For ovarian cancer, the difference in risk predictions are even higher. The lifetime risk of ovarian cancer by the age of 70 for women in the general population is less than 2% (American Cancer Society, 2018). However, for women with a *BRCA1* pathogenic variant, the risk increases to 40-45%. Similarly, for women with a *BRCA2* pathogenic variant, the risk increases to 10-30% (Genetics of Breast and Gynecologic Cancers, 2018).

1.2.3 *BRCA* Pathogenic variant in High Risk Populations

Specific *BRCA* pathogenic variants are clustered among certain groups, including Ashkenazi Jews, specific populations of Blacks and Hispanics, and in families in the Netherlands, Iceland and Sweden (Rafnar et al., 2004; Tryggvadottir et al., 2003; Vallee et al., 2012; Weitzel et al., 2003). Ashkenazi Jews have the highest prevalence of *BRCA* pathogenic variants among all the high-risk groups. In this population, one in 40 women will have a *BRCA* pathogenic variant. Of the Ashkenazi Jewish women in the United States who have been diagnosed with breast cancer, 10% of diagnoses are due to a *BRCA* pathogenic variant (King et al., 2003). Approximately 5-10% of women with breast cancer have a mother or sister with breast cancer and 20% have either a first-degree or second-degree relative with breast cancer.

1.2.4 Inheritance of a *BRCA* Pathogenic Variant

Individuals can be assessed for their individual likelihood to carry a *BRCA* pathogenic variant based on their own personal and family histories of cancer. *BRCA* pathogenic variants are inherited in an autosomal-dominant pattern, meaning that if one parent has the pathogenic variant, each offspring has a 50% chance of inheriting it (National Institute of Health, 2019). Typically, most individuals discover that they are carriers when another family member, typically a mother, grandmother, aunt or sister, is diagnosed with either breast or ovarian cancer. When an individual is found to carry a variant in one of the *BRCA* genes, there are a variety of surveillance, chemoprevention, and risk reducing surgical strategies available for consideration.

1.2.5 Risk Management Strategies

Clinical decision-making regarding which strategy to pursue for cancer risk reduction involves a consideration of life expectancy and quality of life. Past research has suggested that decision aids or data from models may help individuals choose among various options (Grann et al., 2010; Kurian et al., 2009; Schrag et al., 1997, 2000; van Dijk et al., 2008). Most of these options include using decision analysis and the concept of time tradeoffs, identifying the years of life saved by one strategy versus another. Though these methods are used in a clinical research, they often are not used in clinical practice. Clinical practice options include surveillance, chemoprevention and risk-reducing surgery.

1.2.5.1 Surveillance

Women with a *BRCA* pathogenic variant are encouraged to begin breast self-awareness at the age of 18, schedule clinical breast exams every 6 to 12 months beginning at age 25, and depending on the breast cancer history within the family, undergo annual breast MRI's (magnetic resonance imaging) starting at the age of 25 (Committee on Practice Bulletins- Gynecology, 2017). Annual mammograms and MRI's are recommended after the age of 30 years, preferably one or the other every 6 months. For comparison, women without an increased risk to develop breast cancer begin mammograms at the age of 40 or ten years prior to the earliest diagnosis of breast cancer in their family. There is no effective screening method to detect ovarian cancer (Committee on Practice Bulletins- Gynecology, 2017). Surveillance is especially critical for women with *BRCA1* and *BRCA2* pathogenic variants because of their increased risk.

1.2.5.2 Chemoprevention

Chemoprevention has been evaluated as an option for high risk women. It is defined as the inhibition of carcinogenesis using natural or synthetic agents (Murthy et al., 2019). In both pre- and postmenopausal women, tamoxifen can be used for risk reduction, which may reduce breast cancer risk by 62% in *BRCA*2 pathogenic variant carriers (Goss et al., 2011; Nazarali et al., 2014; Nelson et al., 2019a). Oral contraceptives have been found to decrease ovarian cancer risk due to the inhibitory effect on ovulation, although contraceptives increase the risk for breast cancer. A case control study (n=799) found that oral contraceptives caused a reduced risk of ovarian cancer in carriers of *BRCA1* pathogenic variants (odds ratio 0.56) and carriers of *BRCA2* pathogenic variants (odds ratio 0.39) (McLaughlin et al., 2007). In fact, individuals who use oral contraceptives for 5-10 years decrease their risk by 30-50% (National Cancer Institute, 2018b). Women with a *BRCA* pathogenic variant seek for cancer risk reduction while maintaining fertility.

1.2.5.3 Risk-Reducing Surgery

Risk reducing surgeries have proved successful in reducing breast and ovarian cancer occurrence. Previous research focusing on *BRCA* pathogenic variant carriers found that women with *BRCA* pathogenic variants who underwent risk reducing bilateral mastectomies reduced their risk of developing breast cancer by 90% or more (Domchek et al., 2010; Geiger et al., 2005; Heemskerk-Gerritsen et al., 2007; Ingham et al., 2013; Ludwig et al., 2016; Meijers-Heijboer et al., 2001; Rebbeck et al., 2004).

To reduce the risk for ovarian cancer, a woman who has a *BRCA* pathogenic variant may have a risk-reducing salpingo-oophorectomy (RRSO). This typically occurs after 35-40 years of age for *BRCA*1 and by 40-45 years of age for *BRCA*2 or after she has completed her family. This risk-reducing surgery not only decreases the risk of ovarian cancer in *BRCA* pathogenic variant carriers, but also decreases mortality (Domchek, 2019; Domchek et al., 2010; Kauff et al., 2008; Rebbeck et al., 2009). Rebbeck and authors found that the relative risk of ovarian and other gynecologic cancers after RRSO was 0.04 (95% CI 0.01 – 0.16), while Kauff and authors found that the relative risk of breast and ovarian cancer could be as high as 0.25 (95% CI 0.08 – 0.74) (Kauff et al., 2008; Rebbeck et al., 2002).

1.2.6 Reproductive Choices

The challenge with adhering to risk reducing guidelines for women with *BRCA* pathogenic variants is that at the point that surgery is discussed, some women may not have started their families, or are unsure if they are finished. This can lead to difficult discussions as the woman must balance their desire for family completion with their own risk reduction measures. The United States Preventive Services Task Force recommends guidelines that state RRSO should be

performed after childbearing is completed or at 35-40 years of age for *BRCA1* pathogenic variant carriers or at 40-45 years of age for *BRCA2* pathogenic variant carriers(Force et al., 2019). Women who discover their high-risk status while their families are incomplete are faced with making a decision about this risk-reducing surgery. After the diagnosis of a *BRCA* pathogenic variant, women who already have children may be less likely to desire additional children than non-carriers (Smith et al., 2004). Subsequently, women who have not had children yet are significantly more distressed about treatment-related infertility, even ten years after diagnosis (Camp-Sorrell, 2009; Canada et al., 2012). This concern may be compounded when discussing the implications of a positive result for future and current children (Lynch et al., 2006; Speice et al., 2002).

Women without children are often more concerned about future childbearing (Brunstrom et al., 2016; Hoskins et al., 2008; Patenaude et al., 2006). Decision-making conflict surrounding the timing of risk-reducing surgery and childbearing has been commonly expressed by women who are young adults, and is a particularly distressing topic for those who feel they are too young to be considering such decisions (Brunstrom et al., 2016). For women in partnered relationships, an awareness of their own cancer risk increases the complexity of decision-making about the timing of pregnancy. (Hoskins et al., 2008). Bearing young children who might have a heightened risk of cancer raises challenging issues for partners who are discussing surveillance and maternal life expectancy (Hamilton, 2012; Hoskins et al., 2008; Werner-Lin et al., 2012). Risk perception for mothers appears strongly linked to their parenting role. Several studies found that young women's greatest concern was the possibility of leaving children motherless, especially for women who had experienced the death of their mother (Brunstrom et al., 2016; Hamilton, 2012; Hoskins et al., 2008; Werner-Lin, 2008; Werner-Lin et al., 2012).

1.2.6.1 Preimplantation Genetic Diagnosis

For women who choose to undergo prophylactic surgery before their family plans are completed, decisions need to be made about whether they want their children to be biological, and if so, free of the *BRCA* pathogenic variant (Woodson et al., 2014). Preimplantation genetic diagnosis (PGD), as part of the IVF process, allows for the selection and transfer of unaffected embryos that begins with standard IVF. Following fertilization, embryos are tested for the pathogenic variant. Embryos without a *BRCA* pathogenic variant are reserved for implantation. Clinical and moral dilemmas arise when all embryos are affected with a *BRCA* pathogenic variant or if the pathogenic variant cannot be determined. In situations where the couple only has affected embryos that can be used, some couples may elect not to transfer any, if the concern for their future offspring having a *BRCA* pathogenic variant outweighs the desire for biological children.(Herlihy, 2018). If one parent is a carrier, consideration may be given to consider using donor ova or sperm (Lin et al., 2017; Murray, 2005).

Previous research has identified that the use of PGD for *BRCA* pathogenic variants is growing and has become the most common indication in some settings, but the awareness regarding its availability varies among countries and is still low (Derks-Smeets et al., 2014b; Gietel-Habets et al., 2017; Gietel-Habets et al., 2018a; Gietel-Habets et al., 2018b; Quinn et al., 2009; Quinn et al., 2010b). Governmental regulation of PGD varies among countries. In France, the Netherlands, and the United Kingdom, the use of PGD is regulated by the government and is case-specific. A *BRCA* pathogenic variant is one of the most frequent indicators for PGD, consequently women in those countries would have positive opinions regarding PGD. In the United States, the use of PGD is not regulated. As a result, it may be used at the discretion of fertility specialists and their patients. Infertility specialists, OB/GYN's, geneticists and genetic

counselors prioritize the needs of patients when assisting with the decision for whom PGD should be used (Bayefsky, 2018). A recent survey of 1081 *BRCA* pathogenic variant carriers highlighted that patients are supportive of reproductive counseling, with 59% stating that PGD should be offered(Chan et al., 2017).

1.2.6.2 Cryopreservation Techniques

Established cryopreservation techniques include the freezing of embryos and oocytes and the use of in-vitro fertilization (IVF). These techniques are associated with a high likelihood of successfully generating offspring. Other options, such as the use of a gestational carrier or adoption, are also viable options for women looking to complete their families under the constraint of being a high-risk pathogenic variant carrier(Chan et al., 2017; Derks-Smeets et al., 2014b; Donnelly et al., 2013b; Fortuny et al., 2009; Friedman et al., 2005; Gietel-Habets et al., 2017; Insogna et al., 2016; Mor et al., 2018; Pellegrini et al., 2014; Quinn et al., 2010b; Rubin et al., 2014; Woodson et al., 2014). In addition to family planning, parents are confronted with the question of preventing their children from inheriting the pathogenic variant. Since carrying a *BRCA* pathogenic variant is associated with an autosomal dominant inheritance pattern, the probability of transmitting a pathogenic variant to each offspring is 50% (Gietel-Habets et al., 2017). This high probability is one of the main reasons for undergoing genetic testing (Meiser et al., 2006; Pasacreta, 2003).

For women who do not have a preference as to whether the child is biological or not, adoption is an option that they can pursue. For those who wish for their children to be biological, they might choose between using a surrogate after risk-reducing surgery, or IVF. Women who

wish for their children to be free of a *BRCA* pathogenic variant must further decide about the use of PGD or IVF.

Embryo cryopreservation following in vitro fertilization is the most widely used and available method of fertility preservation (Farland et al., 2014). Cryopreserved, thawed embryos are used in approximately 20% of all assisted reproductive technology cycles. Live birth rates occur in 45% of patients under the age of 35. In this method, ovum are removed and combined with sperm to form embryos, which are frozen. Embryos can be thawed and placed in the uterus when decision-making is complete, and the woman is ready for childbearing. Another opportunity is ova freezing, a process where ova are extracted, frozen, and stored, for future fertilization.

A surrogate is a woman who agrees to carry a pregnancy for another woman. The intended mother and father provide the egg and sperm. IVF is used to create embryos, which are transferred for implantation. Adoption is another option for women who want to proceed with risk-reducing surgery. Women may also make the decision to not have children.

Ethical and moral dilemmas arise when all the embryos are affected with a *BRCA* pathogenic variant, or it is unable to be determined if the embryos carry the *BRCA* pathogenic variant. The ethical question is whether the burdens of carrying susceptibility genes are so great for the child and parents that the burdens of IVF to screen embryos to avoid giving birth to affected children are justified (Robertson, 2003). These moral dilemmas include cases where couples have only affected embryos and they decide to discontinue the process when the concern for their future offspring having a *BRCA* pathogenic variant outweighs the desire for biological children (Herlihy et al., 2018).

1.2.7 Decision-Making

Decision-making is a broad term that applies to the process of making a choice between options in of action (Thomas et al, 1991). In decision theory, when making decisions while dealing with uncertainty, if information about the best course of action arrives after making a fixed decision, the human response of regret is often experienced (Bell, 1982). Making decisions under uncertain circumstances is especially relevant for women who are *BRCA* positive. Much research has focused on decision-making in regards to the surgical decisions as well as the decision to undergo genetic testing in women who have a known family history of breast or ovarian cancer (Brunstrom et al., 2016; Cherry et al., 2013; Finch et al., 2012; Garcia et al., 2014; Hartmann et al., 2016; Hesse-Biber, 2014; Hoskins et al., 2013; Howard et al., 2009; Kim et al., 2013; Kim et al., 2015; Mai et al., 2017; Singh et al., 2013; Watts et al., 2012; Westin et al., 2011).

Several qualitative studies focusing on women with a *BRCA* pathogenic variant have laid the groundwork for future research. Women are reported to face complex decisions regarding reproduction, when learning their pathogenic variant status. Women in committed relationships placed an emphasis on pregnancy and having as many children as desired before undergoing the risk-reducing surgery(Dean, & Rauscher, 2017a; DiMillo et al., 2013; Donnelly et al., 2013b; Ormondroyd et al., 2012a; Rowland et al., 2016). Women with a *BRCA* pathogenic variant experience urgency to have children by the age of 35, but when that is not possible, they consider extending their preventive surgery timeline in order to bear children despite their own personal cancer risk (Hamilton et al., 2016; Quinn et al., 2010b; Werner-Lin, 2008; Woodson et al., 2014; Young et al., 2019). Making such decisions is an emotionally charged experience.

1.2.7.1 Individual Factors and Reproductive Decision-Making

Various factors have been shown to influence patients' decision-making, especially pertaining to family formation. Age contributes significantly to a woman's decision to reproduce. Women who are older and childless place a greater emphasis on getting pregnant and having as many children as desired (Donnelly et al., 2013b; Gietel-Habets et al., 2017). This is especially true in women with a *BRCA* pathogenic variant, since after undergoing surgery that renders them infertile, they are unable to have biological children. Marital status also plays a role. Women without partners reported that knowledge of a *BRCA* pathogenic variant influenced their decisions regarding marriage (Chan et al., 2017; Hamilton, 2012; Hoskins et al., 2008; Werner-Lin et al., 2012). Forty percent had a greater desire to be married and fifty percent felt more pressure to be married after learning their *BRCA* pathogenic variant status.

1.2.7.2 Emotional States and Reproductive Decision-Making

Reproductive decision-making is highly individualized and difficult. It can affect the decision makers negatively, resulting in conflict or regret (Derks-Smeets et al., 2014a; Ormondroyd et al., 2012b). Previous research has demonstrated that female *BRCA* carriers seek assistance for reproductive decision-making (Quinn et al., 2010a). Specifically, they identified themes concerning the psychosocial impact of carrying a *BRCA* pathogenic variant, including feelings of guilt about passing the pathogenic variant to current and future children. Young women with a *BRCA* pathogenic variant experienced a broad range of intense feelings (Hamilton et al., 2010; Hoskins, & Werner-Lin, 2013; Werner-Lin, 2008; Young et al., 2017). Decision-making was not easy and did not occur quickly. This is consistent with previous qualitative research highlighting the challenges facing this population (Hamilton, & Hurley, 2010). Several other

studies identified motives and considerations that played a role in the decision-making process (Dekeuwer et al., 2013; Derks-Smeets et al., 2014a; Donnelly et al., 2013a). To mitigate decisional conflict and regret, it was important for couples to make an informed decision. Counselling should help couples obtain relevant information and make a methodical and deliberate decision (Jackson et al., 2008; van den Berg et al., 2005). Emotions play an important role in decision, but it is unclear which emotions are predominant. Acknowledging these emotions can guide nurses to recognize patient concerns, discuss healthcare issues and provide the decision support needed for this vulnerable population.

1.2.8 Transactional Model of Stress- Appraisal of Life Events scale

The Appraisal of Life Events (ALE) scale was developed in response to the need to measure primary appraisals based on of the Transactional Model of Stress. In this model by Lazarus and Folkman, stressful experiences are presented as person-environment transactions, in which the impact of an external stressor is mediated by the person's response to the stressor (Lazarus, 1987). According to Lazarus and Folkman, the way that people appraise their stressors is related to the choice of coping strategies. An appraisal is defined as 'a cognitive predisposition to appraise future events that triggered the emotion (Lerner, & Keltner, 2001). Patterns of cognitive appraisals along dimensions of emotion provide a basis for comparing and contrasting discrete emotions (Ferrer et al., 2013). When individuals confront a stressful situation, primary and secondary appraisals are initiated (Lazarus, 1991). In primary appraisal, a person considers the quality and the nature of the stimulus event and the relevance of that event to themselves. When a stressor is appraised as requiring a coping response, individuals evaluate their resources and abilities to cope with the stressor. This is known as secondary appraisal (Lazarus, 1987). An

appraisal driven approach allows one to systematically examine the effects of emotions on decision-making. Basic dimensions are believed to underlie primary appraisals, such as threat, challenge and loss/benefit. This study will investigate emotions influencing reproductive decision-making.

The ALE scale was developed to allow respondents to reflect on the impact of a previously experienced event. Three dimensions underlie primary appraisals: threat, challenge, and loss/benefit. Threat is referred to as the anticipation of psychological or physical damage or loss; challenge results from demands that a person feels confident about mastering and loss/benefit refers to psychological loss or gain that has yet to occur.

A previous study explored the relationship of appraisal, coping and adjustment in women and men experiencing infertility concerns. Evidence supported significant associations of the ALE scale with stress measures, and with coping (Bayley et al., 2009). They found that appraisals of infertility as threat or loss were associated with increased infertility-related stress, whereas viewing infertility as a challenge was related to increased well-being. Another study used the ALE to assess appraisals in women experiencing infertility. In this study, Gourounti and colleagues used the ALE and found that loss and threat were two factors experienced by individuals experiencing infertility (Gourounti et al., 2010).

1.3 Innovation

Previous research has focused on the emotional distress experienced by women undergoing genetic testing for a *BRCA* pathogenic variant (Bredart et al., 2013; Hamilton, & Hurley, 2010; Mella et al., 2017). No research has explored the relationship between emotions and reproductive

decision-making in women with a *BRCA* pathogenic variant. Since these women face difficult decisions with limited time it is critical to focus on emotions that are key to decision-making. This exploratory study should lead to future research that will address how complex emotional states are associated with reproductive decision-making.

2.0 Research Design and Methods

2.1 Design

This exploratory, descriptive, IRB Approved study is designed to describe the association between emotion and reproductive decision-making in women who have been tested positive for a *BRCA* pathogenic variant. A secondary data analysis will be conducted using the Cancer Family Registry (CFR), housed at the Cancer Genetics Program at UPMC Magee-Womens Hospital. The CFR serves as a depository of data that can be used by researchers (Institutional Review Board) approval. Most information in the Registry is self-report.

The principal investigator and co-investigators of the Cancer Family Registry have approved this study to collect data retrospectively and prospectively.

2.2 Sample and Sampling Procedures

2.2.1 Sample Selection

374 women with a known *BRCA* pathogenic variant are enrolled in the Cancer Family Registry at UPMC Magee-Womens Hospital. Women included in this database have been contacted by a questionnaire regarding their interest in participating in future research studies. The convenience sample for this study includes individuals who agreed to participate.

Inclusion Criteria. 1) Women 18 years of age and older, 2) Women who have a known *BRCA* pathogenic variant, confirmed by genetic testing and 3) Literate English speaker with telephone access.

2.2.2 Sample Size Justification

The CFR was established to enroll individuals who have been found to carry a genetic predisposition to cancer, or a personal or family cancer history suggestive of a genetic predisposition. The original parent sample contains 374 individuals from the CFR who have a *BRCA* pathogenic variant. Prior to this study, individuals who were part of the Registry were mailed a follow-up questionnaire to 1) assess interest in being a continued part of the Registry and other studies and 2) update any demographic or personal information from when they were consented to the Registry. 75 individuals with a *BRCA* pathogenic variant responded to the mailing. 93 mailings were returned as undeliverable. Based on the response rate from these follow-up surveys, we will expect approximately a 40% response rate for the current survey. Thus, the sample size is estimated to be 75 subjects available for the analysis of all aims. This 40% response rate was chosen as a conservative measure because studies that have been performed previously in this population have found typical response rates to be between 40-50%. The distribution of *BRCA*1 vs *BRCA*2 in the CFR is approximately 58% *BRCA*1 pathogenic variant and 42% *BRCA*2 pathogenic variant.

2.2.3 Projected Precision of Estimators

When estimating precision for Aim 1, since the aim is a descriptive one, proportions will be estimated. The sample size is fixed at 75 individuals. When estimating continuous variables, the precision would be 0.23σ with a two-sided confidence interval and a standard deviation of 1.00. When estimating categorical variables, with a fixed sample size of 75, a two-sided confidence interval of 95% and a standard deviation of 1.00, the margin for precision would be 0.113.

Specific Aims #2 and #3 explore associations. When exploring associations, identification of precision when estimating correlation coefficient would be calculated. The precision will be dependent on the size of the correlation (see Table 2). If there is a small correlation (0.1), the margin of precision would be expected to be 0.225. If there is a medium correlation, the margin of precision would be expected to be 0.21 and finally, with a large correlation, the margin of precision would be expected to be 0.175.

