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The Experiences and Needs of Individuals With a Variant of
Uncertain Significance (VUS) on Genetic Tests for Hereditary Cancer Syndromes:
A Grounded Theory Study

A Dissertation Presented

by

DANIELLE MARIE GOULD

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

February 2022

Nursing

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This dissertation may have my name on it, but it would have never been completed without the support of many people in my life.

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ABSTRACT

THE EXPERIENCES AND NEEDS OF INDIVIDUALS WITH A VARIANT OF UNCERTAIN SIGNIFICANCE (VUS) ON GENETIC TESTS FOR HEREDITARY CANCER SYNDROMES: A GROUNDED THEORY STUDY

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Background: The use of multigene panel testing for identifying individuals with hereditary cancer susceptibility has expanded in recent years. The number of individuals who have a variant of unknown significance (VUS) result is increasing. However, little is known about the experiences and needs of this group. This study's purpose was to describe the experiences and needs of individuals with a VUS result by focusing on their experiences in communicating with healthcare providers and family members.

Methods: A constructivist grounded theory approach was used. Recruitment took place from January–July 2021 through social media: the Prospective Registry of Multiplex Testing (PROMPT), and the Facing Our Risk (FORCE) websites. A total of 20 individuals participated in the study. Data were collected through semistructured interviews, and the verified transcripts were analyzed in NVivo.

Results: Categories were sorted into by time: pretest, testing, and posttesting process. Categories included motivations, communication with family, family characteristics, communication with healthcare providers, other factors affecting the testing experiences, feelings about having a VUS, recall and understanding of the test result and its implications, coping strategies used, and risk management strategies used. From these categories, a theoretical model to describe the experiences of individuals with a VUS

was developed. In the theory, contextual factors such as personality, coping style, and cancer history, decisions about medical care, communicating with healthcare providers and family members, and needs such as knowledgeable and trustworthy providers, support for emotional needs, and open lines of communication were part of the experience described by participants.

Conclusion: This study describes the experiences of individuals who have a VUS from their point of view. The proposed theoretical model proposes the key themes that impact the experience: context; decision-making; communication with healthcare providers and family; and the need for knowledgeable and trustworthy providers; met emotional needs; and open lines of communication.

Key words: Grounded theory, VUS, Genetic testing, Patient experience, Cancer, Hereditary cancer

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LIST OF ABBREVIATIONS

CPM: Contralateral prophylactic mastectomy

FAMMM: Familial atypical multiple mole melanoma syndrome

FAP: Familial adenomatous polyposis

HBOC: Hereditary breast and ovarian cancer

HCP: Healthcare provider

MGPT: Multigene panel test

PCP: Primary care provider

PJS: Peutz-Jegher's syndrome

PROMPT: Prospective Registry Of MultiPlex Testing

PSA: Prostate-specific antigen test

PV: Pathogenic variant

RRBSO: Risk-reducing bilateral salpingo-oophorectomy

RRM: Risk-reducing mastectomy

UIT: Uncertainty in illness theory

VUS: Variant of uncertain significance

CHAPTER 1

INTRODUCTION

Hereditary Cancer Syndromes

Hereditary cancer syndromes are caused by mutations (changes) in certain genes passed from parents to children. In a hereditary cancer syndrome, certain patterns of cancer may be seen within families (National Cancer Institute [NCI], 2011). One of the most recognized is hereditary breast and ovarian cancer (HBOC), which is caused by pathogenic variants (PVs) on the *BRCA1* or *BRCA2* genes (Petrucelli et al., 2016). Lynch syndrome was first recognized in the early 1900s as a familial colon cancer syndrome and is now linked to PVs on the *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* genes. It has also been linked to multiple other cancers, including ovarian and uterine among others (Kohlmann & Gruber, 2018). These syndromes are inherited in an autosomal dominant manner, meaning that only one pathogenic allele is needed to have the syndrome. However, the penetrance of these syndromes varies based on the type of pathogenic change that was inherited. Genetic testing for these syndromes has been increasingly available since the 1990s (Molteni, 2019).

As genetic testing has expanded, multiple other hereditary cancer syndromes have been identified. Hereditary risks for breast cancer are now linked to the *ATM*, *PALB2*, *PTEN*, and *CDH1* (Kaurah & Huntsman, 2018; Petrucelli et al., 2016). Familial adenomatous polyposis (FAP), which causes severe colon polyposis and colon cancer, is caused by changes in the *APC* gene (Jasperson et al., 2017). An autosomal recessive polyposis syndrome has also been identified, *MUTYH*-associated Polyposis (MAP), which occurs when an individual inherits two PVs in the *MUTYH* gene (Nielsen et al., 2019).

There are other, rarer hereditary cancer syndromes as well. Peutz-Jegher's syndrome (PJS) is caused by PVs in the *STK11* gene and causes increased risk for hamartomatous polyps and pancreatic and other cancers (McGarrity et al., 2016). Von Hippel-Lindau is caused by mutations in the VHL gene and increases the risk of renal cancer (van Leeuwen et al., 2018). Familial atypical multiple mole melanoma syndrome (FAMMM) causes melanocytic moles as well as an increased risk for melanoma and has been linked to mutations on the CDKN2A gene (MedlinePlus Genetics, 2020).

Li-Fraumeni Syndrome was first discovered in the 1960s and is linked to a greater than 90% risk of some form of cancer by age 70. Individuals with this syndrome are at higher risk of breast and colon cancer, but also childhood cancers, rare soft tissue sarcomas, and many other types of cancers. Screening and risk reduction for individuals with this syndrome can begin as early as childhood, and often need to be done at larger cancer centers due to the complex nature of the screenings (Schneider et al., 2019).

This is just a brief summary of the most widely known cancer syndromes. PVs now exist in over 30 genes associated with an increased cancer susceptibility, and in another 30–50 that possibly cause an increased risk. With a higher volume of genetic testing, more discoveries are being made (Milanese & Wang, 2019).

Types of Genetic Testing

There are several varieties of genetic testing that an individual might have if hereditary cancer syndrome is suspected. Site-specific analysis would be used if a PV has previously been detected in the family. In this case, analysis is focused on just detecting the one variant, and does not analyze the whole gene, and could not detect any other existing PVs (UW Medicine Laboratory for Precision Diagnostics, 2015a).

Single gene testing is a slightly broader test. This might be used when tumor analysis has indicated a possible PV in a specific gene, such as loss of MLH1 on immunohistochemistry of a colon tumor. Other reasons to do single gene testing would be cancers that are associated with a specific gene, such as diffuse gastric cancer and CDH1 (Human Genetics Laboratory, 2019). These examples of single gene analysis are also considered diagnostic testing, as the individual usually has a cancer associated with the gene being analyzed (MedlinePlus Genetics, 2020).

Asymptomatic individuals may have genetic testing based on family history, which would be considered screening (MedlinePlus Genetics, 2020). There are a variety of guidelines depending on the type of cancers in the family, but in general, if a first-degree relative would have qualified for testing and did not have it or the results are unavailable, then their asymptomatic relative would be eligible. Additionally, having a family history with multiple second- or third-degree relatives on the same side of the family with certain cancers would be a reason for an individual to consider genetic testing. It should be noted that the recommended strategy is to always begin with the family member who has been diagnosed with cancer if at all possible (NCI, 2019).

Prenatal or preconception carrier screening is less common in hereditary cancer syndromes than it is with other genetic syndromes (MedlinePlus Genetics, 2020; NCI, 2019). This is likely due to the fact that most of these cancers would not affect the offspring until adulthood in most cases. Carrier screening might be done when there is a family history of Li Fraumeni Syndrome, as this could affect very young children (Schneider et al., 2019). Additionally, if one partner is a known carrier of a *BRCA1/2* or *ATM* mutation, the other partner may undergo screening; recessive conditions are associated with these mutations (Fanconi anemia, ataxia-telangiectasia; Petrucelli et al., 2016).

Who Should Get Tested?

Criteria for who should get genetic testing vary by syndrome, but some common guidelines exist. Testing guidelines for several hereditary syndromes are available from groups such as the National Comprehensive Cancer Network (NCCN, 2020). Individuals with a personal or family history of certain rare cancers should be assessed, as well as if there is a history of cancers at unusually young ages (NCI, 2019). Members of certain ethnic groups may also be at higher risk for hereditary cancer syndromes and therefore should consider testing. One example is the Ashkenazi Jews, who have three founder mutations in the *BRCA1* and *BRCA2* genes (Levy-Lahad et al., 1997). Anyone with a family history of a known pathogenic variant in a close relative should be assessed to determine whether testing is necessary, and anyone with a family history of multiple cancers or certain patterns of cancer should be assessed to determine what testing is needed (NCI, 2019).

Testing Process

Historically, individuals would be referred to a genetics specialist if a hereditary syndrome is suspected, usually a geneticist or genetic counselor. The genetics specialist would have a pretest visit with the patient, where they would gather three generations of family history and the individual's medical history. This would include cancer diagnoses, surgeries, medications, and other medical details. The patient would also be educated on genetics, possible outcomes, and the process. Insurance coverage and costs would be reviewed, and the patient would have a sample collected if they choose to have testing. The whole visit could last approximately 45–90 minutes, depending on the facility's processes.

Testing occurs mostly through a variety of commercial laboratories. Results can take anywhere from 5 to 21 days (Ambry Genetics, 2020; Invitae, 2020) to process and

can be disclosed to the patient in a few different ways. Some facilities disclose solely through in-person visits, while others will reserve these visits only for individuals with a PV and will disclose negative or VUS results over the phone unless a patient requests a follow up-visit. Implications and recommendations for the results are discussed. A letter is written summarizing the visit and the test results, as well as the recommendations for screening and risk reduction. Referrals may be made to specialists, depending on what further medical care is needed.