Aims #4 and #5 would use the logistic regression model to detect the interaction terms and the relationship of emotional states and reproductive decision-making.

Table 1 *Estimation of Small, Medium and Large Correlations*

Confidence Level	**Sample Size N**	**Target Width**	**Actual Width**	**Margin of Error**	**Sample Correlation r**	**C.I. Lower Limit**	**C.I. Upper Limit**	**Width if r = 0.0**
0.950	75		0.345	0.173	-0.500	-0.653	-0.308	0.454
0.950	75		0.415	0.207	-0.300	-0.493	-0.078	0.454
0.950	75		0.450	0.225	-0.100	-0.320	0.130	0.454
0.950	75		0.454	0.227	0.000	-0.227	0.227	0.454
0.950	75		0.450	0.225	0.100	-0.130	0.320	0.454
0.950	75		0.415	0.207	0.300	0.078	0.493	0.454
0.950	75		0.345	0.173	0.500	0.308	0.653	0.454

2.2.4 Sampling Procedures

Individuals were mailed a study packet containing an introductory letter, a consent form, a demographic and history questionnaire and an Appraisal of Life Events scale survey. Individuals were asked to complete the signed consent form and return it to the PI with study information if they are interested in participating.

2.2.5 Recruitment Procedure

The recruitment process for this study is shown in Figure 2. Individuals who met the inclusion criteria were emailed a study packet consisting of an introductory letter, a consent form, a demographic and history questionnaire, and an Appraisal of Life Events scale. The participants were asked to read the consent form and the introductory letter before completing the paperwork. Upon return of the signed consent form, demographic and history questionnaire, and ALE scale, the participant was mailed a copy of their consent form, along with a thank-you note and a $20 payment. The data received from the participants were entered into Qualtrics and verified by an undergraduate student worker. The data were downloaded from Qualtrics for data analysis.

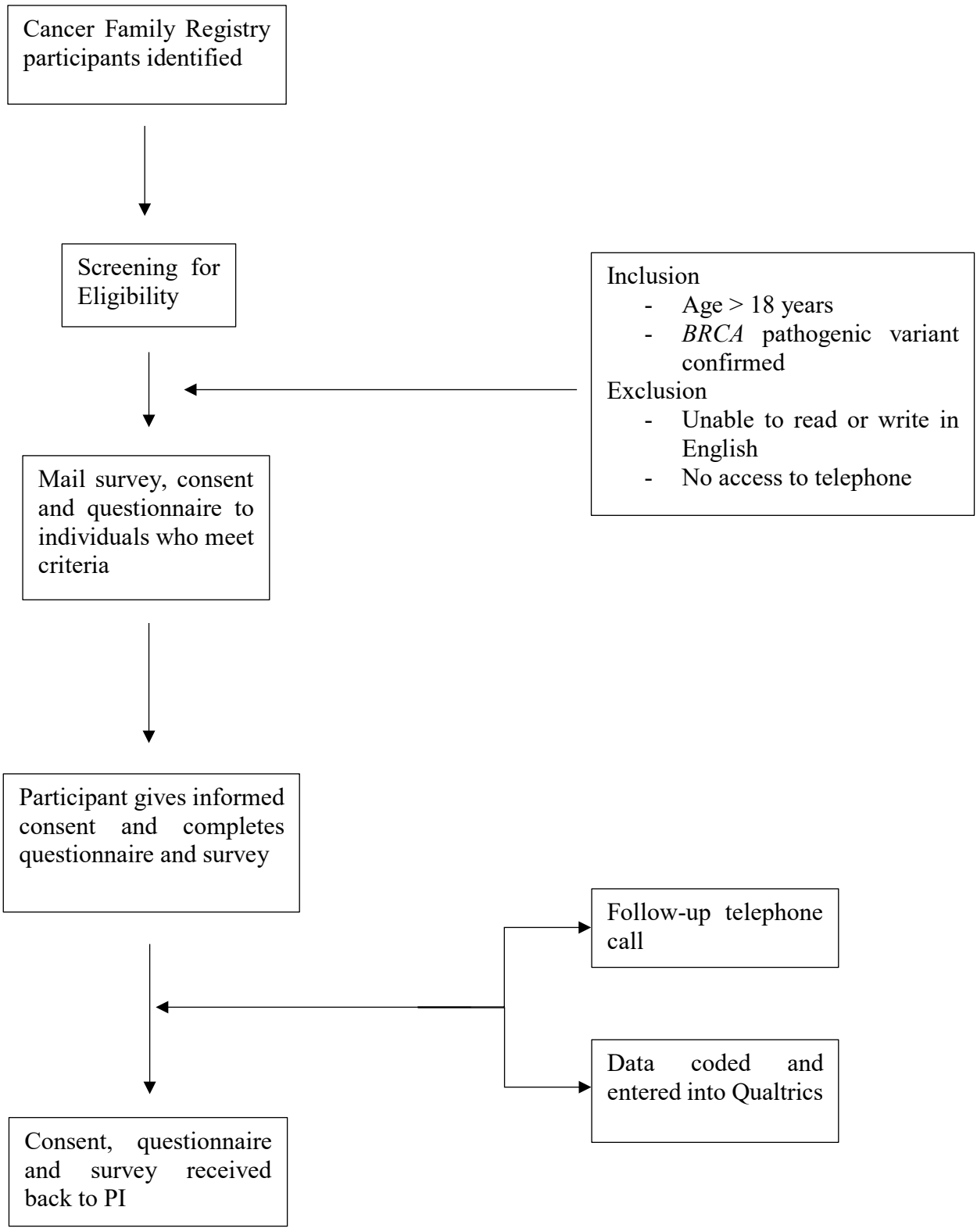

Figure 2 Study Flow Chart for Recruitment

2.3 Instrumentation

Table 2 *Variables and Level of Measurement*

Variable	Level of Measurement	Definition
Age	Continuous, ratio	Single number in complete years
Age at Diagnosis of *BRCA* pathogenic variant	Continuous, ratio	Single number in complete years
Race	Nominal	American Indian, Alaska Native, Asian, Black or African-American, Native Hawaiian or Other Pacific Islander, White
Ancestry	Nominal	Maternal or Paternal self-report
Marital Status	Nominal	Never married, married or living with a partner, separated, divorced, widowed
Number of Children	Continuous, ratio	Single whole number
Family History of Breast and/or Ovarian Cancer	Binary	Yes or No
Reproductive Decision-making	Dichotomous, nominal	"Are you finished having children' measured as Yes or No
Emotional States	Approximate, interval	Rating of emotions including loss, threat and challenge
BRCA pathogenic variant status	Categorical, dichotomous	*BRCA*1 or *BRCA*2

2.3.1 Instrumentation

Sociodemographic form. This form was designed to collect participants' demographic information on current age, age at diagnosis, race, ethnicity, marital status, number of children and family history of breast and/or ovarian cancer. These items are self-reported from the Cancer Family Registry, but will be confirmed through the use of this form. Current age will be a

continuous ratio variable measured by a single number self-reported in complete years. Age at diagnosis of *BRCA* pathogenic variant will be a continuous ratio variable measured by a single number in complete years. Race will be a nominal variable, defined as American Indian, Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander and White. Ancestry will be the self-reported ancestral background of the individual, reported nominally as both the maternal and paternal ancestry (e.g. German, Croatian, Irish). Marital status is a nominal variable and will be defined as never married, married or living as married (with a partner), separated, divorced, or widowed. Number of children will be a continuous ratio variable measured by a single number and family history of breast and/or ovarian cancer will be a binary variable, measured as yes or no. This information will be obtained from the data collection form.

Reproductive Decision-Making. Reproductive decision-making will be measured as a dichotomous, nominal variable measured by the single question "are you finished having children?" with the responses being either "yes" or "no".

Emotional States. Emotional states will be measured by the Appraisal of Life Events scale (Ferguson et al., 1999). Developed in 1999 in the United Kingdom by Eamonn Ferguson, Gerald Matthews and Tom Cox, the Appraisal of Life Events scale has been used in various studies including women experiencing infertility, maternal coping with fetal anomalies and examining the relationship of coaching behaviors in football (Gourounti et al., 2010; Horsch et al., 2013; Peter et al., 2014). The items on the Appraisal of Life Events scale are measured according to dimension. There are 32 response items, 16 in each of two categories, asking to what extent an adjective describes or described an event. In the case of this scale, the event is making a family planning decision under a *BRCA* diagnosis. Each item is ranked on a scale from 0-5. These measures will be approximate interval type measurement. From those individual scores, the sum of certain

individual items will correspond to one of the dimensions: threat, loss/benefit or challenge. The higher the score, the higher the appraisal of threat, challenge or loss/benefit respectively. These three dimensions have demonstrated good internal reliability- Cronbach's α of threat = 0.82, 0.85, 0.86; challenge = 0.87, 0.85, 0.85 and loss/benefit = 0.75, 0.82- respectively (Gourounti et al., 2010; Horsch et al., 2013; Peter et al., 2014).

BRCA pathogenic variant status. *BRCA* pathogenic variant status will be recorded from the Cancer Family Registry and measured as a categorical, dichotomous variable. The responses will either be *BRCA*1 or *BRCA*2. The distribution of *BRCA*1 and *BRCA*2 is 58% and 42% respectively in the Cancer Family Registry.

2.4 Procedures for Data Collection

2.4.1 Data Collection

Upon receipt of the participant questionnaires, data will be entered into a Qualtrics-based electronic database by the study PI and double checked by the undergraduate student research assistant using direct data entry. Qualtrics allows for data merging and transfer to a single file and allows for assurance for direct data entry variables (Agency for Healthcare Research and Quality, 2014).

2.4.2 Data Management

IBM Statistical Package for the Social Sciences for Mac (Version 24, IBM, Inc., Armauk, New York, 2015) will be used for data management. Data will be entered into the database and visually verified by a member of the research team. All data will be checked and corrected through medical record review and by a member of the research team. Once when data are fully verified, variables and values will be labeled, and missing values will be identified to create the data files for analysis. All data will be stored in a password-protected computer and the locked office of the PI for this study. All personal identifiers for the data will be stored in a separate, password protected computer in a locked office. All data analysis will be performed using SPSS. Statistics with p-value of less than or equal to 0.05, two-tailed, will be determined to be statistically significant.

2.5 Data Analysis

2.5.1 Preliminary Data Analysis

2.5.1.1 Descriptive Statistics

Descriptive and exploratory analyses will first be performed using SPSS software to identify any data anomalies (missing data or outliers that may be a result of data entry error) that might invalidate findings of the primary aims analyses to be conducted. To confirm external validity, sample characteristics will be compared to what is currently known in the literature about *BRCA* pathogenic variant carriers.

For continuous variables, appropriate descriptive statistics will be computed to describe sample characteristics and determine observed variable distributions. For categorical variables, frequency distributions will be examined to ensure adequate category size. Pairwise correlations will be calculated to summarize bivariate associations between variables. For categorical variables, frequency counts and percentages will be reported. For the central tendency and dispersion for categorical variables, mode and range will be reported for nominal variables and the median and interquartile range will be reported for ordinal variables. For continuous variables, we will describe central tendency as means and dispersion as standard deviations for normally distributed data.

If the interval and ratio-scaled variables are non-normally distributed, median and semi-quartile range (SQR) or inter-quartile range (IQR) will also be computed as an alternative to mean and standard deviation (SD). The amount and pattern of missing data will be explored and an appropriate imputation strategy, such as stochastic regression or multiple imputation will be performed. Cases with standardized scores (*z*-scores) exceeding the absolute value of 3.29 ($p < .001$, two-tailed test) will be considered as potential univariate outliers. In addition to inspection of *z*-scores, histograms, box plots, and normal probability plots will be used to identify univariate outliers. To reduce the influence of outliers, identified univariate outliers from continuous type interval/ratio scaled variables will be transformed to the next highest/lowest (non- outlier) values plus one-unit increment higher/lower.

The independent variable of emotional states, which is a continuous, interval variable, will be measured by the Appraisal of Life Events (ALE) scale. Frequency distributions will be generated to determine frequency counts and percentages. Central tendency will include examining the mean, and the variability will be examined by the standard deviation. For data that

appears to be non-normally distributed, outliers will first be examined. If the data appears skewed, extreme high or low values will be removed. The dependent variable of reproductive decision-making is a dichotomous, nominal variable. Frequencies will again be used to determine frequency counts and percentages. For the moderator variable of *BRCA* pathogenic variant status, frequencies will once again be used to determine frequency counts and percentages due to the dichotomous nominal nature of the variable.

2.5.1.2 Data Screening

Data accuracy (meaningfulness of the data) and completeness will be checked at the time of data collection and data entry to ensure quality of the data. Data coding and data entry will be rechecked to ensure that no discrepancies exist. Pattern of missingness among data will be checked (look for missing completely at random). Univariate and multivariate outliers will be checked using z-scores and Mahalanobis distance. To check to see if cases will be statistically significant, the standard deviation will be used.

2.5.1.3 Treatment of Missing Data

The first step for dealing with missing data is to observe patterns and determine if the data are missing consistently or missing at random. If missing values are concentrated around a few variables that are not critical to the analysis, these missing values are highly correlated with each other, or they are less than 5% of the sample, then they can be dropped (Osterlind et al., 2001). However, 'non-randomness' methods should be used to preserve all cases. If there are missing values throughout the cases and variables, an option could be to utilize data imputation, using prior knowledge to insert mean values. If the missing values are stochastic, we can consider using regression, expectation maximization and multiple imputation. Another option is to treat the

missing data as data using a dummy variable with complete cases as 0 and missing cases as 1. The mean can then be inserted for missing values and analyzed.

2.5.1.4 Outlier Assessment

For the dichotomous variable, reproductive decision-making, and the demographic variables of race, ethnicity, ancestry, marital status and current occupation, univariate outliers need to be examined using frequency distributions. For the continuous variables, age, number of children and the ALE, univariate outliers will be determined by calculating and examining the z-scores. Any cases with z-scores greater than 3 are potential outliers. Histograms can be used to visually screen for univariate outliers, which would be seen as 'unattached' to the rest of the distribution. Box plots will be used to screen for outlying or extreme values for continuous type variables, since observations typically center around the median. Cases that are far away from the box are viewed as extreme cases or outliers (Osterlind et al., 2001).

When considering the pairs of continuous dependent variables and continuous independent variables, bivariate plots between variables or scatterplots can be used to determine the outliers. The Mahalanobis distance, which is the distance of a case from the centroid of the remaining cases, can also be calculated (Mertler et al., 2016). Creating interaction terms would also be important to examine the effects of emotional states and individual factors on reproductive decision-making.

In regression models, the influence of the outliers must be considered after identifying and describing outliers after model fit by examining Cook's D (Chatterjee et al., 2013) This measures how much the residuals have changed if a particular case has been excluded. Data points that have either high leverage and large residuals greater than 3 need to be further investigated (Chatterjee, & Hadi, 2013). Another influence diagnostic to consider is using the DFBETA. In using this statistic, any values larger than 2/sqrt(n) in absolute value or greater than 1 are considered highly

influential. Studentized residual may also be used to determine outliers for values greater than 3. These outliers may also exert undue influence on the regression results. Outlier assessment will also be completed post-model fit. For all fitted models, we will conduct residual analysis and assessment of influence diagnostics in terms of (1) the predicted values of potential influential observations, (2) regression coefficients, and (3) the standard errors for regression coefficients.

For all fitted models, we will conduct residual analysis and assessment of influence diagnostics in terms of (1) the predicted values of potential influential observations, (2) regression coefficients, and (3) the standard errors for regression coefficients.

2.5.1.5 Checking Assumptions

The underlying assumptions for a binary logistic regression include: 1) The dependent variable of reproductive decision-making must be binary; 2) Logistic regression requires the observations to be independent of each other. Observations should not come from repeated measurements or matched data; 3) There should be no outliers in the data. This can be assessed by converting the continuous predictors to z-scores and removing any value below -3.29 or greater than 3.29; 4) There should be little to no multicollinearity among the predictors. This can be assessed by using a correlation matrix among the predictors; 5) There should be a linear relationship between the continuous predictor and the logit transformation of the dependent variable. Testing for linearity of the logit must also occur. The assumption of linearity in logistic regression assumes that there is a linear relationship between continuous predictors and the logit of the outcome variable. This assumption can be tested by looking at whether the interaction term between the predictor and its log transformation is significant. Any interaction that is significant will indicate that the main effect has violated the assumption of linearity of the logit.

After the data are screened for accuracy and completeness, appropriate assumptions of study variables will be checked for all statistical tests. Assumptions of normality for each variable will be assessed through observation of test statistics including skewness and kurtosis, as well as graphics such as histograms, scatter plots and normal Q-Q plots. Residual plots and bivariate scatter plots between study variables will be examined for linearity. In order to check homoscedasticity, the Levene's test and scatter plots will be assessed to determine if all data points of the study variables cluster around the horizontal line. In testing multicollinearity for regression models, the tolerance and variance inflation factors (VIF) will be examined among variables. A VIF value near 10 or greater than 10 and a small tolerance value will be considered as an issue for multicollinearity. No multicollinearity and heteroscedasticity should be observed among study variables.

2.5.1.6 Multicollinearity

Multicollinearity can be determined using a correlation matrix among the predictor variables. For simple multicollinearity cases, if the correlations coefficients among the independent variables are less than 0.80, then this assumption can be met (Osterlind et al., 2001; Schroeder et al., 1990). Another way to determine if there is multicollinearity among the predictor is to examine the VIF- the Variance Inflation Factor. The VIF's of a linear regression indicates the degree that the variances in the regression estimates are increased due to multicollinearity. A VIF of 1 represents the absence of multicollinearity. VIF values of 10 or more suggest serious multicollinearity and the greater the VIF, the greater the degree of collinearity. If multicollinearity is found in the data, one solution could be to center the data. A simpler solution would be to identify the variables that are causing the multicollinearity issues and remove them from the regression. Tolerance can also be considered when determining multicollinearity. Tolerance is

estimated by 1-R. The minimum value of 0.10 will be used as the threshold for tolerance (Osterlind et al., 2001).

2.5.1.7 Transformation of Data

A binary logistic regression assumes a linear relationship between continuous predictors (measured interval or ratio) with the logit of the binary response. Each of these variables will need to be checked to ensure that each one is linearly related to the log of the outcome variable. VIF which is a more rigorous approach than correlation coefficient will also be checked. If the VIF goes beyond 10, data transformation will be considered (e.g., centering the variables) to reduce the impact of multicollinearity. Since logistic regression analyses will be conducted to examine the association between emotional states and reproductive decision-making, underlying assumptions will also be checked. The normality of sampling distributions will be assessed by either statistical (skewness and kurtosis) or graphical (frequency histograms, normal probability plots) methods. Box-Tidwell approach (Hosmer & Lemeshow, 1989) will be used to check linearity in the logit for a linear relationship between continuous independent variables and the logit transform of the dependent variable, reproductive decision-making when using logistic regression.

Transformations are dependent on the shape and the degree to which the sample distribution diverges from the normal distribution. To help determine which type of transformation to use, a scatter plot will be utilized. If there is a moderate difference between the sample distribution and the normal distribution, a square root transformation will be considered. If there is severe distribution, then the inverse transformation will be used (Osterlind et al., 2001).

2.5.2 Data Analysis

The aims of the study will be addressed through the following analytic approaches.

Specific Aim 1: Describe the distribution of a *BRCA* pathogenic variant among women who are in the Cancer Family Registry (CFR).

The demographic and history questionnaire will be used to describe the sample of women in this study. Categorical variables will report frequency distributions, frequency counts and percentages. Mode and range will be reported for nominal variables and the median and interquartile range will be reported for ordinal variables. For continuous variables, central tendency will be described as means and dispersion as standard deviations for normally distributed data.

Aim 2: Explore the relationship between emotional states and reproductive decision-making.

A binary logistic regression will be used to assess Aim 2. The emotional state items may need to be centered and/or scaled. A centered variable can be calculated by subtracting each of the observations from the mean of all observations. The same data analysis procedures from Aim 2 will be conducted in Aim 3.

Aim 3: Explore the relationship between individual factors (age, race, ethnicity, marital status, number of children and family history of breast and ovarian cancer) and reproductive decision-making.

A binary logistic regression analysis will be used. Because the magnitude of the regression coefficients in a multiple linear regression equation depends on the unit of measurement of the variable, the emotional scale items may need to be centered and/or scaled. A centered variable

can be calculated by subtracting each of the observations from the mean of all observations. There are two types of scaling that can be used: unit-length scaling or standardizing.

To assess for model fit in both the binary logistic regression model and multiple linear regression model, residual analysis and the assessment for influential observations will be performed. Goodness-of-fit tests for the binary logistic regression include examining the Chi-square goodness of fit test, using the Homer-Lemeshow test to compare the observed and expected frequencies of events and non-events, an examination of the ROC curve with cut-off values from 0-1 and the maximum likelihood ratio test. Goodness of fit for the multiple linear regression will include the R^2 and F-test.

The binary logistic regression results to be reported include: the odds ratio, the 95% confidence intervals and the *p* value. The multiple linear regression results will report the standardized regression coefficient.

Specific Aim 4: Explore the moderation of *BRCA* pathogenic variant status on the relationship between emotional states and reproductive decision-making.

A binary logistic regression will be used to explore the moderation of *BRCA* pathogenic variant status on the relationship between emotional states and reproductive decision-making. Hierarchal multiple regression will be used to assess the effects of the moderating variable, *BRCA* pathogenic variant status. To test moderation, we will examine the interaction effect between emotional states and *BRCA* pathogenic variant status.

Specific Aim 5: Explore the moderation of individual factors on the relationship between emotional states and reproductive decision-making.

Binary logistic regression will be used to determine the relationship of a predictive model in reproductive decision-making. The study model suggests that individual factors could be a

moderator between the relationship of emotional states and reproductive decision-making. To test moderation, we will look at the interaction effect between emotional states and individual factors and whether such an effect is significant in predicting reproductive decision-making. The Hosmer Lemeshow test will be employed to evaluate the goodness of fit of the model and the Omnibus test of model coefficients (traditional chi-square method) will be used to determine the overall significance of the predictors in the model.

2.6 Research Participant Risk and Protection

2.6.1 Human Subjects Protection

Human Subject Involvement: Participants are women aged 18 and older who have been identified to have a *BRCA* pathogenic variant. Those individuals that do not speak the English language were excluded.

Inclusion of Women: The sample of this study is only women. With a specific focus on individuals who must make a reproductive decision, this study focused on the recruitment of a sample whose gender distribution generally corresponded to the number of individuals who make reproductive related decision under the guise of having a *BRCA* pathogenic variant.

Inclusion of Minorities: This study sought to represent racial and ethnic minorities in its sample. No one was excluded from participation in this study based on race or ethnicity.

Inclusion of Children: No children are included in this study. The age limit was set at 18 years of age with no upper limit. Subjects younger than 18 were excluded because genetic testing for the *BRCA* pathogenic variant is not performed on individuals younger than 18.

Sources of Materials: Data will be self-reported. In addition, individual factors will be confirmed with the medical records. All data will be identified by code numbers only (participant IDs) and will be stored in secure locations, including locked file cabinets and password-protected computers. Participant ID's will be linked to participants' names in a password-protected file that is accessible only to the PI and research team.

Potential Risk and Protection against Risk: One potential risk is a breach of confidentiality. To protect participants' privacy, only members of the research team will be aware of individuals' participation in this research study. Participant names will not be included on the paper questionnaires completed. All data will be kept in secure, locked file cabinets at the School of Nursing. All information will be identified by a study ID number. The information linking ID numbers with identifiable information will be kept separate from the research records and will be stored under lock and key. The PI will manage access to the identifiable data; access will be provided only to team members who require access for study-related work. All team members involved in this study are current in all required research modules. Individual identities will not be revealed in any description or publications of this research, and data will only be presented in aggregate.

Completion of questionnaires by study participants creates a potential risk for inducing stress. Another possible risk of this research study may include stress from having to complete the questionnaires. Participants are advised to take a break if the questions induce stress or discomfort, they can take a break from completing the questionnaires and do not have to complete all individual questions at once. Study participants are reminded that survey responses are not sent to their healthcare providers. If they experience bothersome emotional symptoms, they should

contact their health care team. It is estimated that time to complete the survey is estimated to be 20-30 minutes.

Recruitment and Informed Consent: Participants were recruited from the Cancer Family Registry at UPMC Magee-Women's Hospital. After identification, the principal investigator will assure that individuals meet the study eligibility criteria and are willing to participate. For those individuals willing to participate, detailed information regarding the study design and procedures (e.g., purpose of study, risk/benefits, nature of questions asked, time commitment) will be provided and all questions answered prior to signing consent. Participants will likely not receive direct benefit from participating in the study.

2.6.2 Importance of Knowledge to be Gained

Previous research has focused on the emotional distress experienced by women undergoing genetic testing for a *BRCA* pathogenic variant. No research has explored the relationship of emotions and reproductive decision-making in women who are *BRCA* positive.

Since these women face difficult decisions along a very tight timeline related to their reproductive choices, it is critical to focus on the important emotions that are key to their decision-making. Data from the proposed study will provide critical information regarding emotions and reproductive decision-making. This will inform further research leading to successful nursing interventions to support women with a *BRCA* pathogenic variant.

2.6.3 Summary of Study

2.6.3.1 Changes to Proposed Study

This section is intended as a bridge between the proposed study, as approved by the committee and the actual study as it was conducted. These changes, along with the rationale for these changes, are provided below.

Recruitment: The original focus was revised to include only women who were below the age of 45 at the time of their *BRCA* test disclosure. Through discussion with committee members, it was decided that it would be unfair to ask post-menopausal women about their reproductive planning since it is likely that they were finished with childbearing.

Supplemental Material: Through discussion with the committee, it was decided to add a follow-up component to the study to garner more thorough information regarding the specific reproductive planning that women undertook. This follow-up questionnaire would involve calling the women who sent back their original mailing packet with consent form, and giving them to choice to complete the additional questions over the phone, or through a Qualtrics survey link emailed to them.

2.6.4 Conclusions, Implications for Nursing and Future Studies

Overall, this dissertation study has both strengths and limitations. This study seeks to expand and challenge our current understanding of emotional states, particularly in individuals at high genetic vulnerability. No study has specifically examined the emotional states around reproductive decision-making and family planning in women with a *BRCA* gene mutation. Continuing to engage patients in the planning and interpretation of results, and what they mean for

their family planning is key to enriching the understanding of the emotional states of these women. This design may have limitations in that it only sent one mailing out to participants, as opposed to multiple mailings to strengthen the response rate.

In conclusion, this dissertation provides an increased understanding of the range of emotions that impact reproductive decision-making, especially women with increased genetic susceptibility and also provides and avenue towards next steps. Taken together, these findings have implications for nursing science as these emotions and its trajectories can be used towards identifying those most at risk and implementing interventions that can be used towards proactive decision-making around family planning.

3.0 Manuscript 1: A Review of Reproductive Decision Making in Women who are *BRCA* Positive

Presented here is the full-text version of the manuscript accepted for publication, which was subsequently published in the Journal of Obstetric, Gynecologic and Neonatal Nursing. A copy of this manuscript can be accessed at: https://www.sciencedirect.com/science/article/abs/pii/S0884217520301179?via%3Dihub.

3.1 Abstract

Objective: To synthesize research findings regarding reproductive decision-making among women who are *BRCA* positive.

Data Sources: PubMed and CINAHL.

Study Selection: Articles published in English between 2000 and June 28, 2020 about the reproductive decision-making of women with a confirmed *BRCA1* or *BRCA2* mutation.

Data Extraction: We extracted data on participants, study design, analysis, follow-up, and results. We rated studies for quality and applicability by using the Modified Downs and Black Checklist and Kennelly's Qualitative Data Analysis.

Data Synthesis: We included five of 257 screened articles in our synthesis. The total sample size of the five studies was 1468 women. The most prevalent factors related to reproductive decision-making were the impending decisions regarding childbearing and family choices, including decisions about biological children, preventive surgery, PGD and prenatal diagnosis to prevent further transmission of a *BRCA* mutation, and family planning.

Conclusion: A lack of knowledge exists regarding the reproductive decision-making processes of women who are *BRCA* positive. Understanding this process would provide nurses and other clinicians with the knowledge needed to support these women.

3.2 Introduction

*BRCA*1 and *BRCA*2 genes produce tumor suppressor proteins. The role of these proteins is to repair damaged DNA and ensure the stability and integrity of each cell's genetic material

(National Cancer Institute, 2018a). When either of these genes is mutated, the repair work of damaged DNA does not occur. Because of the inability to repair DNA, additional genetic alterations occur that can lead to cancer. Specific, inherited *BRCA* mutations increase the risk for ovarian and breast cancers. Women who inherit mutations in *BRCA1* and *BRCA2* tend to develop breast and ovarian cancers at younger ages than those without these mutations. These gene mutations are responsible for 5% to 10% of all breast cancers and 10% to 15% of all ovarian cancers (Heald et al., 2016). *BRCA1*, located on chromosome 17 and discovered in 1994, contains more than 1,800 variants that cause increased risk of cancer (Nelson et al., 2019b). The *BRCA*2 gene, located on chromosome 13 and discovered in 1995, contains more than 1,300 variants (Nelson et al., 2019b).

BRCA mutations are inherited in an autosomal dominant pattern (Julian-Reynier et al., 2012). Either parent who has a *BRCA* mutation has a 50% chance of passing the mutation to offspring. To date, hundreds of variants have been identified within the *BRCA* genes. Women are typically not aware that they have *BRCA* gene mutations until a close female relative is diagnosed with breast or ovarian cancer. Many choose to undergo genetic testing as early as age 18 to determine their risk. However, cancer risks associated with *BRCA* gene mutations rarely manifest before the late twenties or early thirties. (Stopfer, 2012).

Women who have *BRCA*1 mutations have an 85% lifetime risk for breast cancer and a 65% lifetime risk for ovarian cancer; women who have *BRCA*2 mutations have an 80% lifetime risk for breast cancer and a 23% lifetime risk for ovarian cancer (Kuchenbaecker et al., 2017a). Because of these risks, specific risk reduction strategies are recommended, including salpingo-oophorectomy at the age of 35 or when childbearing is complete and a bilateral mastectomy (American College of Obstetricians and Gynecologists Committee on Practice Bulletins-

Gynecology et al., 2017; Daly et al., 2017; see Table 1). Because of the current trend among women to postpone childbearing until their 30s, a growing number of women will be diagnosed with cancer before they complete their families (Waimey et al., 2015). This has resulted in an increased focus on fertility and reproductive choice by women who are *BRCA* positive and view childbearing as a priority (Flink et al., 2017; Hoskins et al., 2014). Unfortunately, many women have not yet considered how many biological children they want by the time they become aware of risk-reducing guidelines. Subsequently, when these women reach the recommended age for surgery, they have lost the window of opportunity to complete their families. Depending on their choices, they may have varying levels of regret afterward (Di Prospero et al., 2001; Gietel-Habets et al., 2017; Stan et al., 2013; Werner-Lin et al., 2012).

3.3 Family Planning Options

Among couples in which one partner carries a *BRCA* mutation, multiple options for family planning are available, including conceiving naturally, pursuing in-vitro fertilization (IVF), or deciding not to have children. Fertility preservation options such as embryo cryopreservation, surrogacy, and adoption can also be considered (Chan et al., 2017; Derks-Smeets et al., 2014; Donnelly et al., 2013; Fortuny et al., 2009; Friedman & Kramer, 2005; Gietel-Habets et al., 2017; Insogna & Ginsburg, 2016; Mor et al., 2018; Pellegrini et al., 2014; Quinn et al., 2010; Rubin et al., 2014; Woodson et al., 2014). Couples who have biological children already and those who are preparing for biological children may find themselves confronted with the question of preventing their children from inheriting the mutation.

Preimplantation genetic diagnosis (PGD) as part of the IVF process allows for the selection and transfer of unaffected embryos. It begins with standard IVF. After the woman receives 2 weeks of hormonal stimulation, which includes two daily injections of follicle-stimulating hormone and luteinizing hormone, retrieval and fertilization of ova occur. The fertilized ova are tested for mutation after 8 days of development. Embryos without *BRCA* mutations are reserved for transfer. Ethical and moral dilemmas arise when all the embryos are affected with *BRCA* mutations or status cannot be determined. For example, a couple may find that all of their embryos are affected. They may decide to discontinue the process if concern for their future offspring outweighs their desire for biological children (Herlihy et al., 2018). If the ova or sperm carries a *BRCA* mutation, individuals may use a donor to prevent transmission (Lin et al., 2017). However, for women of certain religious or ethnic backgrounds, the use of IVF with PGD may cause moral distress as it allows for the selection and transfer of unaffected embryos only.

Embryo cryopreservation following in vitro fertilization is the most widely used and available method of fertility preservation (Farland et al., 2014). In this method, ova are removed and combined with sperm to form embryos that are frozen. Embryos can be thawed and placed in the uterus when decision-making is complete, and the woman is ready for childbearing.

Cost is likely to be a factor in decision-making. Under the Affordable Care Act, insurance companies are required to pay for genetic counseling and testing when criteria are met. For eligible women, insurance companies cover the entire cost of genetic counseling and *BRCA* testing with no out-of-pocket costs to the individual. However, family planning options, such as PGD and IVF, are often not covered by insurance. Insurance plans may offer coverage in selected cases, but the cost of multiple cycles of IVF and PGD may exceed $15,000 per cycle. Therefore, lack of

insurance coverage and inability to pay the out of pocket costs are barriers for some families (Insogna et al., 2017; Drazba et al., 2014; Green, & Weiss, 2013).

Researchers have examined decisions to undergo genetic testing and the process of decision making regarding bilateral salpingo-oophorectomy (BSO) and hysterectomy in women at risk for a *BRCA* mutation and those already diagnosed (Chan et al., 2017; Friedman, & Kramer, 2005; Garcia et al., 2014a; Garcia et al., 2014b; Hoskins et al., 2014; Pal et al., 2015; Werner-Lin et al., 2012). Despite extensive evidence related to the issues that women with *BRCA* mutations face, reproductive decision-making in this population is not well studied. Therefore, the purpose of our review was to synthesize the research literature regarding reproductive decision-making in women who have *BRCA*1 or *BRCA*2 mutations.

3.4 Methods

The integrative review method is an approach that allows for the combination of diverse methodologies to reach the goal of comprehensive perspectives on a chosen topic. The results capture the depth and breadth and provide information and potential direction for further research. We conducted an integrative review to synthesize data on reproductive decision-making in women with a *BRCA*1 or *BRCA*2 mutation.

3.4.1 Literature Selection

To identify relevant resources, we consulted an expert health science research librarian to conduct a comprehensive search of multiple library databases, including PubMed and CINAHL.

We searched for original research articles on reproductive decision-making by women with *BRCA*1 or *BRCA*2 mutations published between 2000 and 2017 and available in English. Inclusion years were expanded due to increased available publications on the *BRCA* mutation. We conducted the original search in September 2017 and updated it in June 2020. This accounted for variant terminology and indexing variations identified during phases of search term harvesting and testing. Initial search terms used were *BRCA* (including all deviations), Hereditary Breast and Ovarian Cancer Syndrome (HBOC) reproduction, fertility, and decision-making. We identified additional resources through hand searches of relevant resources and examination of the reference lists of the articles returned from the initial search.

Articles that addressed the reproductive decision-making process, included women with confirmed *BRCA*1 or *BRCA*2 mutations, and were published between January 2000 and June 28, 2020 in English were included. We excluded studies that focused on women with unknown *BRCA*1 or *BRCA*2 mutation status or who were in the process of being tested for the mutation. Because the focus of our review was reproductive decision-making, we only included studies related to that topic.

3.4.2 Search Outcome and Study Selection

The search and study selection processes are depicted in the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) flowchart (Figure 1). The preliminary search yielded 257 potentially relevant records. After duplicates were removed and exclusion criteria applied, we reviewed the titles and abstracts of 67 records from which 62 records were excluded, leaving only five eligible full-text articles in our review.

The remaining five articles received full-text review, and the two reasons noted for exclusion were unknown *BRCA* mutation status and final decision-making outcome was not fertility related. Despite relatively broad inclusion criteria, only three of the five articles that received full review met the inclusion criteria. Hand searches of reference lists and forward citation searches of the three selected articles yielded two additional articles for analysis, resulting in a total of five articles for our review.

3.4.3 Data Extraction and Synthesis

We extracted and tabulated the following data for the five selected articles: authors, study design, purpose, inclusion criteria, sample, measures, and results (see Table S2). After we reviewed all articles, the first author (ES) read and analyzed each and noted themes and characteristics. The second, third, and fourth authors (JDJ, CD, SW) reviewed all themes and discussed and agreed upon the findings.

3.5 Results

A total of 1468 women participated in the five included studies. The largest sample size was 1081 participants (Chan et al., 2017) and the smallest was 20 (Dean & Rauscher, 2017). One study was conducted in the United Kingdom and one in the Netherlands. The remaining three studies were conducted in the United States. The average age of participants in the studies was 41.1 years of age (range 24 to 48 years), and most participants were married (68%) and were White (91.1%).

3.5.1 Measurement of Reproductive Decision-Making

How reproductive decision-making was measured varied across the studies. Authors used semi-structured interviews to discuss the effects of *BRCA*1 and *BRCA*2 mutations on life decisions, especially related to plans to have children (Donnelly et al., 2013) and how women with *BRCA* mutations but not cancer diagnosis made decisions regarding family planning (Dean & Rauscher, 2017). Cross-sectional surveys were used to determine fertility consultation and fertility preservation treatment (Gietel-Habets et al., 2017; Kim et al., 2015).

We used a modified Downs and Black Checklist (Downs, & Black, 1998; Figure 2) to appraise the quality of the three quantitative studies included in our review. Questionnaires were used in the three cross-sectional studies; Chan et al. (2017) and Gietel-Habets et al. (2017) used literature searches to develop questionnaires, while Kim et al. (2015) engaged reproductive experts to develop questions to assess participants' views of fertility preservation treatments. External validity was high due to the sample sizes in these studies (range 151 to 1081).

Two of the studies were qualitative, and the researchers used semi-structured interviews for data collection in both (Dean & Rauscher, 2017, Donnelly et al., 2013). Figure 3 shows our assessment of the two qualitative studies (Dean & Rauscher, 2017; Donnelly et al., 2013) using the Guidelines to Evaluate the "Quality and Evidence" of Qualitative Studies, adapted by Joan Kennelly (Kennelly, 2011). With the exception of the data analysis category, both studies ranked moderate to high in all remaining categories (research design, sampling, data collection, findings/results, research value, and research design). Based on the assessment of quality and evidence of the studies, we rated one study (Dean & Rauscher, 2017) as 'fair' and the other (Donnelly et al., 2013) as 'high'. We identified themes related to reproductive decision-making among the five included studies, including *Effect on Relationships and Childbearing*, *Acceptability*

and Awareness of PGD and Prenatal Diagnosis, and *Choices and Attitudes Regarding Childbearing and Passing Mutation to Offspring*.

Effect on Relationships and Childbearing

Researchers evaluated the effects that a *BRCA* mutation had on relationships and childbearing (Chan et al., 2017; Donnelly et al., 2013). Descriptive studies were used to assess demographic information and answer questions regarding the influence of *BRCA* status on marriage, relationships, and family planning. Chan et al. (2017) demonstrated that 22% of 1081 participants reported that knowledge of their carrier status made them more anxious to get married while 38% of participants reported that their carrier status influenced the selection of a partner. Participants sought partners who were emotionally and financially secure, understood their carrier status, and supported their decision-making (Chan et al., 2017). Donnelly et al. (2013) found that among 25 women participants, their husbands did not agree about family planning especially if they had children from a previous marriage. These men were reluctant to engage in discussions about having additional children with the risk of a *BRCA* transmission. For women who were in committed relationships and were over 30 years old, the priority was to have children while for younger women, the priority was finding the right partner. These findings were consistent across studies (Chan et al., 2017; Dean & Rauscher, 2017; Donnelly et al., 2013).

Acceptability and Awareness of PGD and Prenatal Diagnosis

Authors of three studies explored the acceptability and awareness of (PGD) and prenatal diagnosis (PND) (Chan et al., 2017; Dean & Rauscher, 2017; Gietel-Habets et al., 2017). Researchers identified whether the participants were aware of the possibility of PGD or prenatal diagnosis, their level of knowledge regarding these two reproductive options, and if they viewed them as an acceptable means for creating their families. The authors also assessed the use of these

reproductive options in the prevention of transmission of the *BRCA* mutation. Findings of these studies indicated that childless women who were younger, had a higher educational level, and more immediate child desires were more aware of diagnostic options and cancer risk (Chan et al., 2017; Dean & Rauscher, 2017; Gietel-Habets et al., 2017).

Chan and colleagues (2017) found that a personal history of cancer, already having children, older age, and type of *BRCA* mutation were not associated with acceptance of PGD or prenatal diagnosis. Of the 1081 women who would choose to use PGD or prenatal diagnosis, 376 (34.8%) would consider undergoing PGD to reduce the risk of a *BRCA* mutation transmission and 600 (55.5%) believed that prenatal diagnosis should be offered to pregnant women who are *BRCA* mutation carriers (Chan et al., 2017). Further, of the 600 women who believe that prenatal diagnosis should be offered to pregnant women, only 180 (30%) report that they would actually use it themselves (Chan et al., 2017). Despite these values, few women would consider pregnancy termination if the fetus carried a mutation (Chan et al., 2017; Gietel-Habets et al., 2017).

Choices and Attitudes Regarding Childbearing and Passing Mutation to Offspring

Some women struggled with knowing they could pass the mutation to their children and experienced guilt after learning that they were pregnant (Dean & Rauscher, 2017). These feelings of guilt were consistent with the results of Chan et al. (2017) who found that out of 116 women, 20 (17.2%) would not have children because they were concerned about the risk of transmission to their offspring. Despite the concern of passing mutations to offspring, many women with *BRCA* mutations still want to have children naturally (Chan et al., 2017; Dean & Rauscher, 2017). Few researchers have examined women's attitudes and experiences regarding PGD or prenatal diagnosis. Of the 635 women who believe that PGD should be offered to individuals with a *BRCA* mutation, only 222 (35%) would consider it (Chan et al., 2017). Among 284 women whose

families were not complete at the time of *BRCA* test disclosure, 116 (40.8%) said that the knowledge of their *BRCA* status affected their decisions to have biological children (Chan et al., 2017) and 50 (17.7%) would pursue fertility treatments. Further, of the 50 women whose families were not complete at the time of *BRCA* test disclosure, 20 (40%) would consider IVF to freeze their eggs for future use (Chan et al., 2017). Women who already had biological children were less likely to pursue fertility treatments in light of their *BRCA* status (Chan et al., 2017; Dean, & Rauscher, 2017). Despite the small number of women who would choose fertility treatments, the majority of mutation carriers, especially those who did not have children and were non-white, expressed positive opinions about fertility preservation treatments (Chan et al., 2017; Donnelly et al., 2013; Gietel-Habets et al., 2017; Kim et al., 2015).

3.6 Discussion

Women diagnosed with a *BRCA* mutation face difficult decisions about childbearing. Results of our integrative review suggest that marriage and relationship status, as well as views about the use, acceptability, and awareness of fertility options, affect women's childbearing decision-making. Women with a known *BRCA* mutation have a sense of urgency in prioritizing childbearing over cancer risk management (Chan et al., 2017).