With the expansion of genetic testing, more individuals are seeking testing without genetic counseling. Primary care, gynecology, gastroenterology, and oncology are just a few areas where patients may receive genetic testing (Shields et al., 2008). In fact, some genetic testing laboratories will market directly to providers in these areas. Some may have training in genetics, but not all providers do. A misunderstanding of a VUS on genetic testing due to a lack of knowledge can have serious consequences. Additionally, the implication that their healthcare provider (HCP) doesn't understand the test result can cause increased stress and frustration for patients. Patients with a PV or VUS detected on testing ordered by a non-genetic provider will sometimes be referred for posttest genetic counseling.

Possible Results and Benefits of Genetic Testing

Genetic test results generally fall into three categories: positive, negative, or VUS (Centers for Disease Control and Prevention [CDC], 2020). A positive test result means that the genetic test found a pathogenic or likely pathogenic variant that is associated with an inherited cancer-susceptibility syndrome. A positive result may give some indication of the cause of an individual's cancer, guide cancer treatment decisions, indicate that an individual is at higher risk of cancer, as well as guide family testing. It does not indicate that a person will definitely have cancer in their lifetime.

A negative genetic test result means that in the genes that were analyzed, no pathogenic variants were found. It does not mean that there is definitely no hereditary cancer risk, as a pathogenic variant may exist in a gene that wasn't tested. Management of individuals with negative genetic test results depends on personal and family history.

A VUS test result means that genetic testing shows a variant that has not been definitely associated with cancer risks. This result is uncertain, and the information does not help to clarify individual risk and is not recommended for use in making healthcare decisions. Some VUS may be reclassified as more population data is gathered, but this process can take years. Most VUS are reclassified as benign. Recommendations for screening and risk reduction are based on the individual's personal and family history (Schleit, 2019; University of Washington, 2015a).

Over the past decade, multigene panel testing for hereditary cancer risk has expanded to include more than 60 genes. With this expansion, the chance of a VUS increases. Exact VUS rates are difficult to estimate, as each lab reports this data differently. It is reported that BRCA1/2 analysis, a genetic test that has been used for more than 2 decades and only covers two genes, has a 1–3% chance of a VUS result. For a 25-gene panel test, the chance increases to 30% or more (Idos et al., 2019; Rosenthal et al., 2017).

Uncertainty of Having a VUS Test Result

A VUS result is uninformative. It therefore is not recommended that clinicians use this information to decide on medical management strategies. Instead, recommendations should be made based on personal and family history. For example, a woman with a VUS and a family history of breast cancer in her mother at age 40 should still consider mammography at age 35, according to current guidelines. Unfortunately, it is not always clear to HCPs without training in genetics how to manage these situations.

Occasionally a VUS will be overmanaged, leading to inappropriate surgeries; other times it is undermanaged, which leads to missed opportunities for screening based on family history. This confusion among healthcare professionals can lead to increased stress and poorer outcomes for patients (J. G. Hamilton et al., 2019; Reuter et al., 2019).

Many studies have focused on the psychosocial impacts of a pathogenic result, but few have looked at the effects of a VUS result. Through a better understanding of the experiences of individuals living with this uncertainty, HCPs will be equipped to provide more holistic care. The studies that have been conducted show that even if an individual remembers the specific nomenclature of their test result, they do not necessarily understand what it means for themselves and their family.

Communication

Good communication begins before the genetic testing. Expectations for the process can be set by the referring provider. Genetic counseling visits are traditionally face-to-face, but telehealth visits are expanding. During the counseling visit, it is important that the provider ask clear questions about the patient's personal and family history of cancer and other diseases. The provider also needs to communicate about potential outcomes of the process, such as what recommendations exist for managing a pathogenic result. This is also when the patient should be informed of the possibility of a VUS result. Counseling includes a discussion of emotional impacts of genetic testing, as well as coping mechanisms and individual preferences. Patients are informed of legal rights, and potential risks of testing. Informed consent is collected if the patient decides to pursue testing.

Posttest results disclosure can occur via telephone, telehealth, or in person. Facilities vary on their procedures, and often patients can choose what they prefer. The results of the test, implications, and recommendations for follow-up are discussed. If a

PV is identified, this may involve facilitating referrals to other specialties, and identifying family members who should also consider testing. For a VUS or negative result, the patient's risks for cancer will be reassessed using various calculations, such as the Tyrer-Cusik score for breast cancer (Ikonopedia IBIS, 2017). Ideally, patients with a VUS will be advised to check in periodically for updates on reclassification, as it gives them some control over recontact.

Communication is an important aspect of healthcare that has not been frequently examined with regard to VUS results. Communication between family members regarding genetic test results and medical history is important, as it can have implications for future genetic testing, screening, and other risk-reduction measures. Understanding these patterns and any barriers to communication will help provide support to these families.

Similarly, communication between individuals and their HCPs regarding VUS results is not well understood. A few studies noted confusion and frustration related to this area. Frequently, genetic counseling is provided in a manner that educates the patient regarding genetic testing, but not about handling uncertainty. Additionally, an individual may only see a genetic counselor or other genetics specialist only once or twice, and the remainder of their medical management is left to primary care or women's health providers. Because these individuals may not understand what a VUS is, they may make incorrect or discordant recommendations to the patient. This can result in either under- or overscreening, unnecessary testing and procedures, and negative psychosocial impacts for the patient.

Although genetic counseling requires some specialized education, there is a role for nurses at all levels of practice. Nurses working in oncology, gynecology, and primary care are in a position to identify patients who should be referred to genetics. Nurses can assist patients in understanding and following screening and risk-reduction guidelines.

None of these activities require specialized education, and most of these skills can be learned in the same way most nursing skills are learned—on the job.

Aims

In order to expand on the current knowledge of experiences of individuals with a VUS result on genetic testing for hereditary cancer susceptibility, this study aimed to answer the following research questions:

1. What does having a VUS result for hereditary cancer susceptibility mean to individuals for themselves and for their first-degree relatives?
2. What is the experience of individuals with a VUS result for hereditary cancer susceptibility in communication with healthcare professionals?
3. What is the experience of individuals with a VUS result for hereditary cancer susceptibility in communication with family members?

To accomplish the aims of this study, a constructivist grounded theory approach was used. A constructivist approach acknowledges that the individual creates their reality, and the researcher's experience plays a role in interpreting data and developing an explanatory theory. Purposive sampling was used to recruit at least 25 participants, with efforts focused on capturing a more diverse population than had previously been seen in other studies. Data were collected using semistructured interviews either by phone or video/voice conference. Interviews were expected to last approximately 45–60 minutes. To identify initial codes, the research team began analyzing transcripts after three interviews were completed. Subsequently, theoretical sampling and constant comparison were used.

Importance

This study contributes valuable insights on the experiences of these individuals in making sense of their test results as well as communicating with healthcare providers

and family members. Clinically, this information identifies ways to improve genetic testing experiences of for individuals with a VUS result.

CHAPTER 2

SCOPING REVIEW

Objectives

The purpose of this scoping review was to identify the literature on experiences of individuals receiving a variant of uncertain significance (VUS) on genetic testing for hereditary cancer susceptibility. The research question was “What is the current evidence on the experiences of individuals with a VUS genetic test result for hereditary cancer susceptibility.” For this review, “experience” was defined broadly to include any biological, psychological, or social effect of generic test result on individuals, whether positive or negative.

Inclusion and Exclusion Criteria

Studies were deemed eligible if they (a) were original research published in the English language, (b) exclusively or partially included individual with a VUS result in their sample, (c) focused on an adult sample of any gender, and (d) included individuals tested for any type of hereditary cancer syndromes with or without a personal history of cancer. Studies that examined non-VUS genetic test results or non-cancer genes were also included if either of these two areas were explored in addition to individuals with VUS results in the gene associated with cancer risks. The articles with any type of genetic testing—single gene, small panels, or multigene panels—were also included. Exclusion criteria were review articles, dissertations, or topics not consistent with the review's aims.

Search Strategy

We conducted this scoping review according to the recommendations outlined by the Joanna Briggs Institute (Peters et al., 2020). The search was conducted in June 2020 using the PubMed, CINAHL, Web of Science, and PsychInfo databases. We used

search terms to capture all possible articles to map current evidence on experiences of individuals with a VUS result for hereditary cancer. The exact search used for PUBMED was (hereditary cancer risk OR hereditary cancer syndrome) AND (experience OR need OR belief OR attitude OR reaction OR perception OR perspective OR consequence OR view)) AND (VUS OR variants of uncertain significance). Similar combinations were used for CINAHL, Web of Science, and PsychInfo. Preliminary search to decide databases and the search term was conducted with the consultation of library liaison for UMass Amherst College of Nursing.

Study Selection

We used the RefWorks reference manager to manage citations from multiple databases. All titles and abstracts that we identified in the search process were imported into RefWorks. An initial identification and removal of duplicates were conducted using the automated feature in RefWorks. The remaining articles were then imported into Rayyan QCRI (<https://rayyan.qcri.org>). A manual check for duplicates was then performed. An initial title scan was conducted, followed by a scan of the abstracts. The full text of any articles identified as relevant after the abstract scan was obtained. Full texts of included articles were retrieved and reviewed by the researchers using the inclusion and exclusion criteria resulting in a final sample of articles. The reference lists of the full text of all articles identified seven articles, which were also assessed against the inclusion criteria, resulting in a final sample of 19 articles. The results of the search process are depicted in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (Figure 2.1).

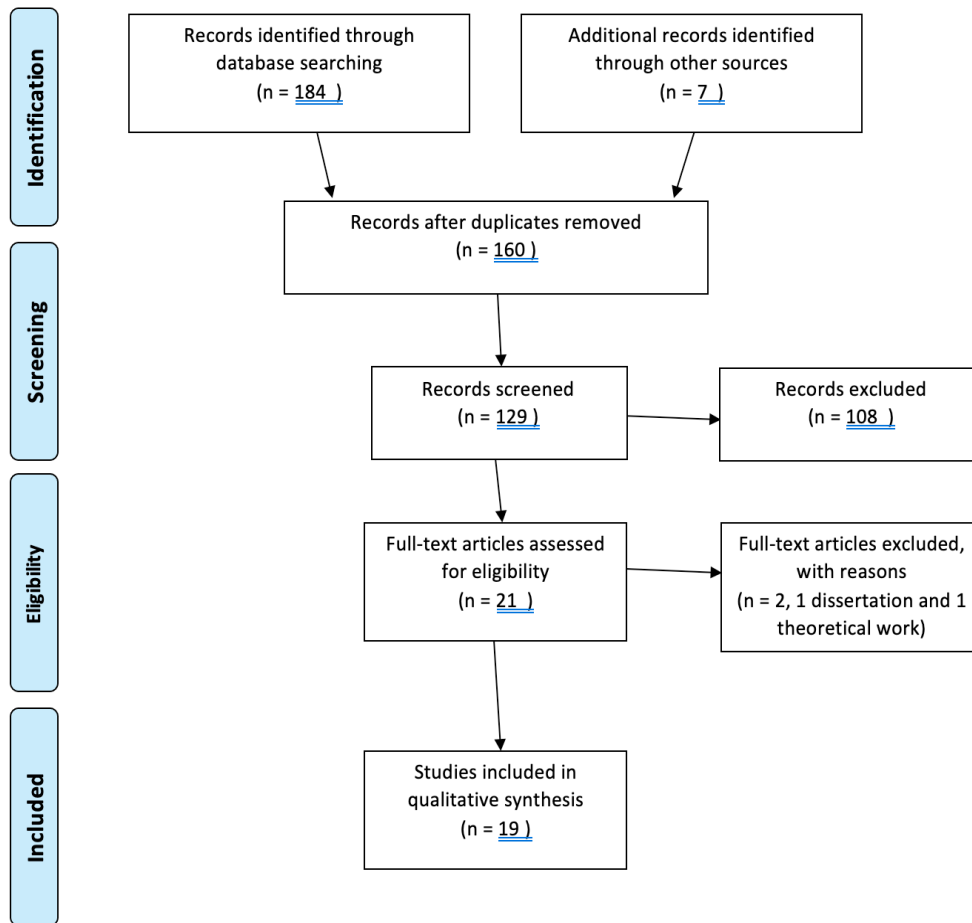


Figure 2.1: PRISMA flow diagram.

Data Extraction

Data was extracted from the eligible articles using a table developed by the author based on the chart's key information suggested by Joanna Briggs Institute (Peters et al., 2020). In addition to the authors, the year of publication, and the country of origin of the articles, the extracted data included study aims, genetic test results for the sample, sample size and characteristics, assessment and measures, methods, results,

and interpretation or recommendations. A narrative summary accompanies the tabled results with a description of how the results relate to this review's objectives (Appendix A).

Description of the Studies

Of the 19 studies included in our final review, 13 were conducted in the United States, and one was conducted both in the U.S. and Canada. The remainder were conducted in Canada (n = 1), Europe (4), and Singapore (1). A quantitative design was used by 11 of the studies, qualitative design was used in six studies, and two studies used a mixed-methods design. There were six studies using a prospective approach, while 13 were retrospective. The sample consisted of only women in 11 of the studies, men were included in only two of the studies, and six included any gender. Probands were the focus of 16 studies, probands and families in two studies, and probands and clinicians in one study.

A theoretical framework was used in only a small proportion of the reviewed studies (n = 5). Mishel's Theory of Uncertainty in Illness was utilized by two studies (Reuter et al., 2019; Solomon et al., 2017). A grounded theory model was utilized by Li et al. (2018). Vos (2008) used the distorted perception hypothesis. Makhnoon, Shirts, et al. (2019) used Han's Taxonomy of Uncertainty as a framework.

The sample of the studies had undergone multigene panel testing in nine studies (Conley et al., 2019; Esteban et al., 2018; Garcia et al., 2014; Giri et al., 2018; Li et al., 2018; Makhnoon, Garrett, et al., 2019; Makhnoon, Shirts, et al., 2019; Reuter et al., 2019; Tsai et al., 2020). J. G. Hamilton et al. (2019) examined a population that had testing for CDH1 variants, which causes hereditary diffuse gastric cancer, and Solomon et al. (2017) examined individuals who had testing for gene mutations associated with Lynch syndrome. Another eight studies examined a population who had genetic testing

for BRCA1 or BRCA2 gene mutations only (Brédart et al., 2019; Chern et al., 2019; Culver et al., 2013; Cypowyj et al., 2008; Elsayegh et al., 2018; Miron et al., 2000; Richter et al., 2013; Vos et al., 2008).

Of studies included in this review, seven only included individuals with VUS results (Cypowyj et al., 2008; Makhnoon, Garrett, et al., 2019; Makhnoon, Shirts, et al., 2019; Reuter et al., 2019; Solomon et al., 2017; Tsai et al., 2020; Vos et al., 2008). Two studies compared individuals with a VUS result with those who had a negative test result (Chern et al., 2019; Culver et al., 2013). A sample with a VUS result was compared with those who had a positive result in four studies (Garcia et al., 2014; Giri et al., 2018; N. M. Hamilton et al., 2017; Miron et al., 2000). In six studies, samples with different genetic test results including a VUS result, positive, or negative result were compared (Brédart et al., 2019; Conley et al., 2020; Elsayegh et al., 2018; Esteban et al., 2018; Li et al., 2018; Richter et al., 2013).

Table 2.1: Descriptive characteristic of studies included in the scoping review.

		N	%
Country	USA	12	63.16
	USA and Canada	1	5.26
	Canada	1	5.26
	France, Germany, and Spain	1	5.26
	France	1	5.26
	Spain	1	5.26
	The Netherlands	1	5.26
	Singapore	1	5.26
	Study design	Quantitative	11
Qualitative		6	31.58
Mixed		2	10.53
Sample	Women only	12	.16
	Men only	1	5.26

	Any gender	6	31.58
Outcome measurements	Recall/ understanding of the test result	10	52.63
	Communication with healthcare provider	9	47.37
	Family communication on the test result	5	26.32
	Emotional/Psychological effects of test result	10	52.63
	Risk perception for cancer	6	31.58
	Screening and risk reducing surgery decision-making	7	36.84
	Type of genetic test	<i>BRCA 1/2</i> genes	9
Lynch or single gene		2	10.53
Multigene panel		8	42.11
Results of sample	VUS only	7	36.84
	PV or VUS	4	21.05
	Negative or VUS	2	10.53
	PV or VUS or Negative	6	31.58
Publication date	2000-2004	1	5.26
	2005-2009	3	15.79
	2010-2014	3	15.79
	2014-2020	12	63.16

Study Results

Understanding, Knowledge, or Recall

Measurements of knowledge, understanding, or recall of test results were included in 11 of the studies included in this review (Conley et al., 2020; Cypowyj et al., 2008; Esteban et al., 2018; Giri et al., 2018; J. G. Hamilton et al., 2019; Makhnoon, Garrett, et al., 2019; Makhnoon, Shirts, et al., 2019; Reuter et al., 2019; Richter et al., 2013; Solomon et al., 2017; Vos et al., 2008). A common theme was a lack of understanding or recall of the VUS result. Giri et al. (2018) found that having a VUS result was associated with this lack of understanding, versus a different result, and other factors such as literacy did not explain this phenomenon. In Giri et al.'s study, 101

participants stated that they understood their results, but 80 of these individuals incorrectly responded that they carried a PV. This study also found that a VUS was associated with misunderstanding. In J. G. Hamilton et al. (2019), 12/56 participants stated their results incorrectly; Reuter et al. (2019) found 2 out of 14 participants did not recall having a VUS at all; Cypowj et al. (2008) showed that the group with a VUS had the highest rate of incorrect recall (36%). Richter et al. (2013) found that those with a VUS had the highest rate of incorrect recall (36%); Vos et al. (2008) found 79% interpreted a BUS as a PV. In Solomon et al. (2017), 7 individuals stated that they did not have Lynch Syndrome.

There are some studies showing the misunderstanding about the recommendation after having a VUS result. Makhnoon, Garrett, et al., (2019) found that individuals misunderstood the recommendations of their HCPs, while Makhnoon, Shirts, et al. (2019) described the misunderstandings as a “non-technical conceptual ambiguity.” Esteban et al. (2018) noted that those with a high-penetrance PV reported that they understood their recommendations more than those with a VUS or moderate penetrance PV. Reuter noted that most did not understand that a VUS didn't impact medical management.

Communication

In this review, six of the included studies examined aspects of family communication on genetic test result and the risk for cancer. N. M. Hamilton et al. (2017), Cypowj et al. (2008), and Solomon et al. (2017) found that most participants had communicated the test results to their family members. Cypowj et al. showed that 76% had communicated the information within 2 years after the test, with most of these individuals doing so because of a misunderstanding whether their family members would need to know this result.

Various motivations of the proband to share the test results were reported in the studies. Participants in the Tsai et al. (2020) study were motivated by a desire to help their families. Both Li et al. (2018) and Tsai et al. found that some participants were cautious about sharing the result because a VUS was considered confusing and a desire not to cause a false alarm. Conley et al. (2020) found that there were discrepancies in disclosure based on family members.

Some studies also reported the factors influencing the decision to communicate the test result with family members. Li et al. (2018) noted a willingness to share based on closeness and a feeling of duty. Cypowj et al. (2008) noted that a belief that the family members also needed tested or increased surveillance resulted in sharing the information with family members. VUS results were less likely to be shared if the proband did not think they would be useful for the family or did not think the family members would understand them (Li et al., 2018). In one study looking at variant reclassification, discussing the VUS led to more discussions about family medical history (Makhnoon, Garrett, et al., 2019).