Some researchers have noted that single women who test positive for a *BRCA* mutation experience urgency to find a partner (Donnelly et al., 2013; Hamilton & Hurley, 2010; Werner-Lin, 2008). These women desire someone who is emotionally and financially secure, understands their mutation status, and is supportive of their reproductive decision-making (Chan et al., 2017; Donnelly et al., 2013). Others found that women place greater emphasis on having children rather

than finding a partner (Donnelly et al., 2013; Gietel-Habets et al., 2017). Women with a *BRCA* mutation expressed urgency to bear children if possible before surgery is recommended that will decrease their cancer risk but render them infertile. When that was not possible, they considered extending their preventive surgery window to bear children despite their increasing cancer risk (Chan et al., 2017). We found that women with children were more likely to undergo preventive surgery than childless women, analogous to previous research findings from a survey of women at increased risk for breast and ovarian cancer, but who were not confirmed as *BRCA* mutation carriers (Howard et al., 2009; Padamsee et al., 2017). Regardless of relationship status, a sense of urgency towards childbearing is still prevalent among women since they recognize that fertility declines with age (Chan et al., 2017; Dean & Rauscher, 2017; Donnelly et al., 2013). While this desire for children can cause strain on relationships, counseling may be helpful for couples to assess the risks to both the woman's health and that of future children against not having a complete family (Hoskins et al., 2014).

We found that childless women who considered PGD tended to be younger with higher educational levels and more immediate desires for children (Chan et al., 2017; Donnelly et al., 2013; Gietel-Habets et al., 2017). However, because PGD provides couples the opportunity to select non-*BRCA* positive embryos, individuals may be conflicted about this choice due to ethical or moral dilemmas. Although few researchers have assessed women's attitudes and experiences regarding PGD, those that have, found that while the majority of women believe PGD should be offered to individuals testing positive for a *BRCA* mutation (Chan et al., 2017), relatively few would consider it for themselves (Donnelly et al., 2013; Gietel-Habets et al., 2017).

Governmental regulation of PGD varies among countries. For example, in France, the Netherlands, and the United Kingdom, PGD use is regulated by the government. A *BRCA*

mutation is one of the most frequent indicators for PGD; consequently, women in those countries would have positive opinions regarding PGD. In the United States, the use of PGD is not government regulated. As a result, its use is at the discretion of fertility specialists, obstetrician/gynecologists, geneticists, and genetic counselors who independently prioritize the needs of patients when assisting with the decision for whom PGD should be used (Bayefsky, 2018).

Research findings show that women are strongly motivated to do whatever they can to control the risk of genetic mutations for their future children (Julian-Reynier et al., 2012; Quinn et al., 2010). For most women with *BRCA* mutations and their partners, the decision to use reproductive technologies is far more difficult than previous decisions and they may find themselves paralyzed by an inability to move forward (Ormondroyd et al., 2012).

We found that women with *BRCA* mutations struggle with the idea that their children may inherit the mutation and often have feelings of sadness and guilt. These findings are consistent with previous research that has focused on opinions influencing the decision to be tested for a *BRCA* mutation (Hesse-Biber, 2014; Hesse-Biber & An, 2016; Kridli & Austin, 2018; Sankar et al., 2006). We also found that knowledge of a *BRCA* mutation status influenced women's decisions to have children. Findings of our review show that among women diagnosed with a *BRCA* mutation, 25% would pursue fertility treatments and 50% would freeze their eggs for future use (Chan et al., 2017; Donnelly et al., 2013). Many women desire to have children naturally, without the use of PGD, knowing that the risk of transmission is not eliminated.

Over 90% of the participants in the studies reviewed were White, although findings of other studies suggest that *BRCA* mutations have comparable prevalence among African-Americans (Pal et al., 2015), Asian (Wong et al., 2016), White, and Hispanic (Villarreal-Garza et al., 2015)

populations. However, there are significant racial/ethnic factors that influence the ability to access genetic testing and *BRCA* risk management interventions.

3.6.1 Limitations

The limitations of this study include the exclusion of articles that were not published in English and the omission of reviewed papers in which the authors addressed participants' desire for more children. We feel the addition of these studies would provide key information about fertility intentions. Also, participants of diverse, ethnic groups are not well represented in the studies reviewed, and this lack of sample diversity limits the generalizability of our findings.

3.6.2 Implications

The most important implication in this study is the recognition that women with *BRCA* mutations, particularly younger women, feel a sense of urgency to complete their families. These challenges provide the recognition that younger women need more support and provides the opportunity for nurses and advanced practitioners to offer this support. These women are in need of guidance regarding marriage and family planning and visits and guidelines using well-established professional guidelines can be useful in addressing these challenges. In addition, the use of evidence-based counseling to develop tailored nursing interventions, including a detailed family history, the documentation of these results in the electronic health record, and awareness of the Advance Practice Nursing genetic/genomic competencies would be helpful in addressing these challenges (Greco et al., 2011; see Table 3). It is evident that reproductive decision making among women with a *BRCA* mutation is an emotionally charged experience. However, the emotional

aspects of women's reproductive decision making in light of *BRCA* mutations were not included in any of the studies in our review. Acknowledging these emotions can guide nurses to recognize patient concerns, discuss healthcare issues, and provide the decision support needed for this vulnerable population.

3.7 Conclusion

The paucity of research regarding women's reproductive decision-making when they have *BRCA* mutations presents an important opportunity for future research. As more women learn their genetic breast or ovarian cancer risks, they must grapple with difficult decisions about reproductive life planning. The recurring themes from our review included *Effects on Relationships and Childbearing, Acceptability and Awareness of PGD and Prenatal Diagnosis,* and *Choices and Attitudes Regarding Childbearing and Passing Mutation to Offspring*. The emotional aspects of this decision-making are not well understood and require additional study. Identifying the emotions and personal values influencing reproductive decision-making will help nurses provide psychological support and compassionate, knowledgeable care. Providing women with clear guidance and information regarding choices concerning the multiple options available to them is paramount. The sensitivity and complexities of these issues and the likelihood that they will require discussion with nurses indicate a critical need for additional research.

Table 3 *Table of Recommendations for BRCA1/BRCA2 mutation carriers*

Organization	Recommendation(s)
American College of Obstetricians and Gynecologists (American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Gynecology et al., 2017)	Risk-reducing bilateral salpingo-oophorectomy recommended at age 35-40 years for *BRCA*1 carriers and at age 40-45 for *BRCA*2 carriers
American Society of Clinical Oncology (Tung et al., 2020)	Preventive, risk-reducing salpingo-oophorectomy should be performed at the completion of childbearing or by the age of 40 Risk-reducing salpingo-oophorectomy should be considered earlier for *BRCA1* carriers (before 40) than for *BRCA2* carriers given the earlier onset of ovarian cancer in *BRCA1* mutation carriers
National Comprehensive Cancer Network (National Comprehensive Cancer Network, 2019)	Risk-Reducing salpingo-oophorectomy is recommended between ages 35 and 40 years, when childbearing is completed, but may be delayed to age 45 years for *BRCA*2 carriers if necessary
Society of Gynecologic Oncology (Society of Gynecologic Oncology, 2017)	Risk-reducing bilateral salpingo-oophorectomy recommended at age 35-40 years for

	*BRCA*1 carriers and at age 40-45 for *BRCA*2 carriers with addition of risk-reducing mastectomy

Table 4 *Studies Included in Review*

Authors	**Study Design**	**Purpose**	**Inclusion Criteria**	**Sample**	**Measures**	**Results**
Chan et al, 2017	Cross-sectional study	Investigate how knowledge of *BRCA* carrier status impacts women's' decisions regarding 1) marriage and relationships, 2) childbearing and fertility treatments and 3) the use of PGD and prenatal diagnosis to prevent transmission of the mutation to their offspring in self-reported *BRCA* mutation carriers whose families were not complete at the time of test disclosure	Inclusion: self-reported germline *BRCA* mutation and were greater than 18 years at the time of enrollment Exclusion: if never tested for *BRCA* mutation, tested negative for the mutation or variant of unknown importance	N=1081 Partnered: 81% (876) *BRCA1*: 51% (550) *BRCA2*: 47.5% (514) *BRCA1&2*: 1.6% (17)	Information obtained included: demographic information (age, race, and ethnicity), medical and social history, menstrual and fertility history, relationship history, pregnancy history, desire for pregnancy, and age at *BRCA* testing. Participants were asked to answer questions about how their *BRCA*	Amongst the 284 women whose families were not complete at the time of *BRCA* test disclosure, 41% responded that knowledge of *BRCA* mutation status impacted decision to have biological children- 4% would pursue adoption, 17%

		Hypothesized that age at the time of *BRCA* mutation test disclosure, personal history of cancer and already having biological children were factors that would influence the decision to have children or pursue infertility treatments			mutation status influenced decisions about childbearing, including the timing of conception, decisions not to conceive or to pursue adoption and about their attitude towards diagnostic tools including PGD and prenatal diagnosis 18% of women whose families were not complete reported that knowledge of *BRCA* mutation	would not have children due to concerns of passing to offspring, 10% of women stated they "would not have children out of concern that pregnancy would cause cancer" 40% would consider IVF to freeze embryos or oocytes for future use and 34% would utilize IVF

					would influence them to pursue infertility treatment; 34% reported that knowledge of *BRCA* status made them more likely to consider fertility treatments to get pregnant more quickly	with PGD to avoid transmission to offspring In logistic regression, women with a personal history of cancer were more likely to report that the knowledge of *BRCA* status impacted their decision to have a child and women who were partnered were less likely to report that this

						knowledge impacted their decision
Dean et al, 2017	Semi-structured qualitative	Investigate how women who test positive for *BRCA* mutation, but have not been diagnosed with cancer make decisions regarding family planning	Inclusion: received positive *BRCA* genetic test results before completion of family planning, at least 18 years of age, have a committed partner, had a conversation with a partner about family planning	N=20*	Open-ended questions: describe how it felt for you to be diagnosed with a mutation, thoughts about family planning, yours and partners' conversations about family planning, relatives' and friends' reactions to family planning, conversations with health care professionals	Two major health decisions emerged- when to have children and when to have preventative surgeries- that were guided by logical and emotional decision-making styles

					around family planning	
Donnelly et al, 2012	Qualitative methodology and thematic analysis	How do young women, who were identified as carrying a *BRCA* mutation before they had children, approach reproductive decision-making and what are their attitudes towards reproductive decision-making	Inclusion: diagnostic or pre-symptomatic *BRCA* testing in the preceding 5 years, no serious mental health contraindications	N=25*	Semi-structured interviews including topics: how participants found out about their inherited cancer predisposition, why they opted for genetic testing, and the effects that genetic test information has had on their life decisions, including planning	4 central themes: impact of cancer on reproductive decision-making, motivation for a genetic test, risk management and timing of planning children, and optimism for future medical advancements

				*Demographics not available	children, relationships, work, and risk management	

Gietel-Habets et al, 2016	Cross-sectional survey	To determine the extent to which *BRCA* mutation carriers and their partners in the Netherlands are aware of pre-implementation genetic diagnosis and prenatal diagnosis as reproductive options and what their attitude is towards these options	Inclusion: Confirmed carrier of *BRCA* 1/2 mutation Knowledge of the Dutch Language	N= 191 Male: 12.6% (24) Female: 87.4% (167) Partnered: 88% (168) Unpartnered: 12% (23) *BRCA1*: 55% (105) *BRCA2*: 45% (86)	Questionnaire formed as a result of a focus group study about decision-making on PGD and prenatal diagnosis among couples with HBOC Measured: 1) awareness, whether the participant was aware of the possibility of PGD or prenatal diagnosis for HBOC before filling out the questionnaire; 2) the level of knowledge of PGD	Majority of respondents were female (87%), of reproductive age (86%) and about half reported desire for children in the future 2/3 aware of PGD and 61% aware of prenatal diagnosis. Individuals with higher education level more likely to be aware of PGD and

					for HBOC among participants who were previously aware of PGD; 3) whether the participant regarded PGD or prenatal diagnosis for HBOC acceptable and 4) whether the participant would personally consider using PGD or prenatal diagnosis for HBOC or for another serious genetic condition. Demographic factors, medical	prenatal diagnosis and those with more immediate child wish were more often aware of PGD and had more knowledge about PGD

					factors also measured	

Kim et al, 2014	Cross-sectional single institution web survey	Investigate 1) Knowledge about the clinical impact of PBSO; 2) views on fertility consultation/fertility preservation treatment and 3) difficulties in conceiving compared to non-carriers	Inclusion: women, screened for *BRCA* mutations before age 42, current age of 18-50, did not have cancer at the time of the genetic testing and can read English	N=151* *Demographics not available	Demographic information (age, ethnicity, education level, marital status), reproductive and cancer history, knowledge about the clinical impact of PBSO, prior exposure to information about FP treatment options and opinions about FC and FP treatment options	59% had positive views about FC/FP treatments More likely to have difficulty conceiving Limited knowledge about the reproductive clinical impact of PBSO or the benefit of FP before PBSO Those who had not completed childbearing or had no children were interested in FC/FP treatment

Table 5 *Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcomes (Jenkins, & Calzone, 2007)*

Professional Responsibilities Competencies

- Recognize when one's own attitudes and values related to genetic and genomic science may affect the care provided to clients
- Advocate for clients' access to desired genetic/genomic services and/or resources including support groups
- Examine competency of practice on a regular basis, identifying areas of strength, as well as areas in which professional development related to genetics and genomics would be beneficial
- Incorporate genetic and genomic technologies and information into registered nurse practice
- Demonstrate in practice the importance of tailoring genetic and genomic information and services to clients based on their culture, religion, knowledge level, literacy, and preferred language
- Advocate for the rights of all clients for autonomous, informed genetic- and genomic-related decision-making and voluntary action

Professional Practice Domain

Nursing Assessment: Applying/Integrating Genetic and Genomic Knowledge

- Demonstrates an understanding of the relationship of genetics and genomics to health, prevention, screening, diagnostics, prognostics, selection of treatment, and monitoring of treatment effectiveness
- Demonstrates ability to elicit a minimum of three generation family health history information
- Constructs a pedigree from collected family history information using standardized symbols and terminology
- Collects personal, health, and developmental histories that consider genetic, environmental, and genomic influences and risks
- Conducts comprehensive health and physical assessments which incorporate knowledge about genetic, environmental, and genomic influences and risk factors
- Critically analyzes the history and physical assessment findings for genetic, environmental, and genomic influences and risk factors
- Assesses clients' knowledge, perceptions, and responses to genetic and genomic information
- Develops a plan of care that incorporates genetic and genomic assessment information

Identification

- Identifies clients who may benefit from specific genetic and genomic information and/or services based on assessment data Identifies credible, accurate, appropriate, and current genetic and genomic information, resources, services, and/or technologies specific to given clients

- Identifies ethical, ethnic/ancestral, cultural, religious, legal, fiscal, and societal issues related to genetic and genomic information and technologies
- Defines issues that undermine the rights of all clients for autonomous, informed genetic- and genomic-related decision-making and voluntary action

Provision of Education, Care, and Support

- Provides clients with interpretation of selective genetic and genomic information or services
- Provides clients with credible, accurate, appropriate, and current genetic and genomic information, resources, services, and/or technologies that facilitate decision-making
- Uses health promotion/disease prevention practices that:
    - Consider genetic and genomic influences on personal and environmental risk factors
    - Incorporate knowledge of genetic and/or genomic risk factors
    - Uses genetic- and genomic-based interventions and information to improve clients' outcomes
    - Collaborates with health care providers in providing genetic and genomic health care
    - Collaborates with insurance providers/payers to facilitate reimbursement for genetic and genomic health care services
    - Performs interventions/treatments appropriate to clients' genetic and genomic health care needs
    - Evaluates impact and effectiveness of genetic and genomic technology, information, interventions, and treatments on clients' outcome

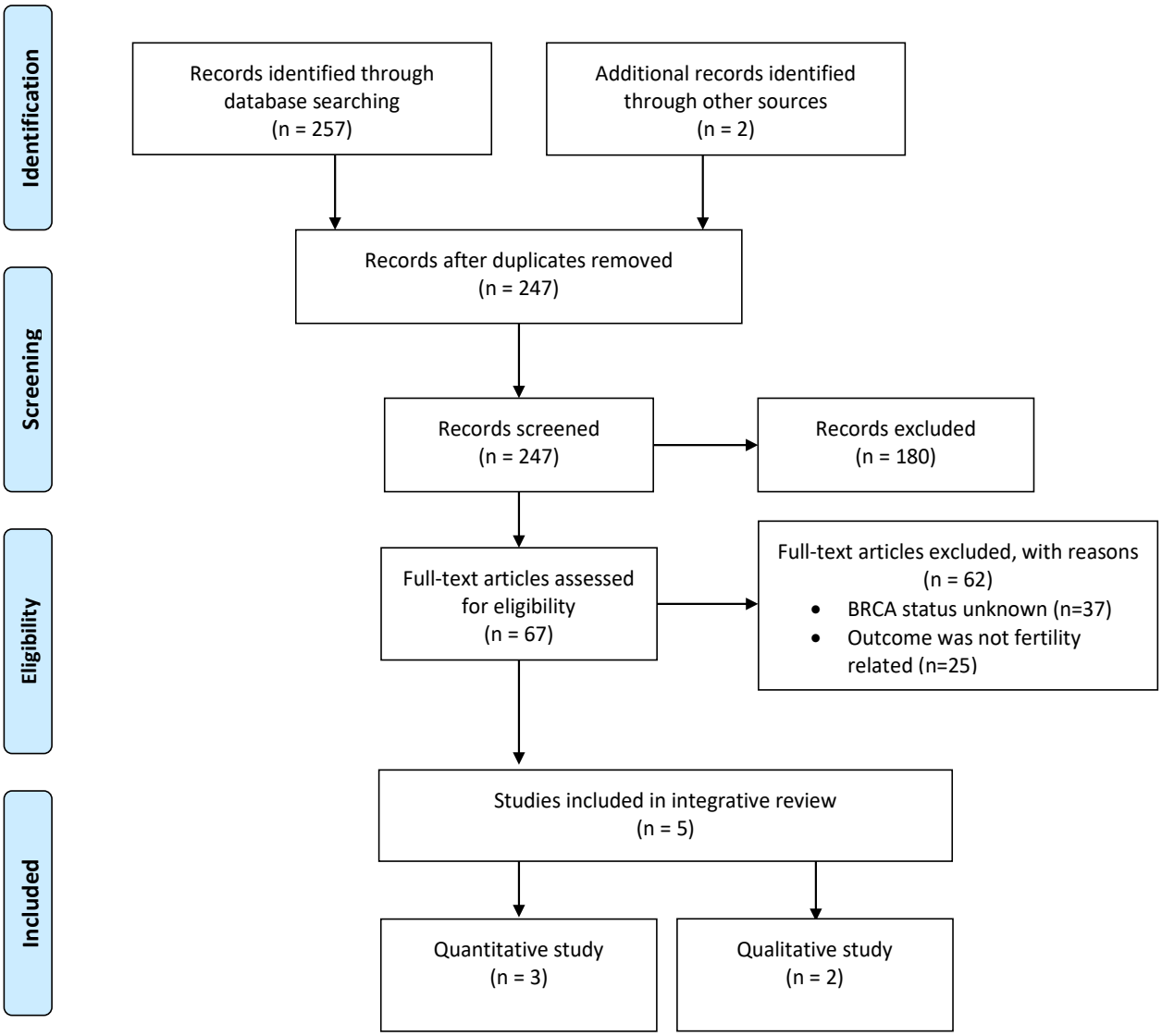

Figure 3 PRISMA Flowchart on literature search process, strategies and outcomes

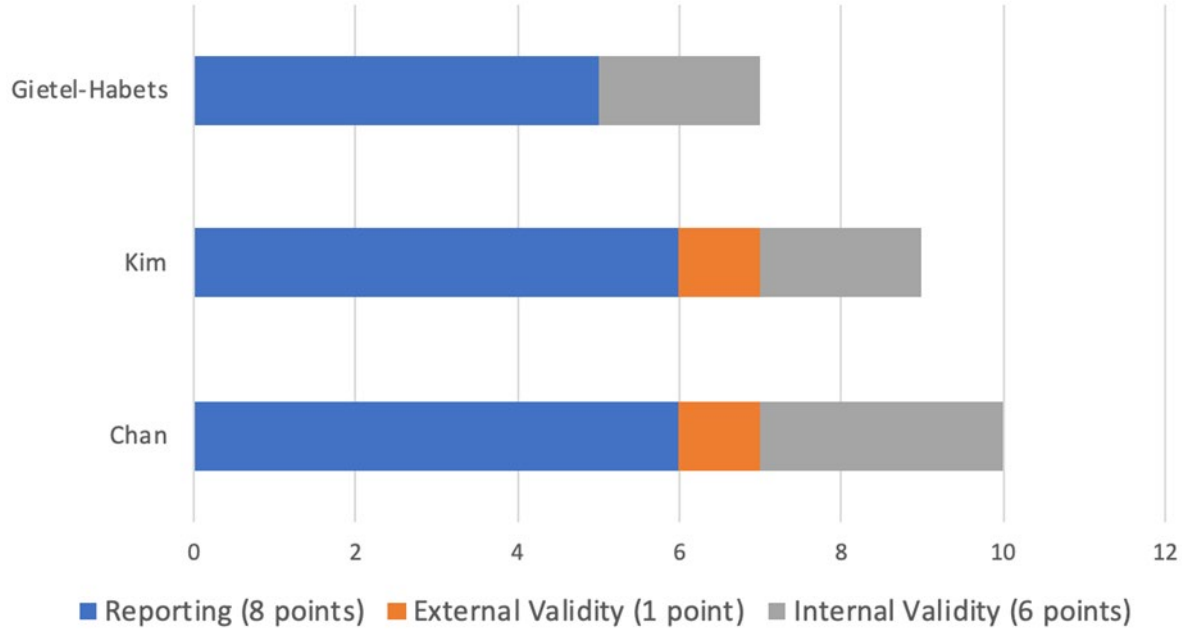

Figure 4 Quality Appraisal of Included Studies Using a Modified Downs and Black Checklist

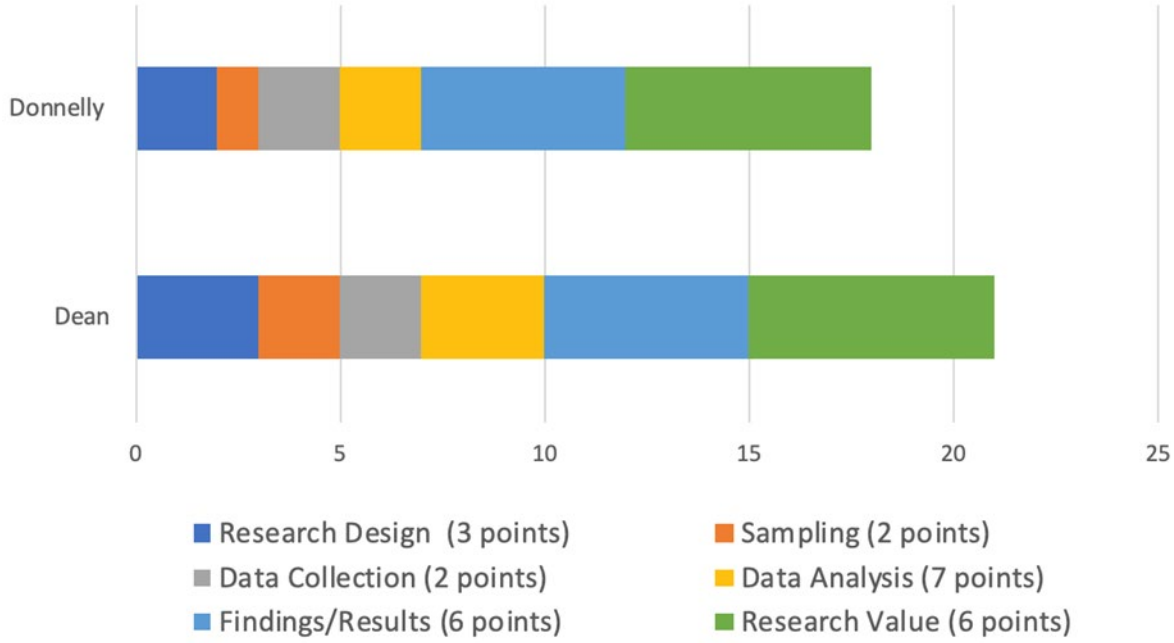

Figure 5 Quality Appraisal of Included Qualitative Studies Using Kennelly's Qualitative Data Analysis

4.0 Data-Based Manuscript: The Association of Emotional States on Reproductive Decision-Making in Women who are *BRCA* Positive

4.1 Introduction

Women who live in the United States have a 12% risk of developing breast cancer and a 2% risk of developing ovarian cancer during their lifetime. For women who carry a pathogenic *BRCA*1 or *BRCA*2 variant, one that affects approximately one in 200-400 women living in the United States, this risk increases (Kuchenbaecker et al., 2017a; Manickam et al., 2018). For breast cancer, lifetime risk ranges from 55-70% for *BRCA*1 carriers by the age of 70 and between 45-70% in *BRCA*2 carriers. For lifetime risk of ovarian cancer, the risk ranges from 40-45% for *BRCA*1 and 15-20% for *BRCA*2 (Kotsopoulos, 2018; Kuchenbaecker et al., 2017a). In addition to the increased personal risk, women with a *BRCA* pathogenic variant have a 50% chance of passing the pathogenic variant to their offspring (U. S. Preventive Services Task Force, 2019).