Nine studies examined communications with HCPs. The two studies by Mahknoon et al. (2019) found that pretest preparation for a possible VUS was more effective in improving understanding of the test result. They also found that participants were frustrated with providers and felt their worries were dismissed. J. G. Hamilton et al. (2019) found that 45.6% of participants recalled being informed about the possibility of a VUS result during pretest counselling and that those with a VUS result were less satisfied with provider' knowledge. Culver et al. (2013) found that different counseling styles influenced risk perception and that assisting in making decisions about medical care was most helpful. Richter found that genetic counselors would make recommendations to patients with a VUS result based on personal or family history. They also found that most physicians would incorrectly refer the family members of a

patient with a VUS for genetic testing. Esteban et al. (2018) noted that most participants wished to be disclosed VUS and variants in moderate penetrance genes. Conley et al. (Conley et al., 2020) found that the only factor affecting the test result disclosure in the family that significantly varied by test result was whether a provider encouraged them to tell their families. Giri et al. (2018) noted that results disclosure via telephone or telehealth was associated with misunderstanding of test results.

Emotional and Psychological Outcomes

A total of nine studies examined emotional or psychological outcomes, including worry, anxiety, depression, or other feelings after having test results. Brédart et al. (2019) found that women with a negative result or a VUS result showed a decrease in scores for concerns about hereditary predisposition. Getting psychological help after testing was associated with problems in the “emotions” domains. Culver et al. (2013) found that the VUS group in their study reported a significant change in concerning thoughts, with 92% reporting a decrease after having the test result. Richter et al. (2013) found that individuals with a VUS result had intermediate scores on the Trask Worry Scale, which was significantly different than those with a PV. Esteban et al. (2018) measured worry and found that scores did not differ significantly over time or by test result. Also, patients with a positive test result had more distress than those with a VUS or negative result.

Emotional reactions to having a VUS result were varied in the studies. Reuter et al. (2019) found that emotional responses varied, but most participants did not think about the VUS result very often. Solomon also found varied reactions, from relief to shock experienced by proband after having their VUS result. They also found that 17 appraised the result as a threat, 17 as an opportunity, and 6 as both; mobilizing or planning was the most common coping mechanism. Tsai et al. (2020) found that

participants' stress and anxiety largely originated from misunderstanding of the VUS result, but most reported a neutral to positive impact on their emotions. Some participants in the Makhnoon, Shirts, et al. (2019) study reported a negative affect after disclosure by their provider or felt frustration with providers who dismissed their worries; others felt relief or indifference.

Risk Perception for Developing Cancer

Only five studies examined risk perception specifically in those with a VUS (Culver et al., 2013; J. G. Hamilton et al., 2019; Makhnoon, Garrett, et al., 2019; Miron et al., 2000; Vos et al., 2008). In Culver et al. (2013), 15% of those with a VUS considered themselves high risk, while only 10% of those with a negative result did. Participants with both PV and VUS results, in the J. G. Hamilton et al. (2019) study, reported their risk at midpoints on the Likert scales. Miron et al. (2000) reported significant differences between self-estimated risks and calculated risks. Makhnoon, Shirts, et al. (2019) found uncertainty and unclear interpretations regarding risks, while Vos (2008) showed that both the VUS and negative groups reported decreases in perceived risk.

Screening and Risk Reduction

No study examined screening uptake based on what is appropriate given a VUS result and family history; however, five studies investigated various aspects of cancer screening uptake (Garcia et al., 2014; J. G. Hamilton et al., 2019; Makhnoon, Garrett, et al., 2019; Solomon et al., 2017; Tsai et al., 2020). In Makhnoon, Shirts, et al. (2019), some participants wanted more frequent screening; Tsai et al. (2020) found that some already thought their medical care was sufficient for their VUS result. Solomon et al. (2017) noted a perceived benefit from a management plan. In J. G. Hamilton et al. (2019), 69.2% of participants with a VUS had a breast MRI, and 92% had mammograms

at least yearly, and 6% had upper endoscopy. Garcia et al. (2014) noted a low rate of ovarian cancer surveillance for both PV and VUS groups, which dropped every year.

Decisions on risk-reduction surgery were examined in six studies (Chern et al., 2019; Culver et al., 2013; Elsayegh et al., 2018; Miron et al., 2000; Richter et al., 2013; Vos et al., 2008). Chern et al. (2019) and Culver et al. (2013) found no significant differences in surgical decisions for those with a VUS versus a negative result. In Culver (2013), all individuals who had a bilateral salpingo-oophorectomy (BSO) met guidelines for surgery based on personal or family history. Miron et al. (2000) found that three out of four of those with a VUS who were interested in risk reducing BSO before the test changed their minds after having their test results. Richter et al. (2013) and Elsayeh et al. (2018) both found that those with a VUS had lower contralateral prophylactic mastectomy (CPM) rates than those with a PV. Elsayeh examined CPM uptake and found a lower election in individuals with a VUS versus a PV result, but the difference was not significant. Age and not hormone receptor status of the tumor were associated with the CPM election in the VUS group. Vos et al. (2008) found that seven individuals had a mastectomy due to the VUS and three due to cancer, and found no difference in surgeries between PV and VUS groups.

Discussion

Recall or knowledge of the VUS result was generally poor among individuals with a VUS result. Many individuals recalled not having a VUS at all. Some reported having a negative result or would state that they had a PV result. In one study some individuals recalled that they did have a VUS result, but they still interpreted it as a pathogenic result. Some individuals referred their family members for testing because they were not aware that this was not routinely needed for a VUS (Cypowyj et al., 2008). There is an interesting differentiation between actual test result and personal interpretation of the

test result, implying that more than simple recall goes into the meaning of the result for the individual (Vos et al., 2008).

There were also some results indicating that HCPs, especially non-genetics providers, made incorrect recommendations regarding testing for family members or screening of probands with a VUS (Richter et al., 2013). This leads to more confusion for the individuals with a VUS genetic result, and it is another opportunity for improved communication not only between healthcare providers and patients but also between genetics specialists and non-genetic healthcare providers. It may also show the need for education among non-genetics healthcare providers.

Individuals with a PV result generally understood their results and screening options much better than those with a VUS. Few studies examined risks or screening uptake directly in individuals with a VUS. This would require an understanding of each participant's family history to know if the individual met criteria suggested by guidelines for increased screening or risk-reduction surgery. As noted before, the personal interpretation of a VUS result as pathogenic or benign appears to have consequences on risk perception (Vos et al., 2008). This shows that some individuals thought they were at higher risk when they were not, leading to frustration with a perceived lack of care (Makhnoon, Shirts, et al., 2019). Some individuals appeared to understand a VUS result as a negative result and did not think that they could still be at elevated risk for cancer. This has potentially dire consequences if the patient is in fact at high risk and does not get recommended screenings or ignores their symptoms. Regarding surgical decision-making, in most of the studies individuals who opted for surgeries and had a VUS met guidelines due to some other factors such as personal cancer history or family history. Although there are no definitive guidelines for management of individuals with a VUS, they may be eligible for increased screening or risk-reduction options based on risk assessment including personal or family history of cancer. High-risk individuals could be

recommended to have early mammography or colonoscopy, breast MRI, as well as pharmacological and surgical options (NCCN, 2020).

The studies that examined communication with family members found that participants were less willing to share VUS test results than PV test results. The reasons for this were that the VUS results were confusing to explain, would not help their family, and might cause more harm than good (Makhnoon, Shirts, et al., 2019). If the proband thought that the VUS could potentially help their family members, they tend to communicate the results. In one study that examined the participation of family members in a reclassification study there was some paternalism noted, in that older individuals wanted to tell their family members what to do, however most of the family members surveyed were happy to participate in order to help their family.

Emotional reactions to receiving a VUS result ranged from relief to distress. Overall, there was less distress among individuals with a VUS result than those with a PV result. Confusion and frustration are also frequently noted by studies examining emotional response. Overall life changes related to the VUS result were not significant, and studies investigating intrusive thoughts did not find that individuals with a VUS frequently thought about it. Moreover, participants often noted they would rather have a definitive result, even if it were a PV result. As a coping strategy, it was reported that interpreting a VUS result as pathogenic and acting as if it was pathogenic may allow for individuals to make more conservative plan (Solomon et al., 2017).

Probands appeared to misunderstand whether they did get the medical care that they perceived as needed (Makhnoon, Garrett, et al., 2019). For instance, patients with a VUS who perceived themselves as high-risk expected more screening, even if it was not supported by current evidence related to test result and their personal or family history. These individuals indicated they felt “brushed off” by their healthcare provider (Makhnoon, Garrett, et al.). This is an area where better communication between HCP

and proband is needed regarding actual risks and recommendations based on the compressive risk assessment.

In individuals with a VUS result, there tended to be less satisfaction with their HCPs when compared with individuals who had a PV or negative result (J. G. Hamilton et al., 2019). In a few studies, participants expressed frustration with their healthcare provider due to a perceived lack of knowledge of providers (Makhnoon, Garrett, et al., 2019). It may show that the patients did not understand that a VUS was uncertain because of a lack of scientific evidence and not due to a lack of knowledge by the healthcare provider. There was also a trend towards patients who were being prepared pre-test for the possibility of a VUS to be more knowledgeable and more satisfied with their care. This may indicate a need for greater focus on a possible VUS result to ensure the proband understand the limited evidence on the implications of a VUS result for proband and their families during pre-test counseling.

There are some methodological issues on the articles included in this review: The design of the study, lack of diversity in sample, and lack of comparison among individuals with different test results. Most of the studies utilized a thematic analysis or qualitative description; none used standard grounded theory. Li et al. (2018) used grounded theory methods but did not state that they followed all the necessary parts of the methodology. The different designs make it hard to compare the findings from these studies. Of the six qualitative studies, five focused exclusively on individuals with a VUS and one compared a VUS with a PV or negative result. This indicates a methodological area that has not yet been explored in order to better understand the needs of individuals with a VUS. Although thematic analysis and other interview-based studies do provide insight into the experiences of the individual, they may not be used to make explicit conclusions from these studies.

Only one study focused exclusively on men (Giri et al., 2018), with six studies including both men and women (Esteban et al., 2018; J. G. Hamilton et al., 2019; Makhnoon, Garrett, et al., 2019; Reuter et al., 2019; Solomon et al., 2017; Tsai et al., 2020). In those studies, less than half of the sample was male. This could be a function of several of the studies focusing on women with breast cancer, or the time frame of the study was when testing criteria was more stringent. However, this highlights that men are frequently left out of research regarding genetic testing for hereditary cancer syndromes, as the focus is frequently on breast and ovarian cancer risk. It is important that men be included in this research, because even if they do not have the highest associated risks, they may still have risks and will also play a role in the family communication surrounding testing. Additionally, there were no studies that noted whether their sample included nonbinary and transgender individuals. This is again problematic, as excluding or miscategorizing these individuals will impact our understanding of risks, perception, and experiences with genetic testing. It ultimately prevents us from using the results of expanded genetic testing to reduce cancer risks.

Black, indigenous, Hispanic, and other people of color have historically been underrepresented in research on genetic testing, and the same is true in this review. Whites make up a vast majority of the sample in studies set in the United States, where the general population is much more racially diverse. One study found that the group with a VUS is more racially diverse, which is likely due to lower rates of testing in non-white, non-European groups. This lack of diversity limits the generalizability of study findings and continues to perpetuate inequities in genetic testing.

Limitations

The scoping review method used here has some limitations. Due to their nature, scoping reviews provide a broad overview of the existing literature, but do not deeply

analyze the quality of the evidence. It is also possible that due to the time-limited nature of the search and choice of search terms, some studies may have been missed in this review.

Recommendations

This review established that individuals with a VUS result have the lowest level of recall and understanding of their test results. Clinicians who are providing VUS results should focus on supporting the patient's knowledge. Research should focus on methods of education that most support the patient's understanding of a VUS result.

Communication between family members regarding genetic testing, and specifically regarding VUS results, needs further investigation. Methods to support and encourage open communication regarding results and medical history should be identified. More studies examining causes of confusion with recommendations is also needed. Clinicians should include a discussion of family communication within their counseling visits, including identification of which relatives to speak to and strategies to do so.

Although the studies in this review showed that individuals with a VUS result had better emotional outcomes compared with those with a PV, continued research into the factors impacting emotional or psychological outcomes in this group would improve the counseling process.

Risk perception was at least in part dependent on understanding and knowledge; therefore similar studies are needed that examine the factors influencing risk perception. Based on current evidence, clinicians should pay close attention to signs that the patient is not understanding the information.

A skewed risk perception can impact screening and risk reduction. Although the studies examining surgical decisions did include some analysis of whether surgery was appropriate according to guidelines, a detailed examination of family history in

individuals with a VUS was not included. More studies are needed that look at whether individuals with a VUS result are getting appropriate medical management based on histories. Furthermore, it is clear that education and support for the clinicians who are managing these individuals is needed.

CHAPTER 3

METHODS

Aims

The aim of this qualitative study employing grounded theory methodology was to explore the experiences of individuals who had a VUS result on genetic testing for hereditary cancer syndromes. This study focused specifically on their experiences and needs in interpretation of the test result for their selves and their family members and the process of communication with healthcare providers and their first-degree relatives about genetic risk and risk management.

Research Questions

1. What does having a VUS result for hereditary cancer susceptibility mean to individuals for themselves and for their first-degree relatives?
2. What is the experience of individuals with a VUS result for hereditary cancer susceptibility in communication with healthcare professionals?
3. What is the experience of individuals with a VUS result for hereditary cancer susceptibility in communication with family members?

Design

This qualitative study used constructivist grounded theory, as described by Charmaz (2014). This version of grounded theory acknowledges that social reality is constructed, and the researcher cannot be a passive, neutral observer. Both participants and researchers bring something to the interactions. Research is a construction, and we might not be aware of all the conditions surrounding it (Charmaz, p. 13). For this study, constructivist grounded theory was chosen as it places emphasis on symbolic interactionism, where the individual makes meaning through words, symbols, and objects.

Sampling Strategy

This study used purposive sampling to initially recruit at least 25 individuals who met our eligibility requirements. Purposive sampling involves selecting participants based on specific characteristics. This method of sampling allows for recruitment from various characteristics, such as personal cancer history, cancer types, age, gender, or recruitment methods from support groups and referrals from local HCPs. It also enhances reliability of the study by recruiting a larger sample. As in purposive qualitative sampling, theoretical sampling involves selecting participants based on specific characteristics.

In grounded theory studies, theoretical sampling occurs as the data collection progresses. If specific themes become more of a focus during the interview process, we will choose subsequent interviewees based on the theoretical needs (i.e., cancer history, genes tested, age, gender or type of provider) or alter the interview guide to focus more on these areas. Using theoretical sampling allows for “the creation of full and robust categories” (Charmaz, 2014, p. 200), as well as making better distinctions between experiences. Theoretical sampling is at the center of grounded theory’s abductive reasoning that allows inferences made regarding experiences supported by empirical evidence (Charmaz, p. 201). It also allows for identifying gaps in understanding to be identified, which results in a thicker description of experiences. Interviews will continue until theoretical saturation is reached (Charmaz, p. 214), meaning no new insights are generated after three interviews.

Recruitment

Recruitment occurred through the local community, support groups, and social media. Sample recruitment messaging is included in Appendices B and C. An initial recruitment goal of 25 was set during the proposal phase, with a deadline of June 1, 2021. At that time the recruitment goal had not been reached, and existing data was

reviewed to determine if it was sufficient to proceed to the next phase of coding and analysis. More data was needed, so recruitment was extended through July 2021, at which time 20 participants had been recruited, and the data collected was sufficient to complete the final rounds of coding and analysis.

Inclusion Criteria

Over age 18

Able to speak English and connect via telephone or video chat

Had a VUS on a genetic test for hereditary cancer risks

Has access to or recall of the result nomenclature

Exclusion Criteria

VUS in non-cancer related gene

Diagnosed with any mental health problems

Ethical Considerations

This study was approved by the Institutional Review Board at the University of Massachusetts Amherst (Appendix D). All participants were provided with informed consent prior to participation in the study (Appendix E). Funding was not available to provide monetary incentives to the participants. Participants were allowed to end their interview at any time and to request that the recording be stopped and deleted.

Data Collection

Pre-interview Assessment

In order to ensure a consistent sample that met our inclusion criteria, participants first completed a screening survey (Appendix F), followed by a pre-interview demographic survey if eligible (Appendix G). Informed consent (Appendix E) was completed at the beginning of the demographic survey. These surveys included the following:

Test results (personal information removed)

Demographics

Personal and family history of cancer (3-generation)

Contact preferences

Preferred interview time

The entire instrument is available in Appendix E.

Outcomes Assessment

Data was collected through semistructured interviews conducted via secure video chat or by phone. The primary investigator (PI) was the interviewer. Interviews were recorded with permission from the participant and transcribed via an automated service. The PI verified the transcriptions. Notes were taken during the interviews. The interview guide appears as Appendix H.

Data Management Plan

All recordings, transcripts, and memos were stored locally on the researcher's password-protected and disk-encrypted computer. Study-related documents that needed to be shared with committee members were uploaded to Box, which is a secure cloud storage platform. Transcription was completed with the NVivo service or Otter.ai. NVivo 12 for Mac was used for analysis.

Data Analysis

Coding Strategy

Coding began with the first interview. As is consistent with grounded theory, no coding schemes were developed before analysis began. Comparative methods were used throughout the analysis, not only comparing codes, categories, and themes, but also the researcher's experience, as is suggested by Charmaz (2014, pp. 132–133). In vivo codes were used for initial coding, as they reflect the meaning of the participants' experiences in their own words (p. 135). Focused coding was used for the second round

of analysis to reveal gaps or trends in data, as well as preconceptions (p. 143). Codes were sorted along with memos into categories that supported further development of the theory. Diagramming was also used to identify how different categories relate to each other and what the underlying processes were. The developing theory was compared back to the data throughout the process.

Trustworthiness

Memo writing by the researcher occurred throughout each step of the study through note-taking and journaling on problems, ideas, and notes on the data (Charmaz, 2014, p. 169). This provided a place to document the research process in detail and a way to analyze and speculate about the ongoing data collections and analysis (p. 171). Memos provided a useful reflection about how codes and categories were developed and enhanced trustworthiness.

To further enhance trustworthiness, coding was completed by the PI and the dissertation advisor. Discrepancies were discussed until agreement was reached or brought to the entire committee for discussion. Peer review and expert consultation were also used.

Additional strategies to optimize the study's trustworthiness were reflexivity, which was enhanced by the use of memos. A constructivist approach does not require the researcher to set aside their experiences; it views the resulting theory as a creation of the interactions between researcher and participant. Therefore, the researcher does not try to take a naive approach, as other versions of grounded theory require.

CHAPTER 4

FINDINGS

Research Questions

The purpose of this grounded theory study was to improve our understanding of the experiences of individuals with a VUS identified on genetic testing for hereditary cancer susceptibility. The specific research questions were the following:

1. What does having a VUS result for hereditary cancer susceptibility mean to individuals for themselves and their first-degree relatives?
2. What is the experience of individuals with a VUS result for hereditary cancer susceptibility in communication with healthcare professionals?
3. What is the experience of individuals with a VUS result for hereditary cancer susceptibility in communication with family members?

Target Population

The target population of this study were adults who have had at least one VUS on genetic testing for hereditary cancer susceptibility. Inclusion criteria were age 18 or above, able to speak in English, able to connect via telephone or chat, had a VUS on a genetic test for hereditary cancer susceptibility, and access to or recall of the result nomenclature. Exclusion criteria were having a VUS in only a non-cancer related gene, and diagnosis with any severe mental health problems (self-report).

Recruitment

Several recruitment methods were used to enlist eligible participants for the study (see Table 4.1). Initially, a survey link was shared via social media, including Twitter and Facebook. This yielded only three individuals who completed the screening survey. The repeated attempts at recruitment via social media failed to yield additional participants. Therefore, we partnered with PROMPT (<https://promptstudy.info/>) and FORCE

(<https://www.facingourrisk.org/>) to recruit from a more targeted population. Of note, the audience who likely saw the Twitter advertisements were more likely to be involved in academia, as this makes up most of the network of the author's followers and any colleagues who shared the study information. On Facebook, the population was likely more varied in education and profession, as these were personal contacts.