Overall survival for *BRCA* associated breast and ovarian cancer is similar than that of women with breast or ovarian cancer who do not carry a *BRCA* pathogenic variant (Lieberman et al., 2019). However, due to the increased risk of cancer in these individuals, primary risk reduction strategies are often recommended, especially in those at increased risk for ovarian cancer. Risk-reducing surgical options may include bilateral mastectomy and bilateral salpingo-oopherectomy (U. S. Preventive Services Task Force, 2019). For a young woman who is not ready to make family planning decisions, these surgical procedures can be significantly life altering (U. S. Preventive Services Task Force, 2019).

Much research has focused on the myriad of issues associated with women who have tested positively for a *BRCA* pathogenic variant. In the past ten years, requests for pathogenic variant testing have increased twofold to threefold (Evans et al., 2015; Juthe et al., 2015). Studies have identified factors influencing the decision to have *BRCA* testing including age, and the number of living children. (Battistuzzi et al., 2019; Claes et al., 2004; Halbert et al., 2011; Hesse-Biber et al.,

2016; Lynch et al., 2006; Nelson et al., 2005; Pasacreta, 2003). Women with a *BRCA* pathogenic variant who have been diagnosed with cancer have experienced an increase in symptoms of distress, anxiety and depression in the first few months after genetic test disclosure (Beran et al., 2008; Bosch et al., 2012; Claes et al., 2004; Graves et al., 2012; Halbert et al., 2011; Schwartz et al., 2002; Smith et al., 2008; van Dijk et al., 2006). Other research has focused on the decision to have risk-reducing surgery. These studies also found this decision to be influenced by age, in addition to the desire for children, gender of living children and a family history of cancer (Battistuzzi et al., 2019; Gavaruzzi et al., 2017; Hesse-Biber, & An, 2016).

Although women want to be logical in their decision-making, emotions may complicate this process. By definition, emotions are complex, multi-dimensional judgments that reflect a great deal of information about one's relationship to social and physical surroundings. One's own internal thoughts regarding these relationships are also reflected (Lambie & Marcel, 2002; Smith & Ellsworth, 1985). Strong evidence supports the association of emotions and the decision to be tested for a *BRCA* pathogenic variant (Dean et al., 2017a; Rini et al., 2009; Werner-Lin, 2008). However, the role that emotions play in the reproductive decision-making process of women with a *BRCA* pathogenic variant is unknown. Qualitative studies have examined the complex decisions influencing finding a partner and the timing of having children (Dean, 2016; Dean, & Rauscher, 2017a; Dean et al., 2017b; Donnelly et al., 2013b; Rauscher et al., 2017). However, no studies were identified that focused on the emotional aspect of reproductive decision-making.

Lazarus and Folkman's Transactional Model of Stress provides the foundation to better understand the effects of emotion on healthcare decision-making (Bagneux et al., 2012; Lerner et al., 2005; Lerner et al., 2001; Lerner et al., 2014; Lerner et al., 1999). This model includes three basic dimensions, or emotional states; threat, challenge, and loss/benefit (Folkman et al., 1985).

These emotional states are accompanied by core appraisal themes, which influence the likelihood of specific courses of action (Frijda, 2002; Lazarus, 1991; LeBlond, 2008). Threat is referred to as the anticipation of psychological or physical damage or loss; challenge results from demands that a person feels confident about mastering and loss/benefit refers to psychological loss or gain that has yet to occur.

Women diagnosed with a *BRCA* pathogenic variant face difficult decisions about childbearing. Previous research suggests that marriage and relationship status, as well as views about their use, acceptability and awareness of fertility options affect women's childbearing decision-making. Women with a known *BRCA* pathogenic variant have a sense of urgency in prioritizing childbearing over cancer risk management. Some researchers have noted that single women who test positive for a *BRCA* pathogenic variant experience urgency to find a partner. These women desire someone who is emotionally and financially secure, understands their pathogenic variant status, and is supportive of their reproductive decision-making.

Research has shown that women with children were more likely to undergo preventive surgery than childless women. They struggle with the idea that their children may inherit the pathogenic variant and often have feelings of sadness and guilt. These findings are consistent with previous research that has focused on opinions influencing the decision to be tested for a *BRCA* pathogenic variant.

As more women learn their genetic breast or ovarian cancer risks, they must grapple with difficult decisions about reproductive life planning. The emotional aspects of this decision-making are not well understood and requires additional study. Identifying the emotions and personal values influencing reproductive decision-making will help nurses provide psychological support and compassionate, knowledgeable care.

The purpose of this study is to explore the role of emotional states on reproductive decision-making in women with a known *BRCA* pathogenic variant.

4.2 Background

The breast cancer genes, *BRCA*1 and *BRCA*2, are tumor suppressor genes that play a role in DNA repair and cellular growth control. When either of these genes have a pathogenic variant, or are altered, DNA damage may not be repaired properly, and as a result, cells are more likely to develop genetic alterations that lead to cancer development. Women with a germline pathogenic variant in the *BRCA* genes have an increased risk of early-onset breast and increased overall risk of ovarian cancers. About 12% of the general population will develop breast cancer at some point in their lives. 72% of women who inherit a *BRCA*1 pathogenic variant and about 69% of women who inherit a *BRCA*2 pathogenic variant will develop breast cancer by the age of 80. Similarly, about 1.3% of women in the general population will develop ovarian cancer sometime during their lives. By contrast, it is estimated that about 44% of women who inherit a *BRCA*1 pathogenic variant and about 17% of women who inherit a *BRCA*2 pathogenic variant will develop ovarian cancer by the age of 80 (Kuchenbaecker et al., 2017b).

In light of these high cancer risks, options available for managing cancer risk in these individuals include enhanced surveillance, chemoprevention and risk-reducing surgery.

Enhanced surveillance consists of screening- some women who test positive for a *BRCA*1 or *BRCA*2 pathogenic variant are recommended to start breast cancer screening at younger ages, than women at average risk of breast cancer. Women with a *BRCA* pathogenic variant are

encouraged to begin breast self-awareness at the age of 18, schedule clinical breast exams every 6 to 12 months beginning at age 25, and depending on the breast cancer history within the family, undergo annual breast MRI's (magnetic resonance imaging) starting at the age of 25 (Committee on Practice Bulletins- Gynecology, 2017). For *BRCA* mutation carriers, annual mammograms and MRI's are recommended at the age of 30; for comparison, those not at an increased risk begin mammograms at the age of 40. Additionally, breast self-awareness should begin at the age of 18.

Chemoprevention is the use of medication in an attempt to reduce the risk of cancer. In pre- and postmenopausal women, tamoxifen can be used for risk reduction which may reduce breast cancer risk. Oral contraceptives have been found to reduce the risk of ovarian cancer due to the inhibitory effect on ovulation. Oral contraceptives are known to reduce the risk of ovarian cancer, although they increase the risk for breast cancer.

Risk reducing surgeries involve removing as much of the 'at risk' tissue as possible. Women can choose to undergo a bilateral prophylactic mastectomy (surgery that removes a woman's breasts) to reduce their risk of breast cancer, and/or bilateral prophylactic salpingo-oopherectomy, surgery that removes a woman's ovaries and fallopian tubes. Previous research results have shown that women with *BRCA* pathogenic variants who undergo risk-reducing mastectomies reduce their risk of developing breast cancer by 90% or more. Similarly, undergoing a bilateral salpingo-oophorectomy reduces a woman's risk of ovarian cancer by nearly 90%.

To manage this increased risk, the American Society of Clinical Oncology, the National Comprehensive Cancer Network and the United States Preventive Services Task Force have put in place recommendations for women with this genetic mutation. Risk-reducing surgery is recommended between the ages of 35-40 for *BRCA*1 pathogenic variant carriers and between the ages of 40-45 for *BRCA*2 pathogenic variant carriers and upon completion of childbearing. It is

emphasized that risk-reducing surgeries remain the most complete way to reduce the risk of breast and ovarian cancer in women with a *BRCA* pathogenic variant.

However, the challenge to adhering to risk-reducing guidelines for women with a *BRCA* pathogenic variant is that when surgery is discussed, some women may not have started their families, or they are unsure that they are finished. This can lead to difficult decisions as the woman must balance her desire for family completion with their own risk-reduction measures.

Since carrying a *BRCA* pathogenic variant is associated with an autosomal dominant inheritance pattern, the probability of transmitting a deleterious pathogenic variant is 50%. For women who desire for their children to be biological, this is something they must consider, as they are made aware that any biological child has a 50% chance of carrying a *BRCA* mutation.

Hence, women without children may be more distressed about completing their families before they may feel that their timeline is up. Decision-making conflict surrounding the timing of risk-reducing surgery and childbearing has been commonly expressed by women who are young adults. For those women who choose to undergo risk-reducing surgery before their family plans are complete, decisions may need to be made regarding whether they want their children to be biological and if so, free of the *BRCA* pathogenic variant. Preimplantation genetic diagnosis (PGD), as part of the standard IVF process, allows for the selection and transfer of unaffected embryos that begins with standard IVF. However, moral dilemmas may arise when choosing between embryos that do or do not carry the *BRCA* pathogenic variant. Consideration may be given to using a donor egg or sperm.

For women who may not be in relationships, cryopreservation techniques, such as the freezing of embryos and oocytes, the use of a gestational carrier, or adoption are other options that these women can pursue.

Making decisions under uncertain circumstances is especially relevant for women who are *BRCA* positive. Much research has focused on decision-making in regard to the surgical decisions, as well as the decision to undergo genetic testing in women who have a known family history of breast or ovarian cancer. Research has demonstrated that women with a *BRCA* pathogenic variant experience urgency to have children by the age of 35, hence making these decisions an emotionally charged experience.

Various factors have been shown to influence patients' decision making, especially pertaining to family formation, including age, risk-reducing surgery, and marital status.

Reproductive decision making is highly individualized and difficult. Previous research has demonstrated that female *BRCA* carriers seek assistance for reproductive decision making. Specifically, they identified themes concerning the psychosocial impact of carrying a *BRCA* pathogenic variant, including feelings of guilt about passing the pathogenic variant to current and future children. Previous qualitative research, primarily from Dr. Rebekah Hamilton, highlighted challenges facing the younger population of women, including difficulties with decision making, and how to disclose pathogenic variant status to potential partners. It is clear that emotions play an important role in the decision, but it is unclear which emotions are predominant. Acknowledging these motions can guide nurses to recognize patient concerns, discuss healthcare issues and provide the decision support needed for this vulnerable population.

The Appraisal of Life Events scale was developed in response to the need to measure primary appraisals based on the Transactional Model of Stress. In this model by Lazarus and Folkman, stressful experiences are presented as person to environment transactions, where the impact of an external stressor is mediated by the person's response to the stressor. According to Lazarus and Folkman, the way that people appraise their stressors is related to the choice of coping

strategies. An appraisal is defined as a 'cognitive predisposition to appraise future events that trigger the emotion'. Patterns of cognitive appraisals along dimensions of emotion provide a basis for comparing and contrasting discrete emotions. When individuals confront a stressful situation, primary and secondary appraisals are initiated. In primary appraisal, a person considers the quality and the nature of the stimulus event and the relevance of that event to themselves. When a stressor is appraised as requiring a coping response, individuals evaluate their resources and abilities to cope with the stressor. This is known as a secondary appraisal. An appraisal driven approach allows one to systematically examine the effects of emotions on decision-making. Basic dimensions are believed to underlie primary appraisals, such as threat, challenge and loss/benefit.

The Appraisal of Life Events Scale was developed to allow respondents to reflect on the impact of a previously examined event. Threat is referred to as the anticipation of psychological, or physical damage or loss; challenge results from demands that a person feels confident about mastering, and loss/benefit refers to psychological loss or gain that has yet to occur.

Previous research has explored the relationship of appraisal and coping in women and men experiencing infertility concerns. Evidence supported significant associations of the Appraisal of Life Events scale with stress measures, and with coping. It was found that appraisal of infertility as threat or loss were associated with increased infertility-related stress, whereas viewing infertility as a challenge was related to increased well-being. Another study used the Appraisal of Life Events Scale to assess appraisals in women experiencing infertility. As more women learn their genetic breast or ovarian cancer risks, they must grapple with difficult decisions about reproductive life planning. The emotional aspects of this decision-making are not well understood and requires additional study. Identifying the emotions and personal values influencing reproductive decision-making will help nurses provide psychological support and compassionate, knowledgeable care.

The primary purpose of this study was to explore the role of emotional states on reproductive decision making in women with a known *BRCA* pathogenic variant.

4.3 Methods

4.3.1 Design and Sample

With Institutional Review Board approval, secondary analysis was conducted using data from participants of the Cancer Family Registry. This registry is a repository of data that can be used by researchers that is housed at the Cancer Genetics Program at UPMC Magee-Womens Hospital. The women included in this database have previously consented to being contacted regarding their interest in participating in new research studies. In this secondary analysis, an exploratory, descriptive study design was implemented, with additional variables collected through participant phone calls. The convenience sample for this study included individuals who agreed to participate in future research studies. Informed consent was obtained at the time of data collection.

The inclusion criteria for this study included women who were between the ages of 18 - 45, had a known *BRCA* pathogenic variant, confirmed by genetic testing, and were literate English speakers. Originally, the inclusion criteria included all women over the age of 18; however, it might not be appropriate to include women who were over the age of 45, since they would likely not be making decisions about having children. Thus, the age range was reduced to 18-45 years of age at genetic testing.

4.3.2 Measures

Demographic and Patient Characteristics

A sociodemographic form, designed to gather participant information, collected current age, age at diagnosis, race, ethnicity, marital status, number of children and family history of breast and/or ovarian cancer. These items were self-reported from the Cancer Family Registry and confirmed through use of this form. Current age and age at diagnosis of *BRCA* mutation were measured as a single number, self-reported, in complete years, confirmed via the medical record. Race was measured as American Indian, Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. Ancestry was self-reported as both the paternal and maternal ancestry. Marital status was measured as never married, married or living as married (with a partner), separated, divorced, or widowed. Number of children was measured as a single number and family history of breast/ovarian cancer was measured as yes/no. Reproduction decision-making was measured as a single response to the question 'are you finished having children?' with responses being either 'yes' or 'no'. *BRCA* pathogenic variant status was recorded from the Cancer Family Registry as either *BRCA*1 or *BRCA*2.

Appraisal of Life Events Scale

Emotional states will be measured by the Appraisal of Life Events scale. The items on the Appraisal of Life Events scale are measured according to dimension. There are 32 response items, 16 in each of two categories, asking to what extent an adjective describes or described an event. In the case of this scale, the event is making a family planning decision under a *BRCA* diagnosis. Each item is ranked on a scale from 0-5. From those individual scores, the sum of certain individual items will correspond to one of the dimensions: threat, loss/benefit or challenge. The higher the score, the higher the appraisal of threat, challenge or loss/benefit respectively.

Follow-Up Phone Call

Based on the preliminary data results, a follow up phone call and questionnaire was appropriate to clarify the data that received. This phone call asked participants whether or not *BRCA* affected their decision to have children, how many children they had after their diagnosis and whether they were biological or adopted, if they froze their eggs, if cost was a factor in their decision-making and other outside factors that may have influenced their decision.

4.3.3 Data Analysis

Analyses were performed using SPSS version 27 for Mac (IBM Corp, New York, USA)

Descriptive Analyses

Descriptive statistics were computed for each variable based on level of measurement, distribution of data and which statistic provided the most meaningful information. Means and standard deviations, as well as ranges were used to describe continuous variables that were normally distributed. For interval/ratio scaled variables that were not normally distributed, as well as ordinal/scaled variables demonstrating normal distributions, medians and inter-quartile ranges will be used. Ranges were reported for nominal scaled variables. For continuous variables with skewed distributions, medians were computed. Frequencies and percentages were reported for categorical variables

Data Screening

Normality

Assumptions for normality were assessed, looking at observation of test statistics, including skewness and kurtosis, as well as histogram and scatter plots. There was no multicollinearity or heteroscedasticity observed among study variables. Normality was assessed

using descriptive statistics, histograms, residual distributions, skewness and kurtosis. Data transformation (e.g. square root transformation, categorizing data) was considered for any variable not meeting this underlying assumption.

Univariate and Multivariate Outliers

An outlier is a case of an extreme value on one variable, termed a univariate outlier, while multivariate outliers have unusual combinations of scores of two or more variables (Tabachnick, & Fidell, 2007). Categorical variables were investigated by determining the frequency distributions over categories. For continuous variables, histograms, boxplots, normal probability plots and de-trended normal probability plots will be used to identify points that are far removed from the bulk of the data. In addition, Z-scores were computed to assess how extreme the identified univariate outliers were for continuous variables. If a z-score was greater than the critical value of 3.29, or less than the critical value, the data point was considered an outlier. Because of the limited variability, the race and ancestry variables were used for descriptive purposes only rather than in multivariate analysis.

A visual screening of histograms and box plots was used to identify univariate outliers, while multivariate outliers were evaluated statistically using Mahalanobis distance. Mahalanobis distance at $p < .001$ was used as the cut-off criteria (Tabachnick et al., 2007). For categorical variables, outliers will be identified using frequency distributions to check for any uneven category splits. All identified outliers were deemed to be valid members of the population and representative of the variability in the scales.

Linearity and Homoscedasticity

Linear relationships among pairs of measured continuous variables were evaluated through visual inspection of bivariate scatter plots. Problems with heteroscedasticity would have been corrected using data transformations, but this was not necessary.

Missing Data

Analysis of incomplete data to determine patterns of missing data was completed. Less than 5% of subjects were missing data on all variables. Evaluation of the patterns of missing data indicated that the data were missing at random. Mean imputation was used to estimate missing values on all continuous variables.

Multicollinearity

Multicollinearity was assessed by screening 1) the correlation matrix for all of the variables, identifying correlations >.90; 2) tolerance values, with values <.3 indicating multicollinearity; and 3) variance inflation factor (VIF), with values >3 indicating possible multicollinearity. None of the variables had correlations greater than .90 and all tolerance and VIF factors fell within the acceptable limits. Interaction terms (used in logistic regression) typically demonstrate problems with multicollinearity. To avoid this problem, continuous variables entered as interaction terms in the logistic regression model were centered. Multicollinearity was not found to be a problem with the measures in this study.

Data Transformations

Linearity in the logit describes a linear relationship between continuous predictors and the logit transformation of the dependent variable. This was tested by running a logistic model with the DV (reproductive decision-making) predicted by each of the continuous variables plus the interactions between each predictor and its natural log. We looked at whether the interaction term between the predictor and its log transformation was significant using Box-Tidwell approach, and

we found that there were no interactions that were significant, thus there was no violation of linearity in the logit.

Specific Aim 1: Describe the distribution of a *BRCA* pathogenic variant among women who are in the Cancer Family Registry.

Analysis: Appropriate descriptive statistics (e.g., mean, standard deviation, range) based on the empirical distribution of the data were used to characterize the sample of women in this study with a *BRCA* pathogenic variant with respect to reproductive decision-making, which was measured as 'Are you finished having children'?