Table 4.1: Recruitment by method.

Source	Screened	Eligible	Consented	Completed
Social media (Facebook, Twitter)	3	1	1	1
PROMPT	29	29	20	15
FORCE	5	4	4	4
Totals	37	34	25	20

The Prospective Registry Of MultiPlex Testing (PROMPT) is a registry of individuals with variants on multigene testing. These individuals receive an initial invitation to participate with their genetic test results from many commercial laboratories in the U.S. The PROMPT team uses this information to understand the risks associated with variants and partners with other researchers to share their data. They maintain an email list, which is how participants received invitations to this study. The invitations were sent out in batches of 50 or 100. A total of 29 individuals recruited from PROMPT filled out the screening questionnaire, and 15 completed the study.

Facing Our Risk Empowered (FORCE) is a group that seeks to improve the lives of individuals with cancer and their families. They provide both peer support and expert information. The FORCE website has a research page that features various studies their members may be interested in. This study was posted to the research page from March to July 2021. A total of five individuals who completed the screening found the study through FORCE, of whom four completed the study.

In total, 37 people completed the screening questionnaire, and 34 were identified as eligible to participate. Of these, 25 consented to the study and provided demographic information, and 20 completed the interview portion. Similar qualitative studies identified in Chapter 2 had response rates of 11%–60%, and quantitative studies reported response rates of 17%–90%.

Data Collection

Interested individuals filled out a screening questionnaire on Qualtrics that asked about genetic test results and contact information. After this information was reviewed, eligible individuals were asked to complete a second survey that asked questions about demographics, history, and scheduling. If participants missed an interview or did not schedule, they were sent up to two reminders, and if at that point they did not complete the study, they were not contacted again.

Primary data collection was done through semistructured interviews conducted by the investigator. The interview guide (shown in Appendix H) was developed based on prior experience, the review of literature, and the research questions. The guide consisted of four broad questions, with 3–6 suggested prompts to use if the participant was having difficulty answering. A fifth question, “Is there anything else you would like to tell me?” was included in order to catch any other details of the individual experience (Charmaz, 2014). All interviews were conducted via Zoom or Skype due to the need for social distancing during the COVID-19 pandemic. Interviews ranged from 15–36 minutes. The interviews were transcribed using Otter.AI, and the primary researcher verified the transcripts. Verified transcripts were then loaded into NVivo for coding.

Sample Description

A total of 20 individuals completed an interview. See Table 4.2 for participant demographics. The average age was 51.25 years (28–81 years). Fourteen participants

identified as female, and although we asked if assigned sex at birth differed from their gender, none responded Yes. Less than half of the sample was white (5 Black/African American, 3 Asian, 1 Native American or Alaskan, 2 multiracial, 7 white). None identified as Hispanic or Latinx. The education level was Graduate or Advanced degree in 11 participants; 11 were working full-time. Regarding insurance coverage, 18 participants had private health insurance, and all stated their insurance covered genetic testing.

Table 4.2: Descriptive characteristics of the participants (N = 20).

	Category	#	%
Age	-	51.25 (28–81)	-
Sex	Female	14	70
	Male	6	30
Race	White	9	45
	Black/African American	5	25
	Asian	3	15
	Native American/Alaskan	1	5
	Two or more	2	10
	Hispanic	No	20
Education	High school	1	5
	Some college	1	5
	4-year degree	7	35
	Grad school/Advanced degree	11	55
Work Status	Full-time	11	55
	Part-time	2	10
	Unemployed/not looking	3	15
	Retired	4	20
Insurance status	Private	18	90
	Medicare	1	5
	Military/VA	1	5
Personal History of Cancer	0	7	30
	1	12	60
	2	1	5
Cancer in first-degree relatives	0	4	20
	1	9	45
	2+	7	35
Cancer in a second-degree or higher relative	0	4	20
	1	9	45
	2+	7	35

Analysis

Coding

Each interview transcript was read in its entirety by the primary researcher and then open-coded in vivo. A second pass was then done to merge codes with similar meanings (Charmaz, 2014; Saldaña, 2021). The dissertation advisor read the interviews and reviewed codes and provided input. Any disagreements regarding codes were few and were resolved through discussion. The final codes and descriptions are delineated in detail below, categorized logically by time period, and subcategorized by theme (Graff & Birkenstein, 2006; Pacheco-Vega, 2017, 2021).

Analytic Memoing

Memos include notes taken during interviews and coding and drafts and sketches of theoretical models that were done during the analysis process (Charmaz, 2014; Saldaña, 2021). Comments made on the manuscript as the writing of the findings progressed, and emails between the researchers, also served as memos. These memos, although not coded, provide insights that contributed to the overall analysis and theory development.

Researcher Positionality

An important factor in grounded theory research is the positionality of the researcher (Charmaz, 2014). It is not possible to completely remove the influence of the researcher on the research; therefore, it is critical to acknowledge it. The researcher is a white, cisgender woman with an advanced degree in nursing and experience as a clinician working with individuals during the genetic testing process. She has never had genetic testing for hereditary cancer, nor have any of her family members. Any of these factors could influence the analysis and interpretation of this research. This positionality was kept in mind during the coding and thematic process. As the themes were

developed, the codes and categories were scrutinized as to whether they were correctly describing the meaning of the participant's words, and not the researcher's own opinions.

Categories and Codes

The codes have captured experiences during the three periods including the pretesting process, testing process, and posttesting process (immediate and long-term period).

Table 4.3: Summary of the codes and categories.

Category	Code	Example(s)
Pretest experience (Time before genetic counseling or genetic testing visit)		
Motivations/ Reasons for testing	Family history of cancer	So now I've got a father and two uncles with it and a couple of cousins, male cousins with prostate cancer." "My mother's father had bone cancer, not really sure where it came from, but he was a smoker. Okay. And that's all." "I think, for me, it had more of an impact on what it was because my sister was diagnosed six months after me.
	Personal history of cancer	I have an aggressive growth and so it slaughtered me
		Yeah, we did find a growth in your abdomen area. We don't can't say for sure what it is.
	HCP recommended	So about a month after the genetic testing results came back, I was supposed to have my prophylactic mastectomy. But the last sonogram that they did, they found breast cancer.
		No, I had not considered it on my own. I really wasn't even aware that it never crossed my mind to do this before. If there would have been like breast cancer, that type of genetic type of cancers, then maybe but that had none of that in my family?
Concern for family	Both my mom and I had breast cancer, and I don't want my daughter to get breast cancer. That's the only thing that I think about, that's all that matters.	
Communication with family members		I thought of my child, it wasn't really about me at that moment, like I need to do what I need to do to be healthy to be here for her."
	Family data collection	And, and when a lot of the cousins came down with prostate cancer, and, and or lung cancer, or breast cancer, and my daughter had breast cancer, I thought, well, maybe there's something that's in the, In my genes.
	Family member testing status	If it was only that they probably wouldn't even recommend I get tested, but I'm, I have I'm of Ashkenazi descent on my dad's side. I actually tested first. She lives in Canada, and there's a bit of a

		different system.
Family characteristics		Yeah, oh, yes. In fact, one of my, I have two sisters, one older, and one about three years older, and one about 10 years younger. And they had mild breast cancer. And both in the younger one got genetic testing, and hers was all negative two for gene.
	Closely related family (children, siblings)	I'm the only one left out in my family. I have two older siblings, with my, my mom, and then I'm one of seven on my father's side. I have two children; one just turned 21. And one is 13.
	Geographical distance	Currently, they live in China. And, okay, that's not easy for them to get that kind of test.
Communication with HCP or GC	Requested referral or HCP suggested	No, I had not considered it on my own. I really wasn't even aware that it never crossed my mind to do this before. If there would have been like breast cancer, that type of genetic type of cancers, then maybe. But that I had none of that in my family. I actually reached out I asked my breast surgeon, breast What? Yeah, yeah, yeah. So I was diagnosed with breast cancer in 2017. And I just knew that I wanted to get, you know, more information, more data. And so that's when I asked her, and she referred me to the genetic counselor there at the same hospital University. I had to go to my primary care doctor, and then they sent me to like, by a female doctor, and then I think it was the OB GYN who had to like confirm, which I don't know how they confirm because it's still me telling the same story.
Testing experience (From referral through results delivery)		
Communication with family members	Family member' involvement in testing process (i.e., support, physically being presence)	I actually had my brother with me during one of my other brothers with me during all of this to make sure that we gave them the right information.
Communication with HCP	Had genetic counselling	They took a family history, and then she kind of talked to me about looking at, and my aunt she also had, I don't know, if it was uterine or ovarian, I'm sure. But my grandmother and my father were better than you. Yeah. And she also and then, yeah, my other aunt had cancer. So we went through, like all the things, and she told me like, what my risk was, and that we deal with the report. She was super great. I forget who I went to, but she just told me, we're gonna do it, we'll get the report. And then we'll figure it out.
	Communication of details regarding test process	No, no, they asked me to go to the clinic here, lab test for lab tests, then took some blood, and then I got the genetic test report.
	Delivery of test results (who, how)	They did the testing and then someone called me from the company and like had this conversation with me that I really don't remember

		but I remember there was something prior but I did not have any conversation with anyone after that I believe.
	Recommendations for screening or risk reduction	Yep. So I will do I mean, she recommended some things and then also the oncologist But you know, just going to the dermatologist twice a year, getting your eyes checked, I will eventually get my ovaries and fallopian tubes out. And just being kind of cognizant of like pancreatic cancer, and what she had said the genetic counselor had said that, you know, it's about a five to 10% higher risk. And if you don't have any family history, they're not as concerned. And that MD and that MD Anderson, I think is the only place that kind of...kind of do that. She said that she has clients that use MD Anderson as like a full test of whether you will get it but also my oncologist said that they would just do screening, you know, once or twice a year for that as well.
	Recommendation for family testing	He said right now it's probably not something they need to get tested for but it's something that we need to keep an eye on to see what develops with this gene and so that's kind of where it was left about three years ago and i've not really had any conversations about it since.
Other factors affecting the testing experiences		
	Cancer treatment (i.e., impact on memory, busy time at start of treatment, need to make surgical decisions)	Like what happens next, because I was, like, fielding calls from insurance companies, and then the surgeon in the hospital and then the plastic surgeon, and it was just like too much, it was just too much. Yeah, I feel my memory is reduced. And especially when I, when I'm talking, it's likely you only can focus on for 10 minutes.
	Delayed cancer diagnosis	I first went to the, to my OBGyn, and she was like, well, you're young, it doesn't seem like anything, it felt... like a cyst to be honest. And even when I finally went back, like five months later, they still thought it was related to nursing, but it had been so long that they wanted to ultrasound it and that they knew immediately, like I knew, you know, just looking at it, that it's probably cancer, because it had spread to a few lymph nodes in the axilla.
Post-test experience		
Feelings about having a VUS	Surprise	I don't think you can be prepared. You can't be? No, because like I said, intellectually, I knew, like, I look for those variants, that's what I do for a living. But I don't think it would have changed anything because it's either there or it isn't right. And at the time, I was sure that I probably wouldn't have BRCA as like, Oh, it's fine. It's not going to come nothing. It's going to be clean. They're just doing it for whatever reason, right. But yes, I was surprised. I'm not gonna lie. No, I wasn't surprised. I didn't really? I didn't know that there could be a VUS. I thought it would either be positive or negative. Okay.
	Curiosity	And so I really wanted to know about the genetics of cancer, because I teach it in general biology to some degree, not, you know, extensively, but I have a lecture on cancer where I talk about colon cancer. Curious as I don't think I fully understood what that variant meant, and what impact it could have on my future.
	Negative (stress, anxiety, frustration)	A terrible, horrible, probably weeklong, stressful experience, because I was like, Well, I didn't have any, you know, clarity so far. And then I

was like reading about all these rare mutations. And I was like, Oh, god, what if I have this thing that causes multiple types of cancers and right syndrome? So then I was just like, you know, what, for my own like, sanity, since it's not going to change, how I am sort of operating with surveillance. And my daughter is nine. I'm not going down that road. So I didn't.

So it for me personally, it was like, extremely nerve wracking, like because it's, it's unknown.

Worry (for themselves or their family)

Am I going to be my sister very soon here?

I could have 15 VUS's, what worries me is that one or another mutation causes my self to get some other form of cancer or my daughter to get a cancer.

Positive/Relief

I'm relieved, and I will tell you why. I'm relieved that it wasn't a definite, like, the way it was explained to me is that this is kind of nebulous, and it's indefinite, they will continue to test this gene, to see if it's harmful or not. But at least there's no definite, hey, you have BRCA Hey, you have this that will definitely or very likely cause you cancer.

Uncertainty

And it's, so you know, it's important to talk to them as well, like, people need to know that. Just because they haven't found the gene, that doesn't mean that the gene doesn't cause it, right. We just, we don't know.

So I'm just in this very kind of state of I don't know if I'm saying purgatory.

When you understand these things, you know, that it can be like, I feel like a sitting duck, because I'm like, Well, what if it is pathogenic, and you guys are doing nothing about it?

Recall and understanding of test result and its implications

Recall of result and implications

The genetic doctor called me to explain the results kind of tell me that there was a little bit change in my genetic line. That's number one. But I think it's not a big deal for me.

Understanding of test result and implications for herself and their family

You know, it seems to me to be one of those things that you don't talk to your kids about, like sex and finances, you know, and I'm like, but why, you know, I mean, it's, it's life, it's part of life.

PMS2 was, specifically when for men is common colon cancer. So, but then, it may be maybe, maybe pancreatic cancer, slightly linked, PMS2 is slightly linked with pancreatic. pancreatic cancer, also, you see, our upper endoscopy type of testing, or, or maybe when I went through colonoscopy.

Misunderstanding of the test result and its implication

But I guess for me, it kind of gave me a reason, right? I mean, so wasn't that I just sort of happened. You know, so that was helpful for me. It wasn't, I mean, I wasn't disappointed, or I didn't have any like horrible feelings about it. And I think like I said, just for me, the significance was that it just let me know why this might have happened to me and things that I can do, kind of going forward to be really on top of my health.

Impact of treatment on recall
Remembers any

Like what happens next, because I was like fielding calls from insurance companies, and then the surgeon in the hospital and then the plastic surgeon, and it was just like too much, it was just too

	details of the VUS Personal understanding of meaning for self and family	much.
	Recall of what was done	A panel of them of what? I don't think it was like a full genetic test from what I remember. ...sent the sample in and it wasn't getting processed.
Coping strategies used	Volunteerism	And I'm like, you know, when I saw this, I didn't know if I should, because I'm still very anti engaging in anything cancer, because I was still dealing with the, you know, the after effects, but I thought, if I'm gonna encourage other people to be a part of these, I need to be a part of this, because there's another woman who's probably been told the exact same thing as me, who doesn't understand this either. So I actually volunteer a lot for other young women with breast cancer. And so I'm using sort of my VUS status to, and obviously, my, my educational background, I guess, to sort of educate more, and that's one of the reasons I wanted to participate in this is because, you know, if, if my input can somehow help.
	Information-seeking (episodic or continual)	I don't think I had much of a hope or even expectation that was going to happen anyway. I think that they thought I think they, meaning the bioinformatics people at Fox Chase, thought that I was doing something like that, but I really wasn't. I have a friend of mine who's got, you know, really lots of family history. And I'm like, have you done genetic testing? And he's like, I don't want to know, I'm like, What? Yeah, really smart person, really, you know, and he just doesn't want to know, and I'm like, wow.
	Support groups	Me and my husband went on to do research to make sure that we knew what we were, you know, focusing on and what I needed to worry about and what I didn't need to worry about. I found another...found a support group that I finally fit in for breast cancer. It's an organization that is geared towards young women who have most of the other support groups for like women who had children by age, and none of them have small children. And these women either have no children, or they have very young children. Yeah, so I kind of feel like I found my tribe.
	Personality	Roll with the punches with it, essentially. As long as you're breathing, you've got more things going right for you than wrong. So I'm good.
Communication with family members	Method of sharing the result	My genetic counselor gave me a letter that I could send to them which I've sent to them
	Openness with family	I'm not reporting on my gynecologist. That type of stuff. Yeah, for sure. Yeah, definitely. Um, because it could potentially span the whole family and affect, you know, all five of us, my parents, my sister and my brother. So no, I emailed them. My genetic lab results, my mom did the same. So you know, we have this like, family chain, and that was definitely like, you know, take a look at this, consider it.

	Family wouldn't understand	And I also know that no one is going to remember everything of what I say. So I have to tell more than one person, I have to seed it. Right, make sure they have planted seed.
		Oh, I didn't tell my brother or my father, because they just, like, can't understand these things.
	Concern for family	Of course, the genetic testing became important to me for that reason, because of her, her well being because she had it on both sides.
		Now, if my results indicated it was hereditary, then I think I would go back and pressure the grandkids a little bit.
	Protecting family	My mom has had, like, it's very stressful for her. So my sister, my sister and I were talking about it, and my sister was warning me she, she saw the geneticist before me, and the geneticists originally recommended that my mom have more testing. Before we did, and my sister, you know, was warning me that mom's really worried that means that she might have something and you have to tell her that it's just for, for information for us. So my mom has a lot of anxiety around it. But she's willing to talk about it. But yeah, we're treading lightly.
		I didn't know that I did not talk to my mother about my biopsies, which is related but different. I did not talk to her about that because it was just no, no, no, exactly. Especially when I got the results that they were benign.
	Family testing	My mother ended up with the exact same VUS and her sister ended up with the exact same VUS.
	The effects of the communication (i.e., family members testing- sharing of new results)	So there's some distance between us we, I communicate with some of them. When I was diagnosed with prostate cancer, I sent out a message to all of my cousins and said, Hey, this may be hereditary, make sure you get your PSA regularly and everything. And even then, some of my male cousins didn't follow up on her now I have now passed away because of prostate cancer.
	Frustrations at family's response	A bit irritating that my dad's side of the family hasn't done anything.
Communication with HCP (inc GC)	Frustrations or barriers	Most of your family physicians or general physicians, they don't go through into these specific items. They are not...just not knowledgeable enough to comment on it.
	Racial bias	Then this was a team that really understood me. And they cared about me. And I also it also made me think about physicians that I choose, that are going to understand me, especially the bulk of the health disparities that we see. Yeah. And I chose an African American oncologist, I chose a woman breast surgeon, I chose people that I knew what their client base look like, and that they were open and diverse. Because you can't treat me like you treat someone else with a different cancer.
		Why would you tell me that? Like, why would you say you're clear, but then tell me Oh, but there could still be cancer?
		If you're my breast surgeon, you need to know what this means for me, because I'm going to come in contact with you before I come in

contact with a radiology oncologist or other oncologist.