The analysis involved calculation of descriptive statistics of the key study variables. All variables will be described using frequency distributions and summarized using appropriate measures of central tendency and dispersion given the variable's level of measurement and observed data distribution (i.e., means and standard deviations for interval/ratio scaled variables demonstrating normal distributions; medians and inter-quartile ranges for ordinal scaled variables and interval/ratio scaled variables that are non-normally distributed; modes and ranges for nominal scaled variables).

Specific Aim 2: Explore the association between emotional states and reproductive decision-making.

Analysis: Binary logistic regression was used to investigate the association between individual emotional states and the probability of being finished having children (reproductive decision-making). Emotional states measured mean scores on three dimensions of threat, challenge and loss/benefit. Univariate binary logistic regression analyses were performed to estimate crude and adjusted odds ratios with 95% confidence intervals (CI). For each of the emotional state variables, the test statistics, unadjusted odds ratios, adjusted odds ratios and

corresponding standard errors and p-values were reported. The Hosmer-Lemeshow test was employed to evaluate the goodness of fit of the model. Model fit was evaluated using classification tables and pseudo r-squared values (Cox & Snell and Nagelkerke).

Specific Aim 3: Explore the association between individual factors (age, marital status, number of children and family history of breast and ovarian cancer) and reproductive decision-making.

Analysis: Binary logistic regression was used to investigate the association between individual factors (age at genetic testing, marital status, number of children and family history of breast/ovarian cancer) and the probability of being finished having children (i.e., reproductive decision-making). Certain variables, such as marital status, had relatively small number of cases in certain categories. Therefore, 'married' and 'living with partner' were grouped together as 'partnered' and 'widowed', 'divorced' and 'never married' were grouped together as 'not partnered'. Further, family history of breast cancer was split into individual categories based on relationship with the participant. This included categories of 'mother breast cancer', 'grandmother breast cancer', aunt breast cancer', 'sister breast cancer' and 'cousin breast cancer'.

Univariate analyses were initially performed considering each individual factor singly in the regression model. Unadjusted and adjusted odds ratios with their corresponding 95% confidence intervals (CI) were reported. For each of the individual factor variables, the test statistics, unadjusted regression coefficients, adjusted regression coefficients and corresponding standard errors and p-values were reported. The Hosmer-Lemeshow test was employed to evaluate to goodness of fit of the model. Model fit was evaluated using classification tables and pseudo r-squared values (Cox & Snell and Nagelkerke). The level of significance was set at $p< 0.05$ for two-sided hypothesis testing.

Aim 4: Explore how *BRCA* pathogenic variant status (*BRCA1* vs *BRCA2*) moderates the relationship between emotional states and reproductive decision-making.

Analysis: We constructed hierarchical multivariable binary logistic regression models for the primary outcome of interest, reproductive decision-making. All possible two-way interactions were assessed, entering emotional states and *BRCA* pathogenic variant status hierarchically into the model. Using this approach, emotional states were first entered into the model; *BRCA* pathogenic variant status was then added to the second block in this model. Interaction effects were tested as part of the model building to determine whether there was any moderation by *BRCA* pathogenic variant status on emotional states and the probability of being finished having children. Main effects and 2-way interactions were estimated in the model. Models were estimated hierarchically and subsequent model assessment strategies included residual, outlier and influential case analyses. Model fit was evaluated using change in chi-square statistics, classification tables, pseudo r-squared values (Cox & Snell and Nagelkerke), and the Hosmer and Lemeshow Test for adequate fit of the data. Significance levels were set a priori at .05, except where indicated.

The moderator effect of *BRCA* pathogenic variant status on the relationship between emotional states and reproductive decision-making is indicated by the interaction of emotional states and *BRCA* pathogenic variant status in explaining reproductive decision-making. A hierarchical regression analysis was conducted with emotional state, *BRCA* pathogenic variant, and the interaction of emotional state and pathogenic variant status (created as the product of the two variables) predicting reproductive decision-making. The coefficient of the interaction of two variables measures the moderation effect, with a no-significant coefficient indicating no

moderation effect. Logistic regression was determined to be the type of regression because of the categorical manner of the dependent variable, reproductive decision-making.

Aim 5: Explore how individual factors moderate the relationship between emotional states and reproductive decision-making.

Analysis: A similar regression analysis strategy as outlined for Aim 4 will be used to explore the possible moderator effect of individual factors on the relationship between emotional states and reproductive decision-making. The moderator effect of individual factors on the relationship between emotional states and reproductive decision-making is indicated by the interaction of emotional state and individual factors in explaining the probability of being finished having children. A hierarchical regression will be conducted with each emotional state, individual factor and the interaction of emotional state and individual factors predicting reproductive decision-making. To estimate moderation effects for individual factors on the relationship between the identified outcome variable and emotional states, the change in R2 statistic will be examined with the addition of the interaction term for individual factors with emotional states to the main effects model.

We constructed hierarchical multivariable binary logistic regression models for the primary outcome of interest, reproductive decision-making. All possible two-way interactions were assessed, entering emotional states and individual factors hierarchically into the model. Using this approach, emotional states were first entered into the model; individual factors were then added to the second block in this model. Interaction effects were tested as part of the model building to determine whether there was any moderation by the individual factors on emotional states and the probability of being finished having children. Main effects and 2-way interactions were estimated in the model. Models were estimated hierarchically and subsequent model assessment strategies

included residual, outlier and influential case analyses. Model fit was evaluated using change in chi-square statistics, classification tables, pseudo r-squared values (Cox & Snell and Nagelkerke), and the Hosmer and Lemeshow Test for adequate fit of the data. Significance levels were set a priori at .05, except where indicated.

4.4 Results

4.4.1 Description of Sample Characteristics

Of the 374 women who were sent mailings for this study, 85 (23%) responded to the mailing inquiries and provided demographic information and information relating to their emotions. This study utilized single mailings, however, it is recognized that repeat mailings in an effort to increase response rate would have been preferred.

Demographic data are summarized in Table 6. The women in this sample ranged from 18-45 years of age at diagnosis of *BRCA* pathogenic variant. 48 (56.5%) of the sample carried the *BRCA1* pathogenic variant while 37 (43.5%) of the sample carried the *BRCA2* pathogenic variant. This *BRCA* distribution was similar to the distribution of the Cancer Family Registry, from which this sample was obtained. The majority of the sample (98%) was White, and the ancestry varied. For the most part, the ancestral background of the sample was from Europe. More than half of the sample identified themselves as being Eastern European, both maternally and paternally (61% and 54%, respectively) and most of the sample also reported having ancestry from the British Isles maternally and paternally (69% and 84%, respectively).

For the most part, women were married or partnered (70.6%). Most women in the sample had children (81.2%), with a little more than half having one to two children (54.1%).

Most of the sample was finished having children (82.3%). The majority of the sample (96.5%) had a female relative diagnosed with either breast or ovarian cancer. Specifically, most of the sample (52.9%) had a mother that was diagnosed with breast cancer, followed closely by grandmother and aunt. Not unlike breast cancer, the number of women with a female relative with ovarian cancer was high (45.9%). (See Table 6 for further details.)

Table 6 *Descriptive Variables of Women with a BRCA Pathogenic Variant*

Characteristic	**Are you finished having children?**		**BRreast CAncer (*BRCA*) status**		**Total**
	Yes	**No**	***BRCA1***	***BRCA2***	
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)
Age (years)	36.04 + 6.10 (21-45)	26.13 + 5.93 (18-42)	33.31 ± 6.9 (18-45)	35.57 ± 7.3 (20-45)	34.29 ± 7.13 (18-45)
BReast CAncer gene (*BRCA*)					
BRCA1	39 (55.7)	9 (60)	-	-	48 (56.5)
BRCA2	31 (44.3)	6 (40)			37 (43.5)
Race					
White	68 (97.1)	15 (100)	47 (97.9)	36 (97.3)	83 (97.6)
Black or African-American	2 (2.9)	0 (0)	1 (2.1)	1 (2.7)	2 (2.4)
Marital Status					
Married/Living with a Partner	52 (74.3)	8 (53.3)	34 (70.8)	26 (70.3)	60 (70.6)
Widowed/Separated/Never Married	18 (25.7)	7 (46.7)	14 (29.2)	11 (29.7)	25 (29.4)
Number of Children					
No children	9 (12.9)	7 (46.7)	10 (20.8)	6 (16.2)	16 (18.8)
1-2 children	39 (55.7)	7 (46.7)	23 (47.9)	23 (62.2)	46 (54.1)
3+ children	22 (31.4)	1 (6.7)	15 (31.3)	8 (21.6)	23 (27.1)
Has your mother, grandmother(s), sister(s), aunt(s) or cousin(s) ever been diagnosed with breast cancer?					
Yes	66 (94.3)	14 (93.3)	43 (89.6)	37 (100)	80 (94.1)
No	4 (5.7)	1 (6.7)	5 (10.4)	0 (0)	5 (5.9)
Relative					
Mother	38 (54.3)	7 (46.7)	27 (56.3)	18 (48.6)	45 (52.9)
Grandmother	37 (52.9)	7 (46.7)	22 (45.8)	22 (59.5)	44 (51.8)
Sister	15 (21.4)	2 (13.3)	13 (27.1)	4 (10.8)	17 (20)
Aunt	34 (48.6)	9 (60)	19 (39.6)	24 (64.9)	43 (50.6)
Cousin	6 (8.6)	1 (6.7)	3 (6.3)	4 (10.8)	7 (8.2)
Has your mother, grandmother(s), sister(s), aunt(s) or cousin(s) ever been diagnosed with ovarian cancer?					
Yes	31 (44.3)	8 (53.3)	27 (56.3)	12 (32.4)	39 (45.9)
No	39 (55.7)	7 (46.7)	21 (43.8)	25 (67.6)	46 (54.1)
Relative					
Mother	13 (18.6)	2 (13.3)	11 (22.9)	4 (10.8)	15 (17.6)
Grandmother	12 (17.1)	2 (13.3)	13 (27.1)	1 (2.7)	14 (16.5)
Sister	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Aunt	13 (18.6)	4 (26.7)	8 (16.7)	9 (24.3)	17 (20)
Cousin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

4.4.2 Association Between Emotional States and Reproductive Decision-Making

When looking at the association between emotional states and reproductive decision-making, (Aim 2), the results showed that none of the emotional states were significantly associated ($p \geq .05$) for reproductive decision-making, individually or collectively.

Table 7 *Binary Logistic Regression of the Probability of Being Finished Having Children Considering Emotional States Individually (Crude/Unadjusted) and Collectively (Adjusted)*

Emotional State	Crude (Unadjusted)			*p*-value	Adjusted			*p*-value
	Odds Ratio	95% CI			Odds Ratio	95% CI		
		Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Threat Score	1.016	0.950	1.086	.648	0.985	0.899	1.079	.751
Challenge Score	1.052	0.925	1.197	.441	1.047	0.922	1.189	.478
Loss/Benefit Score	1.056	0.937	1.191	.372	1.071	0.911	1.259	.407

4.4.3 Association Between Individual Factors and Reproductive Decision-Making

When examining the relationship between individual factors and reproductive decision-making, there was significant prediction of reproductive decision-making by age at genetic testing

(p=.001) and number of children (p=.001). Surprisingly, marital status and family history of breast or ovarian cancer were not significant predictors.

Based on the follow up questionnaire, 74% of the sample did not have children after learning about their diagnosis. 26% did have children, and of those individuals, 98% had biological children. 3 individuals used PGD to assist with their reproduction and only 1 individual froze their eggs.

Table 8 *Binary Logistic Regression Results of Probability of being Finished Having Children Considering Individual Factors Indivdually (Crude/Unadjusted) and Collectively (Adjusted)*

Individual Factor	Unadjusted (Crude)			p-value	Adjusted			p-value
	Odds Ratio	95% CI for OR			Odds Ratio	95% CI for OR		
		Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Age at Genetic Test (years)	1.290	1.135	1.466	.001	1.322	1.125	1.553	.001
Marital Status[a]	2.528	0.803	7.962	.113	0.710	0.098	5.149	.735
Number of Children[b]	2.917	1.567	5.432	.001	2.784	1.157	6.702	.022
Aunt with Breast Cancer	0.630	0.203	1.958	.424	0.526	0.104	2.647	.436
Grandmother with Breast Cancer	1.281	0.419	3.918	.664	1.038	0.191	5.650	.965
Sister with Breast Cancer	1.773	0.360	8.731	.482	0.797	0.047	13.475	.875
Mother with Breast Cancer	1.357	0.444	4.151	.592	4.739	0.697	32.214	.112
Cousin with Breast Cancer	1.312	0.146	11.781	.808	1.478	0.086	25.303	.788

Female Relative with Ovarian Cancer	0.696	0.227	2.129	.525	1.982	0.315	12.471	.466

Notes.
[a]The combined category of married/living with a partner was treated as the reference group for marital status compared to widowed/divorced/never married.
[b]The grouped category of >1 child was treated as the reference group for number of children compared to no children.

4.4.4 Moderation of *BRCA* Pathogenic Variant Status on Relationship between Emotional States and Reproductive Decision Making

To the models developed to address Aim 2, *BRCA* was added as a moderator between emotional states and reproductive decision making. In the first step, two variables were included: emotional states and reproductive decision-making. Next the interaction term between emotional states and *BRCA* pathogenic variant status was added to the regression model. None of these interactions were statistically significant. In looking at the variables in the first step of the model, there were no significant interactions between *BRCA* variant status and emotional states. When we expanded the model to include the interactions between emotional states and *BRCA* variant status, we found no significant interactions, considering each emotional state individually, as well as collectively. The Hosmer-Lemeshow test was not significant, suggesting that the data fit the model adequately (X^2 = 7.998, df = 7, p= .333). The model correctly classified 92.9% of participants: 34.6% of those finished having children and 95.7% of those not finished having children.

From the follow-up questionnaire, we found that 75% of the sample said that their *BRCA* diagnosis did not affect their decision to have children. The most significant reasons were that they were done having children (they already had the number of children they desired) or they wanted children regardless and were not letting a *BRCA* diagnosis define their choice to have

children. One average, the participants who were older in the study felt that *BRCA* did not affect their decision.

Of the 25% that reported that a *BRCA* diagnosis did affect their decision to have children, it all came down to timeline. Most of these women felt rushed to complete their childbearing, knowing that they had a limited window.

Table 9 *Multivariate Logistic Regression Results with All Predictors Included*

Predictor	Adjusted			*p*-value
	Odds Ratio	95% CI		
		Lower Limit	Upper Limit	
Threat	0.978	0.865	1.106	0.727
Challenge	1.140	0.913	1.424	0.246
Loss/Benefit	1.057	0.863	1.296	0.590
BRCA2[a]	1.049	0.806	1.366	0.721
Threat × *BRCA* status[a]	1.009	0.824	1.234	0.934
Challenge × *BRCA* status[a]	0.865	0.662	1.131	0.291
Loss/Benefit × *BRCA* status[a]	1.052	0.734	1.507	0.784

Notes.
[a]*BRCA1* pathogenic variant is the reference group

4.4.5 Moderation of Individual Factors on Relationship between Emotional States and Reproductive Decision-Making

The only model that suggested moderation was between loss/benefit and any family history of ovarian cancer ($X^2(1) = 5.760$, $p = .016$). Women who reported higher loss/benefit scores and had a female relative with ovarian cancer were more likely to be finished having children. The Hosmer-Lemeshow test was not significant, suggesting that the data fit the model adequately ($X^2 = 3.234$, df = 7, $p = .863$). The model correctly classified 82.4% of participants: 33.3% of those finished having children and 92.9% of those not finished having children.

Table 10 *Multivariate Logistic Regression Results with All Predictors Included*

Interaction	Adjusted Odds Ratio	95% CI		*p*-value
		Lower Limit	Upper Limit	
Threat × Age	1.008	0.992	1.024	.345
Threat × Marital Status[a]	1.025	0.891	1.179	.729
Threat × Number of Children	0.974	0.906	1.046	.467
Threat × Aunt with Breast Cancer[b]	0.928	0.807	1.068	.296
Threat × Grandmother with Breast Cancer[b]	0.998	0.873	1.141	.978
Threat × Sister with Breast Cancer[b]	1.087	0.896	1.319	.398
Threat × Mother with Breast Cancer[b]	1.041	0.909	1.192	.560
Threat × Cousin with Breast Cancer[b]	1.208	0.718	2.034	.477
Threat × Female Relative with Ovarian Cancer[b]	0.907	0.787	1.045	.177
Challenge × Age	1.009	0.974	1.045	.621
Challenge × Marital Status[a]	0.768	0.563	1.048	.096
Challenge × Number of Children	1.090	0.930	1.277	.287
Challenge × Aunt with Breast Cancer[b]	0.909	0.690	1.199	.500
Challenge × Grandmother with Breast Cancer[b]	1.022	0.788	1.328	.867
Challenge × Sister with Breast Cancer[b]	1.000	0.698	1.432	.998
Challenge × Mother with Breast Cancer[b]	0.900	0.687	1.179	.445
Challenge × Cousin with Breast Cancer[b]	0.516	0.088	3.020	.463
Challenge × Female Relative with Ovarian Cancer[b]	0.965	0.741	1.257	.792
Loss/Benefit × Age	1.023	0.986	1.061	.222
Loss/Benefit × Marital Status[a]	0.872	0.655	1.161	.347
Loss/Benefit × Number of Children	1.027	0.890	1.185	.718
Loss/Benefit × Aunt with Breast Cancer[b]	0.883	0.686	1.137	.336

Loss/Benefit × Grandmother with Breast Cancer[b]	1.004	0.787	1.281	.974
Loss/Benefit × Sister with Breast Cancer[b]	1.283	0.884	1.863	.190
Loss/Benefit × Mother with Breast Cancer[b]	1.309	0.943	1.817	.108
Loss/Benefit × Cousin with Breast Cancer[b]	1.519	0.807	2.863	.195
Loss/Benefit × Female Relative with Ovarian Cancer[b]	0.595	0.390	0.909	.016

Notes.
[a]The combined category of married/living with a partner was treated as the reference group for marital status
[b]Relative with breast cancer was treated as the reference group for family history of cancer

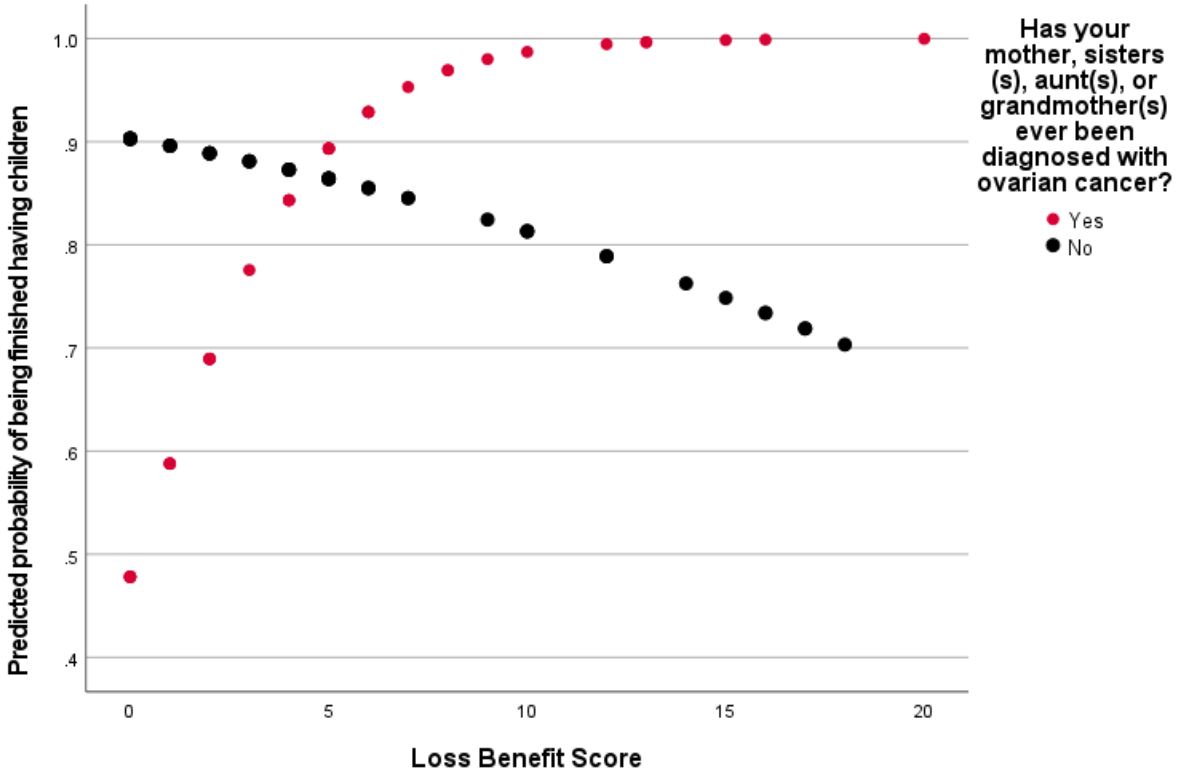

Figure 6 Predicted Probability of Being Finished Having Children for Female Relative with Ovarian Cancer and Loss Beneft Score

Another theme that we found among respondents was around financial constraints. 94.4% of the sample did not feel that financial constraints prevented them from making the reproductive decision that they did.

Women noted that the factors that most influenced their decision to have children came down to their self or spouse's desire to have children, and their quality of life.

4.5 Discussion

To our knowledge, this study was the first to assess the impact of emotional states on reproductive decision-making, while assessing for moderation of a *BRCA* pathogenic variant, and individual factors of age at genetic testing, marital status, number of children and family history of breast and ovarian cancer. In our study of 85 women with a *BRCA* pathogenic variant, we assessed emotions thought to be specific to women making reproductive decisions. Consistent with previous research, *BRCA*-related decisions are wrought with emotions. Specifically, this study identified that women who were older, already had children and had a family history of ovarian cancer were more likely to report being finished having children.

Family history of ovarian cancer was the only familial related variable significant in any of the models. This was not surprising because with the *BRCA* pathogenic variant, family implications are particularly strong, especially when considering the gene's autosomal dominant inheritance and high cancer penetrance. Most research explores family risk in the context of testing choices, when another family member is diagnosed with breast or ovarian cancer. Women in families with a strong cancer history are usually aware that they could follow the family pattern and develop cancer as well (Dean, & Rauscher, 2017a; Graves et al., 2012; Hamilton et al., 2009; Kenen et al., 2003; Kenen et al., 2007; Raveis et al., 2005) and they tend to perceive their personal risk as higher if their mother or sister had cancer (Douglas et al., 2009; Kenen et al., 2004; Raveis, & Pretter, 2005). As a result, women tend to undergo surgery earlier to decrease their chances of

receiving a cancer diagnosis. In addition, with a family history of ovarian cancer, the resulting surgery is the removal of ovaries, which renders a woman infertile. A family history of breast cancer may be considered less severe, since with a mastectomy, one may still be able to bear children.

The emotional scale items from the Appraisal of Life Events Scale were not significant in any model. These results indicate that either these emotions are not predominant in reproductive decision-making, or perhaps a more descriptive question needed to be asked to assess the impact of emotional state. Previous research has shown that it is an emotional experience that presents challenges for women making reproductive-related decisions, particularly those who are younger (Hamilton, 2012). Younger age is associated with both higher perceptions of stigma and cancer-specific anxiety and has also been associated with an increased sense of urgency in both life-partnering and childbearing (Hamilton, & Hurley, 2010; Werner-Lin, 2008). However, further research needs to be done to interpret the impact of timing since test disclosure on decision-making and the role of the emotions in this relationship.

The *BRCA* pathogenic variant status was not a significant moderator. This means that whether having *BRCA*1 vs *BRCA*2 was not a significant moderator in the relationship between emotional states and reproductive decision-making. The *BRCA*1 pathogenic variant is associated with increased risks of cancer, more so than *BRCA*2. Thus, it was hypothesized that *BRCA*1 would have a significant moderating effect. *BRCA*1 carries a higher likelihood of cancer than *BRCA*2, thus individuals with this pathogenic variant are generally recommended surgery earlier than those with *BRCA*2. Previous literature has not identified differences in uptake of surgery, or reproductive decisions among women with *BRCA*1 vs *BRCA*2 pathogenic variants, and this study

was no different. Further research is needed to assess the specific differences, if present, among *BRCA*1 vs *BRCA*2 pathogenic variant carriers.

Age at genetic testing and number of children were significant in the model predicting reproductive decision-making. This was not particularly surprising. Consistent research has shown that women who have children prior to *BRCA* test disclosure feel less conflict with making further reproductive choices. Additionally, women who are older in age are more likely to be partnered, and have children, thus making their reproductive decision plans more concrete. This seemed to be consistent with the findings from this study and further confirmed with use of the follow-up phone call. The women who were older tended to express that their *BRCA* diagnosis had no effect on their reproductive decision-making. Prior research has shown that younger women tend to be more distressed after genetic testing for the *BRCA* mutation than older women (Lodder et al., 2002; Watson et al., 2004). Anxiety and depression also have been found to be associated with age at the time of genetic testing (Bennett et al., 2008). In our study, age at genetic testing was significant when predicting reproductive decision making, but was not significant when assessing emotions.

4.5.1 Limitations of the Study

The study primarily was based upon secondary data analysis; however, several new variables were added. Retrospective research suffers from the risk of missing data, mistakes during the interpretation of data or incorrect documentation. The time difference from genetic testing and reproductive decision-making could have been an extraneous factor not considered during analysis. Based on the follow-up survey, 74% of the study sample was done having children by the time they were tested for *BRCA*, so the findings on decision making are effectively only for

26% of the population. Future studies should correct for this timeline. In addition, some variables were only able to be used as descriptive variables, rather than analytic variables. Future studies should try to include these variables in a manner that they can analyzed, as they may be important to the larger scope of the results.

Despite adequate power to conduct analyses, the response rate to study mailings was lower than expected. A larger sample is preferred to demonstrate more power in detecting significance among statistical tests. Some relationships that were predicted to have significance did not show this, and the small sample size could have played a role in this. Researchers have suggested to have a preferred sample size over 400 for logistic regression (Bewick, Cheek, & Ball, 2005; Hosmer & Lemeshow, 2000). Overall, study participants did not differ extremely from nonparticipants identified by the Cancer Family Registry as potentially eligible. On average, responders were about one year younger than non-respondents and marital status was similar. Even though the response rate was low, there did not appear to be drastic differences between those who responded and those who did not. Had there been differences, strategies to reduce bias would be undertaken in future studies. Additionally, this study only utilized a single mailing to obtain results. The use of repeated mailings and/or the use of reminder postcards would be an effective way to increase the sample size for future studies.

Finally, all instruments used in the study were self-reported measures. While some of the information could be checked with medical records, there is still a chance that the data could not have been completely accurate. Although the use of self-report is often used in research studies, this may introduce recall bias and social desirability.

4.6 Future Studies and Implications

Study design and recruitment are important considerations for the advancement of familial cancer science. Future research should move to longitudinal studies to 1) understand how emotion changes over time and 2) identify vulnerable phases in the reproductive decision-making trajectory. To maximize cancer prevention and risk reduction, as well as give women the most options they can have, it is critical to understand decision-making from a woman's standpoint. Previous research on the impact of counseling on psychosocial impacts of those counseled noted the importance of encouraging individuals to talk more during patient clinical counseling. This might, in turn, lead to improved outcomes in clinical risk communication, such as decreased distress and greater knowledge gains. Considering a range of psychosocial and relational factors in women's nexus of decision-making may facilitate and provide a range of rich pre and post-testing treatment options that empower women's medical decision-making abilities and improve their overall health and psychosocial outcomes.

Although the results of this study did not show us what we expected it to, there is still much more than can and should be done with regard to assessing emotional states and reproductive decision-making in women with a *BRCA* pathogenic variant. One potential future direction for this study includes prospective, longitudinal studies to assess young women receiving *BRCA* testing. A prospective longitudinal study would allow us to study decision regret, which could be an important component of this research. Not only would we be able to get the concurrent experience, but could also observe how that experience plays out over time. Do people becomes more convinced that they made the right decision and are they comfortable with that decision? Or as time goes on, do they begin to regret that decision? Current research presented by Dr. Andrew Dwyer at ISONG 2020, emphasized that perceived behavioral control (autonomy) is important for

increasing satisfaction and minimizing regret, especially among those with familial genetic disorders.. By identifying how risk perceptions change, especially as they near an age when they believe that their risks might increase, as well as following their management options over time, it will allow for a full-circle view and exactly what these individuals go through with their family planning and allow for exploration of that decisional regret component. Additionally, collecting data at the time of decision-making would likely give a more reliable view of emotions and decision making as the memory of emotions may fade over time.

Also, men may experience distress due to guilt associated with a cancer of *BRCA* diagnosis in their daughters and would be an avenue to explore. Additionally, there are specific ancestral backgrounds that research has suggested *BRCA* mutations have comparable prevalence in. By utilizing a study where women undergo ancestry testing to get the specific ancestry background, this might allow for a more precise look at ancestries that are associated with higher incidences of the *BRCA* pathogenic variant.

There are social and ethical implications associated with reproductive decision-making-such as the use of fertility assistance through PGD or cryopreservation. Identifying the prevalence of use, as well as the emotions that are associated with the use of these methods would be an area ripe for exploration. Finally, there are women of lower socioeconomic status that are underrepresented in terms of receipt of genetic services. Interventions to increase access to genetic testing and counseling in these women would allow for more well-rounded and holistic care.

With increased demands being placed on people's time and attention, survey response rates have been declining and costs have been rising. Attention should be paid to addressing reasons for non-participation in this study (increased age, privacy/providing information). Future research

should also focus on conducting studies that are sensitive to the challenges and perspective of more diverse groups of *BRCA* affected individuals.

Immediate next studies should include efforts to only include the study sample that responded that *BRCA* affected their decision to have children. By only including these women in the study, it would give a better view as to the significance of emotions on reproductive decision-making. In addition, employing efforts to increase the sample size to validate results would be a way to further confirm the findings from this study.

5.0 Summary of Study

Women who live in the United States have a 12% risk of developing breast cancer and a 2% risk of developing ovarian cancer during their lifetime. For women who carry a pathogenic *BRCA*1 or *BRCA*2 variant, one that affects approximately one in 200-400 women living in the United States, this risk increases (Kuchenbaecker et al., 2017a; Manickam et al., 2018). For breast cancer, lifetime risk ranges from 55-70% for *BRCA*1 carriers by the age of 70 and between 45-70% in *BRCA*2 carriers. For lifetime risk of ovarian cancer, the risk ranges from 40-45% for *BRCA*1 and 15-20% for *BRCA*2 (Kotsopoulos, 2018; Kuchenbaecker et al., 2017a). In addition to the increased personal risk, women with a *BRCA* pathogenic variant have a 50% chance of passing the pathogenic variant to their offspring (U. S. Preventive Services Task Force, 2019).

Due to the increased risk of cancer in these individuals, primary risk reduction strategies are often recommended, especially in those at increased risk for ovarian cancer. Risk-reducing surgical options may include bilateral mastectomy and bilateral salpingo-oopherectomy (U. S. Preventive Services Task Force, 2019). For a young woman who is not ready to make family planning decisions, these surgical procedures can be significantly life altering, especially in bilateral salpingo-oophorectomy, which renders a woman infertile (U. S. Preventive Services Task Force, 2019).

Much research has focused on the myriad of issues associated with women who have tested positively for a *BRCA* pathogenic variant. Although women want to be logical in their decision-making, emotions may complicate this process. By definition, emotions are complex, multi-dimensional judgments that reflect a great deal of information about one's relationship to social and physical surroundings. Strong evidence supports the association of emotions and the decision

to be tested for a *BRCA* pathogenic variant (Dean et al., 2017a; Rini et al., 2009; Werner-Lin, 2008). However, the role that emotions play in the reproductive decision-making process of women with a *BRCA* pathogenic variant is unknown. Lazarus and Folkman's Transactional Model of Stress provides the foundation to better understand the effects of emotion on healthcare decision-making (Bagneux et al., 2012; Lerner et al., 2005; Lerner et al., 2001; Lerner et al., 2014; Lerner et al., 1999). This model includes three basic dimensions, or emotional states; threat, challenge, and loss/benefit (Folkman et al., 1985). These emotional states are accompanied by core appraisal themes, which influence the likelihood of specific courses of action (Frijda, 2002; Lazarus, 1991; LeBlond, 2008). This study strived to determine if the emotional states of threat, challenge and loss/benefit, as outlined by the Transactional Model of Stress and measured using the Appraisal of Life Events (ALE) Scale, played a role on the reproductive decision making in women with a *BRCA* pathogenic variant.

A review of the literature found that women diagnosed with a *BRCA* pathogenic variant face difficult decisions about childbearing. The results of this review suggest that marriage and relationship status, as well as views about their use, acceptability and awareness of fertility options affect women's childbearing decision-making. Women with a known *BRCA* pathogenic variant have a sense of urgency in prioritizing childbearing over cancer risk management. Some researchers have noted that single women who test positive for a *BRCA* pathogenic variant experience urgency to find a partner. These women desire someone who is emotionally and financially secure, understands their pathogenic variant status, and is supportive of their reproductive decision-making.

This review of the literature further found that women with children were more likely to undergo preventive surgery than childless women. Women with a *BRCA* pathogenic variant

struggle with the idea that their children may inherit the pathogenic variant and often have feelings of sadness and guilt. These findings are consistent with previous research that has focused on opinions influencing the decision to be tested for a *BRCA* pathogenic variant. As more women learn their genetic breast or ovarian cancer risks, they must grapple with difficult decisions about reproductive life planning. The emotional aspects underlying reproductive decision-making are not well understood and requires additional study. Identifying the emotions and personal values influencing reproductive decision-making will help nurses provide psychological support and compassionate, knowledgeable care.

This study utilized an exploratory, descriptive methodology designed to describe the association between emotion and reproductive decision-making in women who tested positive for the *BRCA* pathogenic variant. Participants were sought from the Cancer Family Registry, and were mailed a packet containing a consent form, an ALE scale, demographic/family history questionnaire and a prepaid return envelope. The sociodemographic form was designed to gather participant information and collected current age, age at diagnosis, race, ethnicity, marital status, number of children and family history of breast and/or ovarian cancer. These items were self-reported from the Cancer Family Registry and confirmed during data collection. Reproduction decision-making was measured as a single response to the question 'are you finished having children?' with responses being either 'yes' or 'no'. *BRCA* pathogenic variant status was recorded from the Cancer Family Registry as either *BRCA*1 or *BRCA*2. Emotional states were measured by the Appraisal of Life Events scale, measured according to dimension. There were 32 response items, 16 in each of two categories, asking to what extent an adjective described a family planning decision under a *BRCA* diagnosis. Each item was ranked on a scale from 0-5. From those individual scores, the sum of certain individual items corresponded to one of the dimensions:

threat, loss/benefit or challenge. The higher the score, the higher the appraisal of threat, challenge or loss/benefit respectively. Based on the preliminary data results, a follow up phone call and questionnaire was appropriate to clarify the data that received. This phone call asked participants whether or not *BRCA* affected their decision to have children, how many children they had after their diagnosis and whether they were biological or adopted, if they froze their eggs, if cost was a factor in their decision-making and other outside factors that may have influenced their decision.

The sample was split relatively evenly between those with a *BRCA*1 vs a *BRCA*2 pathogenic variant and this was representative of the Cancer Family Registry. On average, women with a *BRCA*2 pathogenic variant were about 2 years older at diagnosis than those with a *BRCA*1 pathogenic variant. 98% of the sample was White, and more than half of the sample identified themselves as being Eastern European. Most of the sample was married or partnered and a little more than half reported having 1-2 children. The majority of the sample had a female relative diagnosed with either breast or ovarian cancer. Specifically, most of the sample (52.9%) had a mother that was diagnosed with breast cancer, followed closely by grandmother and aunt. Not unlike breast cancer, the number of women with a female relative with ovarian cancer was high (45.9%). Again, those numbers were highest among mothers, grandmothers and aunts. Logistic regression results showed that none of the emotional states were significant for predicting probability of being finished having children. The individual variables that were significant for reproductive decision-making were age at genetic testing and number of children. Based on the follow-up questionnaire, 74% of the study participants did not have children after learning about their diagnosis. 26% did have children, and of those individuals, 98% had biological children. 3 individuals used PGD to assist with their reproduction and only one individual froze their eggs.

When the moderating effect of *BRCA* pathogenic variant status on emotional states and reproductive decision-making was analyzed, there were no significant interactions, considering each emotional state individually, as well as collectively. Further, based on the follow-up questionnaire, we found that 75% of the sample said that their *BRCA* diagnosis did not affect their decision to have children. The most significant reasons were that they were done having children (they already had the number of children they desired) or they wanted children regardless and were not letting a *BRCA* diagnosis define their choice to have children. On average, older participants felt that knowing they carried a *BRCA* pathogenic variant did not affect their decision. Of the 25% that reported that a *BRCA* diagnosis did affect their decision to have children, it was due to personal timelines. These women felt rushed to complete their childbearing, knowing that they had a limited window.

Finally, when looking at the moderating effect of the individual factors on emotional states and reproductive decision-making, we found one significant interaction between family history of ovarian cancer and loss/benefit scores, indicating that women who reported higher loss/benefit scores and had a female relative with ovarian cancer were more likely to be finished having children.

This study was the first to assess the impact of emotional states on reproductive decision-making, while assessing for moderation of a *BRCA* pathogenic variant and individual factors. The emotional scale items from the Appraisal of Life Events Scale were not significant. However, further research is needed to interpret the impact of timing since test disclosure on decision-making and the role of the emotions in this relationship. The results of this study are limited by the fact that 74% of the study participants had completed their families by the time they were tested for

BRCA. This means that the results from this study are valid for only 26% of the study population. Future studies should correct for this timeline.

The *BRCA* pathogenic variant status was not a significant moderator. The results of this study are consistent with the literature that has not identified differences in the number of prophylactic surgical procedures, or reproductive decisions made among women with *BRCA*1 vs *BRCA*2 pathogenic variants. Further research is needed to assess the specific differences, if present, among *BRCA*1 vs *BRCA*2 pathogenic variant carriers.

Analysis of study participants compared to the nonparticipants identified by the Cancer Family Registry as potentially eligible did not differ. On average, responders were about 1 year younger than non-respondents (*BRCA1*: 32.45 years and *BRCA2*: 34.94 years) and marital status was similar (*BRCA1*: 69.3% partnered, 30.7% unpartnered and *BRCA2*: 71.7% partnered and 28.3% unpartnered). Had there been differences, strategies to reduce bias would be undertaken in future studies. This study sample included only women who were under the age of 45; there were 374 women who met the initial inclusion criteria. After accounting for those women who were 45 years and younger, 85 women out of the returned 123 surveys were eligible for inclusion in the study.

Future studies should include a prospective, longitudinal design to assess young women receiving *BRCA* testing. Using a prospective design would allow decisional regret to be explored, which could be an important component of this research. Not only would we be able to study the concurrent experience, but could also observe how that experience plays out over time. Are women convinced that they made the right decision and are they comfortable with that decision? Or as time goes on, do they begin to regret that decision? By identifying how risk perceptions change, especially as women near an age when they believe that their risks might increase, as well

as following management options over time, it will allow for a full-circle view at exactly what these individuals go through with their family planning. This will also allow for exploration of a decisional regret component. By collecting data at the time of decision-making, this would likely give a more reliable view of emotions and decision making as the memory of emotions may fade over time.

In conclusion, emotions may play a role in the reproductive decision-making of women with a positive BRCA pathogenic variant. Age at genetic testing and number of children, as well as a family history of ovarian cancer play a significant role in relation to loss/benefit and reproduction decision-making. These findings may, over time, help to guide interventions to empower women's medical decision-making abilities and improve their overall health and psychosocial outcomes.

5.1 Funding

This research was supported by the Jonas Philanthropies, the University of Pittsburgh School of Nursing Margaret E. Wilkes Scholarship, and the University of Pittsburgh School of Nursing Judith Erlen Scholarship, National Institutes of Nursing Research Grant NR0196556 and National Institutes of Nursing Research training grant 5T32NR011972-05.

5.2 Conflict of Interest Disclosures

The authors have no conflict of interest to disclose.

Appendix A IRB Approval for Dissertation Study

University of Pittsburgh
Institutional Review Board

Human Research Protection Office
3500 Fifth Avenue, Suite 106
Pittsburgh, PA 15213
Tel (412) 383-1480
www.hrpo.pitt.edu

APPROVAL OF SUBMISSION (Expedited)

Date:	October 15, 2019
IRB:	STUDY19050345
PI:	Elizabeth Skrovanek
Title:	Emotions Associated with Reproductive Decision Making in Women with a BRCA mutation
Funding:	None
Grant Title:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Initial Study
Approval Date:	10/15/2019

Determinations:	None
Approved Documents:	• Demographic Information, Category: Data Collection; • Appraisal of Life Events Scale, Category: Data Collection; • Consent form, Category: Consent Form; • Introductory letter, Category: Recruitment Materials

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Dana DiVirgilio.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

Appendix B Introductory Letter

Thank you so much for your continued support in the Cancer Family Registry! My name is Elizabeth Skrovanek and I am a doctoral student at the University of Pittsburgh School of Nursing. I am conducting this research study as part of my dissertation work to better understand and support women who have a BRCA mutation and are making decisions about their family planning.

You will receive a $20 gift card for completing the questionnaire and survey.

There will be no benefit to your participation in this study. Your participation is completely voluntary and you may withdraw at any time.

A breach of confidentiality is possible as your name will be collected with your information. However, all measures will be taken to ensure that your privacy will be protected. Your name and personal information will not be associated with any study data and will be kept in a separate location.

First, please review and complete one copy of the Consent form included with this mailing. The signed consent form must be returned along with your questionnaire and survey responses in order for us to include you in the study. You will receive a copy of this consent form when you receive your $20 gift card as thanks for completing the documents.

As a study participant you will be asked to:

- Complete the included paper survey and questionnaire and return it along with the signed consent form in the included prepaid envelope.
- The survey will ask about emotions that you may have experienced while you were thinking about your family planning. This survey should take you less than 30 minutes to complete. If you need a break, you can come back to the survey later.
- The questionnaire will ask for information about your background and family history.
- Your participation in this research study might help us increase our understanding of the support needed by young women with a BRCA mutation as they make family planning decisions.

After we receive your signed consent form, survey and questionnaire, we will mail you a gift card and a copy of your signed consent form.

Please note that your responses to this questionnaire will not be sent to your healthcare providers. It is important that you contact or see your professional

healthcare team if you have any questions or concerns about any emotional symptoms or your genetic testing results.

If you have any questions you can contact me at eas103@pitt.edu.

Sincerely,

Elizabeth Skrovanek BSN, PhD (s)
University of Pittsburgh School of Nursing
415 Victoria Building
3500 Victoria Street
Pittsburgh, PA 15213

Phuong L. Mai, MD, MS
UPMC Cancer Genetics Program
Magee-Womens Hospital of UPMC
300 Halket Street, Suite 1651
Pittsburgh, PA 15213

Appendix C Study Consent Form

VOLUNTARY CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Emotions Associated with Reproductive Decision Making in Women with a BRCA Gene Mutation

PRINCIPAL INVESTIGATOR: Elizabeth Skrovanek BSN, PhD(s)
Doctoral Student
Health Promotion and Development
440 Victoria Building
University of Pittsburgh

CO-INVESTIGATORS:

Susan Wesmiller
PhD, RN
Professor
Health Promotion and Development
School of Nursing
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412-383-7270

Phuong Mai MD
Associate Professor
Department of Obstetrics, Gynecology and Reproductive Services
Magee Women's Hospital
412-641-7449

Susan Sereika PhD
Professor
Health and Community Systems
School of Nursing
University of Pittsburgh
412-624-0799

SOURCE OF SUPPORT: Judith Erlen Scholarship Fund; University of Pittsburgh School of Nursing

About 1 in 200 women living in the United States has a BRCA mutation. You are being asked to participate in a research study to determine the impact of emotions on your reproductive decision making (how you have made or are making decisions around completing your family). We are inviting you to participate because you are a woman above the age of 18 and have been identified to have a BRCA gene mutation.

The goal of this study is to determine the impact of certain emotions on reproductive decision making in women with a BRCA gene mutation. We are aiming to recruit 75 participants for this study.

During the study, this is what will happen:

1). Complete the **enclosed survey**. It will ask you to check off some words that describe the emotions that you might have felt or are feeling while making a decision about your reproductive planning. This survey should take approximately 30 minutes to complete.

2). Complete a **demographics form**. This form will ask you to fill out some information about you, such as your age, your marital status, ancestry, number of children that you have and if you have any family history of breast or ovarian cancer.

If you have any questions regarding the study, consent, survey or anything about the study, please do not hesitate to call the PI.

The following risk could be associated with participation in this research study:

There is a risk of breach of confidentiality: that is, in very rare cases, people not associated with this research study may inadvertently see the identifiable research results.

To protect your privacy and maintain confidentiality of information we obtain from you, we will keep all information about your study information in a secure location. All paper records that could identify you will be stored in locked file cabinets kept in a locked office. All electronic records will be stored in password protected files. Your identity on these records will be indicated by a case number rather than by your name, and the code linking your name to this number will be maintained separately with very limited access to research team members.

Your participation in this research study is entirely voluntary.

Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

- Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

You will be paid $20.00 to take part in this study.

Your participation in this research study is completely voluntary. Whether or not you participate will have no effect on your current or future relationship with the University of Pittsburgh, Magee Women's Hospital or its affiliated health care providers or health insurance providers. If you decide you no longer wish to participate after you have signed the consent form, you should contact the PI, Ms. Elizabeth Skrovanek at 724-719-8068.
You can, at any time withdraw from this research study; you can also withdraw your authorization for us to use your identifiable medical information for the purposes described above. This means that you will also be withdrawn from further participation in this research study. Any identifiable research or medical information obtained as part of this study prior to the date that you withdrew your consent will continue to be used and disclosed by the investigators for the purposes described above.

- To formally withdraw from this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form. Your decision to withdraw from this study will have no effect on your current or future relationship with the University of Pittsburgh.

- Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care provider

****

VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that, such questions or any concerns should be addressed by Ms. Skrovanek. At any point, I may also contact the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns and questions, to obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I agree to participate in this research study and authorize the use and disclosure of my medical record information for the purposes described above. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date

Appendix D Demographic Questionnaire

Demographic Questionnaire

Please fill out the following questions. Please answer the questions to the best of your ability.

Current Age: _____

Age when you had your genetic test: _____

Identified Race- please circle one:

American Indian or Alaska Native

Asian

Black or African American

Native Hawaiian or Other Pacific Islander

White

Ethnicity- please circle one:

Hispanic or Latino

Not Hispanic or Latino

Ancestry- please list the ancestry for your father's and mother's side of the family on the respective lines:

Ancestry (father) _____

Ancestry (mother) _____

Marital Status:

Married

Widowed

Divorced or Separated

Never Married

Living with a Partner

Number of Children you Have: _____

Are you Finished Having Children?

Yes No I Don't Know

Has your mother, sister(s), aunt(s) or grandmother(s) ever been diagnosed with breast cancer?

Yes No

If yes, please tell us which relative: _____

Has your mother, sister(s), aunt(s) or grandmother(s) ever been diagnosed with ovarian cancer?

Yes No

If yes, please tell us which relative: _____

Appendix E Appraisal of Life Events Scale

The following survey will ask you some questions about your family planning and how you felt while making your family plans. Please answer the questions to the best of your ability; there are no right or wrong answers. You may use the back of the paper if you need more space to write.

ALE-Scale (Retrospective recall version)

In the space provided, please describe **your decision making around your family planning and if your BRCA diagnosis affected this planning. This can include how you decided to have children and/or when you decided to have them. You may use the back if you need to:**

We would like you to rate your **perceptions** of the above event you have just described. Use the following six point scales (where 0 = not at all to 5 = very much so) to indicate the extent to which each of the adjectives best describes your **perceptions** of the event when it occurred. Do this by circling the appropriate point on the scales.
Please respond as quickly as possible as first responses are usually more accurate. Please make a response to each adjective.

AT THE TIME IT OCCURRED THE EVENT WAS:

(1) Threatening:
0 1 2 3 4 5

(2) Fearful:
0 1 2 3 4 5

(3) Enjoyable:
0 1 2 3 4 5

(4) Worrying:
0 1 2 3 4 5

(5) Hostile:
0 1 2 3 4 5

(6) Challenging:
0 1 2 3 4 5

(7) Stimulating:
0 1 2 3 4 5

(8) Exhilarating:
0 1 2 3 4 5

(9) Painful:
0 1 2 3 4 5

(10) Depressing:
0 1 2 3 4 5

(11) Pitiful:
0 1 2 3 4 5

(12) Informative:
0 1 2 3 4 5

(13) Exciting:
0 1 2 3 4 5

(14) Frightening:
0 1 2 3 4 5

(15) Terrifying:
0 1 2 3 4 5

(16) Intolerable:
0 1 2 3 4 5

ALE Scale - (Situational version)

We would like you to rate your **perceptions** of your current circumstances. That is your perception of your thoughts and feelings **right now**. Use the following six point scales (where 0 = not at all to 5 = very much so) to indicate the extent to which each of the adjectives best describes your **perceptions** now. Do this by circling the appropriate point on the scales. Please respond as quickly as possible as first responses are usually more accurate. Please make a response to each adjective.

I FIND MY CURRENT CIRCUMSTANCES:

(1) Threatening:
0 1 2 3 4 5

(2) Fearful:
0 1 2 3 4 5

(3) Enjoyable:
0 1 2 3 4 5

(4) Worrying:
0 1 2 3 4 5

(5) Hostile:
0 1 2 3 4 5

(6) Challenging:
0 1 2 3 4 5

(7) Stimulating:
0 1 2 3 4 5

(8) Exhilarating:
0 1 2 3 4 5

(9) Painful:
0 1 2 3 4 5

(10) Depressing:
0 1 2 3 4 5

(11) Pitiful:
0 1 2 3 4 5

(12) Informative:
0 1 2 3 4 5

(13) Exciting:
0 1 2 3 4 5

(14) Frightening:
0 1 2 3 4 5

(15) Terrifying:
0 1 2 3 4 5

(16) Intolerable:
0 1 2 3 4 5

Appendix F Human Subjects Training

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 1 OF 2
COURSEWORK REQUIREMENTS*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)

- **Curriculum Group:** CITI Conflicts of Interest
- **Course Learner Group:** COI PHS Regulated Course
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 25707381
- **Completion Date:** 07-Jan-2018
- **Expiration Date:** 06-Jan-2022
- **Minimum Passing:** 80
- **Reported Score*:** 92

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED	SCORE
Financial Conflicts of Interest: Overview, Investigator Responsibilities, and COI Rules (COI-Basic) (ID: 15070)	07-Jan-2018	5/5 (100%)
Institutional Responsibilities as They Affect Investigators (COI-Basic) (ID: 15072)	07-Jan-2018	5/5 (100%)
Conflicts of Interest Institution-Specific Policies (ID: 15179)	07-Jan-2018	10/10 (100%)
Conflicts of Commitment and Conscience (COI-Basic) (ID: 15073)	07-Jan-2018	3/5 (60%)

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/?kce164da0-d3e4-44f9-b7ca-56eb240e033b-25707381

Collaborative Institutional Training Initiative (CITI Program)
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Phone: 888-529-5929
Web: https://www.citiprogram.org

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 2 OF 2
COURSEWORK TRANSCRIPT**

** NOTE: Scores on this Transcript Report reflect the most current quiz completions, including quizzes on optional (supplemental) elements of the course. See list below for details. See separate Requirements Report for the reported scores at the time all requirements for the course were met.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)

- **Curriculum Group:** CITI Conflicts of Interest
- **Course Learner Group:** COI PHS Regulated Course
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 25707381
- **Report Date:** 19-Oct-2020
- **Current Score**:** 92

REQUIRED, ELECTIVE, AND SUPPLEMENTAL MODULES	MOST RECENT	SCORE
Conflicts of Interest Institution-Specific Policies (ID: 15179)	07-Jan-2018	10/10 (100%)
Financial Conflicts of Interest: Overview, Investigator Responsibilities, and COI Rules (COI-Basic) (ID: 15070)	07-Jan-2018	5/5 (100%)
Institutional Responsibilities as They Affect Investigators (COI-Basic) (ID: 15072)	07-Jan-2018	5/5 (100%)
Conflicts of Commitment and Conscience (COI-Basic) (ID: 15073)	07-Jan-2018	3/5 (60%)

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/?kce164da0-d3e4-44f9-b7ca-56eb240e033b-25707381

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COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 1 OF 2
COURSEWORK REQUIREMENTS*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)

- **Curriculum Group:** Biomedical Human Subjects Research
- **Course Learner Group:** Biomedical Course
- **Stage:** Stage 2 - Refresher Course
- **Description:** Choose this group to satisfy CITI training requirements for Investigators and staff involved primarily in biomedical research with human subjects.

- **Record ID:** 27506219
- **Completion Date:** 21-Apr-2019
- **Expiration Date:** 20-Apr-2023
- **Minimum Passing:** 80
- **Reported Score*:** 100

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED	SCORE
Biomed Refresher 1 - Instructions (ID: 960)	21-Apr-2019	No Quiz
Biomed Refresher 1 – History and Ethical Principles (ID: 975)	21-Apr-2019	2/2 (100%)
Biomed Refresher 1 – Informed Consent (ID: 980)	21-Apr-2019	2/2 (100%)
Biomed Refresher 1 – Regulations and Process (ID: 981)	21-Apr-2019	3/3 (100%)
Biomed Refresher 1 – SBR Methodologies in Biomedical Research (ID: 982)	21-Apr-2019	3/3 (100%)
Biomed Refresher 1 – Records-Based Research (ID: 983)	21-Apr-2019	2/2 (100%)
Biomed Refresher 1 – Genetics Research (ID: 984)	21-Apr-2019	4/4 (100%)
Biomed Refresher 1 - Populations in Research Requiring Additional Considerations and/or Protections (ID: 985)	21-Apr-2019	2/2 (100%)
Biomed Refresher 1 – FDA-Regulated Research (ID: 987)	21-Apr-2019	3/3 (100%)
Biomed Refresher 1 – Research Involving Children (ID: 974)	21-Apr-2019	4/4 (100%)

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/?k9d1d1a3f-b15e-4fa3-9e09-811a6a463771-27506219

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COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 2 OF 2
COURSEWORK TRANSCRIPT**

** NOTE: Scores on this Transcript Report reflect the most current quiz completions, including quizzes on optional (supplemental) elements of the course. See list below for details. See separate Requirements Report for the reported scores at the time all requirements for the course were met.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)

- **Curriculum Group:** Biomedical Human Subjects Research
- **Course Learner Group:** Biomedical Course
- **Stage:** Stage 2 - Refresher Course
- **Description:** Choose this group to satisfy CITI training requirements for Investigators and staff involved primarily in biomedical research with human subjects.

- **Record ID:** 27506219
- **Report Date:** 19-Oct-2020
- **Current Score**:** 100

REQUIRED, ELECTIVE, AND SUPPLEMENTAL MODULES	MOST RECENT	SCORE
Biomed Refresher 1 - Instructions (ID: 960)	21-Apr-2019	No Quiz
Biomed Refresher 1 – Research Involving Children (ID: 974)	21-Apr-2019	4/4 (100%)
Biomed Refresher 1 – History and Ethical Principles (ID: 975)	21-Apr-2019	2/2 (100%)
Biomed Refresher 1 – Informed Consent (ID: 980)	21-Apr-2019	2/2 (100%)
Biomed Refresher 1 – Regulations and Process (ID: 981)	21-Apr-2019	3/3 (100%)
Biomed Refresher 1 – SBR Methodologies in Biomedical Research (ID: 982)	21-Apr-2019	3/3 (100%)
Biomed Refresher 1 – Records-Based Research (ID: 983)	21-Apr-2019	2/2 (100%)
Biomed Refresher 1 – Genetics Research (ID: 984)	21-Apr-2019	4/4 (100%)
Biomed Refresher 1 - Populations in Research Requiring Additional Considerations and/or Protections (ID: 985)	21-Apr-2019	2/2 (100%)
Biomed Refresher 1 – FDA-Regulated Research (ID: 987)	21-Apr-2019	3/3 (100%)

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/?k9d1d1a3f-b15e-4fa3-9e09-811a6a463771-27506219

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COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 1 OF 2
COURSEWORK REQUIREMENTS*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)

- **Curriculum Group:** Information Privacy & Security
- **Course Learner Group:** Privacy & Information Security
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 25714615
- **Completion Date:** 08-Jan-2018
- **Expiration Date:** 08-Jan-2022
- **Minimum Passing:** 80
- **Reported Score*:** 100

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED	SCORE
Basics of Health Privacy (ID: 1417)	08-Jan-2018	5/5 (100%)
Health Privacy Issues for Researchers (ID: 1419)	08-Jan-2018	5/5 (100%)
Basics of Information Security, Part 1 (ID: 1423)	08-Jan-2018	5/5 (100%)
Basics of Information Security, Part 2 (ID: 1424)	08-Jan-2018	5/5 (100%)

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/?kc78db92b-9898-46e3-b31b-9f8555591ca0-25714615

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COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 2 OF 2
COURSEWORK TRANSCRIPT**

** NOTE: Scores on this Transcript Report reflect the most current quiz completions, including quizzes on optional (supplemental) elements of the course. See list below for details. See separate Requirements Report for the reported scores at the time all requirements for the course were met.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)

- **Curriculum Group:** Information Privacy & Security
- **Course Learner Group:** Privacy & Information Security
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 25714615
- **Report Date:** 19-Oct-2020
- **Current Score**:** 100

REQUIRED, ELECTIVE, AND SUPPLEMENTAL MODULES	MOST RECENT	SCORE
Health Privacy Issues for Researchers (ID: 1419)	08-Jan-2018	5/5 (100%)
Basics of Health Privacy (ID: 1417)	08-Jan-2018	5/5 (100%)
Basics of Information Security, Part 1 (ID: 1423)	08-Jan-2018	5/5 (100%)
Basics of Information Security, Part 2 (ID: 1424)	08-Jan-2018	5/5 (100%)

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/?kc78db92b-9898-46e3-b31b-9f8555591ca0-25714615

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COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 1 OF 2
COURSEWORK REQUIREMENTS*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)

- **Curriculum Group:** Responsible Conduct of Research
- **Course Learner Group:** Same as Curriculum Group
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 18438527
- **Completion Date:** 24-May-2018
- **Expiration Date:** 23-May-2022
- **Minimum Passing:** 80
- **Reported Score*:** 89

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED	SCORE
Authorship (RCR-Basic) (ID: 16597)	09-Jan-2018	5/5 (100%)
Collaborative Research (RCR-Basic) (ID: 16598)	09-Jan-2018	5/5 (100%)
Data Management (RCR-Basic) (ID: 16600)	24-May-2018	4/5 (80%)
Mentoring (RCR-Basic) (ID: 16602)	24-May-2018	5/5 (100%)
Peer Review (RCR-Basic) (ID: 16603)	24-May-2018	4/5 (80%)
Research Misconduct (RCR-Basic) (ID: 16604)	24-May-2018	4/5 (80%)
Plagiarism (RCR-Basic) (ID: 15156)	24-May-2018	4/5 (80%)

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COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 2 OF 2
COURSEWORK TRANSCRIPT**

** NOTE: Scores on this Transcript Report reflect the most current quiz completions, including quizzes on optional (supplemental) elements of the course. See list below for details. See separate Requirements Report for the reported scores at the time all requirements for the course were met.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)

- **Curriculum Group:** Responsible Conduct of Research
- **Course Learner Group:** Same as Curriculum Group
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 18438527
- **Report Date:** 19-Oct-2020
- **Current Score**:** 89

REQUIRED, ELECTIVE, AND SUPPLEMENTAL MODULES	MOST RECENT	SCORE
Plagiarism (RCR-Basic) (ID: 15156)	24-May-2018	4/5 (80%)
Authorship (RCR-Basic) (ID: 16597)	09-Jan-2018	5/5 (100%)
Collaborative Research (RCR-Basic) (ID: 16598)	09-Jan-2018	5/5 (100%)
Data Management (RCR-Basic) (ID: 16600)	24-May-2018	4/5 (80%)
Mentoring (RCR-Basic) (ID: 16602)	24-May-2018	5/5 (100%)
Peer Review (RCR-Basic) (ID: 16603)	24-May-2018	4/5 (80%)
Research Misconduct (RCR-Basic) (ID: 16604)	24-May-2018	4/5 (80%)

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COMPLETION REPORT - PART 1 OF 2
COURSEWORK REQUIREMENTS*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)
- **Institution Email:** eas103@pitt.edu
- **Institution Unit:** Nursing
- **Phone:** 7247198068

- **Curriculum Group:** GCP – Social and Behavioral Research Best Practices for Clinical Research
- **Course Learner Group:** Same as Curriculum Group
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 25707382
- **Completion Date:** 08-Jan-2018
- **Expiration Date:** 07-Jan-2021
- **Minimum Passing:** 100
- **Reported Score*:** 100

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED	SCORE
Module 1 - Introduction (ID: 17531)	07-Jan-2018	5/5 (100%)
Module 2 - Research Protocol (ID: 17532)	08-Jan-2018	5/5 (100%)
Module 3 - Recruitment and Retention (ID: 17533)	08-Jan-2018	5/5 (100%)
Module 4 - Informed Consent Communication (ID: 17534)	08-Jan-2018	5/5 (100%)
Module 5 - Privacy and Confidentiality (ID: 17535)	08-Jan-2018	5/5 (100%)
Module 6 - Participant Safety and Adverse Event Reporting (ID: 17536)	08-Jan-2018	5/5 (100%)
Module 7 - Quality Control and Assurance (ID: 17537)	08-Jan-2018	5/5 (100%)
Module 8 - Research Misconduct (ID: 17538)	08-Jan-2018	5/5 (100%)
Module 9 - Conclusion (ID: 17539)	08-Jan-2018	No Quiz

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

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COMPLETION REPORT - PART 2 OF 2
COURSEWORK TRANSCRIPT**

** NOTE: Scores on this Transcript Report reflect the most current quiz completions, including quizzes on optional (supplemental) elements of the course. See list below for details. See separate Requirements Report for the reported scores at the time all requirements for the course were met.

- **Name:** Elizabeth Skrovanek (ID: 4326604)
- **Institution Affiliation:** University of Pittsburgh (ID: 2074)
- **Institution Email:** eas103@pitt.edu
- **Institution Unit:** Nursing
- **Phone:** 7247198068

- **Curriculum Group:** GCP – Social and Behavioral Research Best Practices for Clinical Research
- **Course Learner Group:** Same as Curriculum Group
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 25707382
- **Report Date:** 19-Oct-2020
- **Current Score**:** 100

REQUIRED, ELECTIVE, AND SUPPLEMENTAL MODULES	MOST RECENT	SCORE
Module 1 - Introduction (ID: 17531)	07-Jan-2018	5/5 (100%)
Module 2 - Research Protocol (ID: 17532)	08-Jan-2018	5/5 (100%)
Module 3 - Recruitment and Retention (ID: 17533)	08-Jan-2018	5/5 (100%)
Module 4 - Informed Consent Communication (ID: 17534)	08-Jan-2018	5/5 (100%)
Module 5 - Privacy and Confidentiality (ID: 17535)	08-Jan-2018	5/5 (100%)
Module 6 - Participant Safety and Adverse Event Reporting (ID: 17536)	08-Jan-2018	5/5 (100%)
Module 7 - Quality Control and Assurance (ID: 17537)	08-Jan-2018	5/5 (100%)
Module 8 - Research Misconduct (ID: 17538)	08-Jan-2018	5/5 (100%)
Module 9 - Conclusion (ID: 17539)	08-Jan-2018	No Quiz

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

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Appendix G Follow-Up Phone Call and Questionnaire

Hi _____,

My name is Elizabeth Skrovanek, from the University of Pittsburgh School of Nursing. You recently completed a survey for my study of women at risk for breast and ovarian cancer. Thank you so much.

I had 2-3 follow-up questions that I was hoping you would be willing to answer if you have time?

- (If she says she does not have time now): If not, is there a better time for you?
- (If she says she doesn't have time to complete surveys): I can also send you an email message containing a link to answer the questions. Can you please provide me with an email address?
- If she is not willing to complete over the phone or through email- thank you for your responses to my survey. I appreciate your time.

You indicated that: *BRCA* did not affect your decision about having children

BRCA did affect your decision about having children

How many children did you have after learning about your diagnosis?

- For those children, what was the specific decision that you made? For example, were they biological (biological in this case means using your egg and your partner's sperm)? Adopted?
- How did you decide to make that choice?
- If biological, did you use a surrogate?

Will ask all- Did you freeze your eggs?

- Yes
- No

I would like to ask about any financial constraints that might have influenced your decision, if you feel comfortable.

- No, not comfortable
- Yes, comfortable
    - Were there any financial constraints involved in your decision about having children?
    - If you did not make the choice that you wanted to, did you feel that financial constraints prevented you from making that choice?
    - How much would you say that cost factored into your decision about having children?
        - Not at all
        - A little bit
        - Somewhat
        - Quite a bit
        - Very Much

Finally, were there any outside factors, or individuals, that influenced your decision? These can include things like:

- Age at marriage
- Quality of life
- Social support
- Self/spousal desire to have children
- Feeling of "biological clock" ticking

Thank you so much for your response to these questions. I appreciate the time that you spent to speak with me about your experience.

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