	Supports	And I can still just certain phraseology that she utilized, I was like, ah, she knows what she's doing.
	Keeping in touch/ checking in with GC	Actually, no, I thought it went really well. I really liked my genetic counselor, and I thought she was very open with me, and I was happy with it. Okay. It's very helpful. I mean, she, she got my mom, you know, she, my mom was able to contact her. And then she set everything up for my mother. And my mom was in her 70s. So she was very patient with my mom, as far as going through this process. I really thought it went well.
	Reclassification communication	I'd have to, I don't know, one of them. I got like information that it had, like moved from uncertain significance to likely not significant, but likely benign, or, yeah, one of them. And so that, that was and they might even recently, like got a note that something had changed in my report. And I was scared that that was going to turn into it was an unknown, and I was worried it was gonna go the other way.
Risk reduction/ management strategies used	Surgery	This past year has really kind of turned up the fire for me and it made me honestly consider a preventative mastectomy. So it worries me a little bit, but then I was so kind of caught up in the emotion of, we need to get, I need to get rid of this. Like...what are we doing next? And I'm going no, I'm not looking to remove any more parts of me, but because of a variant.
	Follow-up visits	I see a provider so often, because I have either a mammogram or an ultrasound every 6 months. And now I have a GI doc right, so that I went out and searched for those specialists and then share this information with them. And I immediately burst into tears. And what was interesting about that is, that's when I realized, ah, I've got some trauma here. But other than that, no, and I'm not obsessing on it on a daily basis, I really am not, but around appointment time I start rethinking about it, or you know, breast cancer, or Breast Cancer Awareness Month in February.
	Cancer Screening	Yes, definitely MRI to answer your question. That is one of the things that has been on the table, there has been some confusion about coverage and how much that would cost. It's not changing how I'm going to continue surveillance. Also, definitely not going to change what I intend to do, you know, with my daughter way earlier than myself, like, I started at 36 because of my mom's diagnosis, but like, I'd love to start with my daughter, like, in her 20s, you know, so.
	Further genetic testing	So fast forward then to 2018. That's when I had the second genetic test.

Pretest Experience (Time Before Genetic Counseling or Genetic Testing Visit)

Category: Motivations/Reasons for Testing

This category includes the participant's motivation, reason, and thoughts that led to genetic testing. In addition to personal cancer diagnosis, family history of cancer and suggestions from a HCP were the main reasons for participants to have genetic testing. These motivations appeared to have influences on how the individual understands or interprets the VUS for themselves.

Family History of Cancer

A family history of cancer was one of the reasons the individual had genetic testing. Some participants had not had genetic testing even when they were diagnosed with cancer but decided to get tested when other family members were also diagnosed with cancer. Family history appeared to have an important role in how a person views their risks; for instance, individuals tend to not worry as much about their risks of cancer without a significant family history.

"I think, for me, it had more of an impact on what it was because my sister was diagnosed 6 months after me."

Some participants had a strong pattern of cancer in their family who were worried about their cancer risks, even without a pathogenic variant being identified.

"So now I've got a father and two uncles with it and a couple of cousins, male cousins with prostate cancer."

This individual continued to collect data and encourage family members to take the family pattern of cancer seriously.

When there was less of a pattern of cancer in the family or a known exposure such as smoking, there was less concern.

"My mother's father had bone cancer, not really sure where it came from, but he was a smoker. Okay. And that's all."

Personal History of Cancer

A personal history of cancer impacted the individual's decision to have genetic testing. Like family history, it also influences how an individual views their cancer risks and the experiences in living with a VUS result. Individuals with cancers at a younger age were also worried about their children's risks and were motivated to learn the cause of their cancer diagnosis. The first participant quoted is noting that the new screening guidelines meant that his cancer was found later than it would have been if the screening had been done more often.

"There's a lot of men that have prostate cancer and a lot of women that had breast cancer that wasn't seen early enough, you know, so in my case, I have an aggressive growth, and so it slaughtered me."

The following participant was in the process of pursuing prophylactic surgery because of her sister's history of breast cancer, when she was also diagnosed with breast cancer.

"So about a month after the genetic testing results came back, I was supposed to have my prophylactic mastectomy. But the last sonogram that they did, they found breast cancer."

Non-Cancer Diagnosis

One participant with a VUS result had an adrenal tumor and was referred for genetic testing. He was found to have a VUS in a gene associated with cancer risk. This participant described the surprising way he was informed of the finding of the tumor, which at the time was not known to be benign. This tumor led him to have genetic testing. The participant was informed of the mass in a way that created more uncertainty in his subsequent medical care, including the genetic testing:

"And then she came in about an hour later. And it was actually kind of interesting how she told me the first thing. I'm in Portland, Oregon, and I'm born and raised here. And my whole family said, Do you have a good family network here and support system? And immediately that kind of raised a red flag...And she kind of kept going about that. And she's like, Yeah, we did find a growth in your abdomen area. We don't can't say for sure what it is."

Concern for Family

Concern for family members, especially for children, was often mentioned as a reason to have genetic testing. It also prompted discussions of cancer history and genetic testing with family members.

“Both my mom and I had breast cancer, and I don't want my daughter to get breast cancer. That's the only thing that I think about; that's all that matters.”

“I thought of my child, it wasn't really about me at that moment, like I need to do what I need to do to be healthy to be here for her.”

HCP Recommended

In some cases, individuals both with and without cancer had not considered genetic testing until a HCP suggested it.

“No, I had not considered it on my own. I really wasn't even aware that it never crossed my mind to do this before. If there would have been like breast cancer, that type of genetic type of cancers, then maybe but that had none of that in my family?”

Category: Communication With Family Members

This category includes barriers, supports, and reasons leading to conversation among family members during the pretesting process. Participants described the communication about the family history collection or family member testing experience and how their family characteristics affected their communication before they got tested.

Family Data Collection

Participants described the communication with family members in the pretest period as mostly to gather family cancer history. Some noted that this was an ongoing process, and they now get updates from their relatives as new cancers are diagnosed or if they undergo genetic testing.

“... and when a lot of the cousins came down with prostate cancer, and, and/or lung cancer, or breast cancer, and my daughter had breast cancer, I thought, well, maybe there's something that's in the, in my genes.”

Family Testing Status

Participants explained how the family members had been in contact around the testing and test results to inform other family members who might benefit from this information. In some cases, the participants were tested after a relative with or without pathogenic results. In some cases, the participants were the first person tested in the family and some other family members opted to get also tested after even with a VUS test result.

In some cases, the participants were tested after a relative, for this person, it was her mother. For some participants, the family members shared the same VUS; in others, they do not.

“If it was only that they probably wouldn’t even recommend I get tested, but I’m, I have... I’m of Ashkenazi descent on my dad’s side.”

The participant was the first person tested in some cases, even though a family member had cancer first. This often was due to the lack of availability of genetic testing for the family member.

“I actually tested first. She lives in Canada, and there’s a bit of a different system.”

“Yeah, oh, yes. In fact, one of my... I have two sisters, one older, and one about three years older, and one about 10 years younger. And they had mild breast cancer. And both in the younger one got genetic testing, and hers was all negative two for the gene.”

Category: Family Characteristics

Some participants noted that some family characteristics affected their communication during the pretesting period. Closeness with a family member and geographical distance were among the factors mentioned by the participant affecting their decision to communicate as they were getting ready for testing.

Closely Related Family (Children, Siblings)

Participants explained that closeness with a family member affected their decision to communicate about the testing during the pretesting period.

Having close family members or children influenced the pursuit of genetic testing and the participant's reaction to the result. Some participants came from large families with many siblings:

"I have two older siblings, with my, my mom, and then I'm one of seven on my father's side."

Having children and their ages also influenced the reaction to a VUS, as adult children were more likely to know about the test result or family history:

"I have two children, one just turned 21. And one is 13."

One participant who did not communicate with anyone in the family noted, *"I'm the only one left out in my family,"* which led her to not communicate before and even after the genetic testing.

Geographical Distance

Geographical distance from family seems to play a role in communication with family members during the pretesting process. The participants with relatives in other countries may have discussed family history or genetic testing with their relatives, but they were consulted less before genetic testing than those with relatives who were physically closer. To facilitate timely action or recommended follow-up with those in the family who need genetic counseling or even testing, some selected a physician or scientist relative in the country as a point person to talk about the testing and even the test result. Communication with relatives at a distance appeared to be a source of frustration for participants.

"Currently, they live in China. And, okay, that's not easy for them to get that kind of test."

Category: Communication With HCP or GC

Communication with a HCP pretest largely focused on the referral process. If the participant had a new cancer diagnosis, the oncologist was usually the provider who referred to genetics; sometimes, they ordered the test. If there was not a recent cancer diagnosis, then a PCP or gynecologist may be the one ordering the referral.

Requested Referral

Pretesting process, communication with the HCP appeared to only include referral or ordering the test. Although some participants stated that their HCP referred them due to their personal or family history of cancer, some participants had to go through a long and inconvenient process.

One participant pursued a genetics referral through multiple steps, when their PCP referred them to a gynecologist, who then referred the participant to genetics:

“No, I had not considered it on my own. I really wasn't even aware that it never crossed my mind to do this before. If there would have been like breast cancer, that type of genetic type of cancers, then maybe. But that I had none of that in my family.”

Another participant discussed asking their breast surgeon for the referral:

“I actually reached out I asked my breast surgeon... So I was diagnosed with breast cancer in 2017. And I just knew that I wanted to get, you know, more information, more data. And so that's when I asked her, and she referred me to the genetic counselor there at the same hospital University.”

Requesting a referral was not always easy, and this participant had to go through multiple providers before seeing genetics:

“I had to go to my primary care doctor, and then they sent me to like, by a female doctor, and then I think it was the OB GYN who had to like confirm, which I don't know how they confirm because it's still me telling the same story.”

Testing Experience (From Referral Through Results Delivery)

Category: Communication With Family Members

Communication with family members during the testing process was mostly centered around the participant getting emotional support.

Family Member Involvement in Testing Process (i.e., Support, Physically Being Present)

Some participants had a family member or partner with them for the genetic counseling and testing process, indicating a high level of openness. One participant noted they want to have family with them to make sure they were understanding the information correctly.

"I actually had my brother with me...during all of this to make sure that we gave them the right information."

Communication With HCP

During the testing period with genetic counselors or another provider, the key points of the communication were how the results are delivered, how much details are conveyed, and how recommendations were given for the participants and their family members, and recommendations for family testing (if any).

Genetic Counseling Process

If a person had pretest counseling, what is included can also influence their understanding and reaction to the VUS. Participants who recall being prepared for a VUS were less surprised at the result.

"They took a family history, and then she kind of talked to me about looking at, and my aunt she also had, I don't know, if it was uterine or ovarian, I'm sure. But my grandmother and my father were better than you. Yeah. And she also and then, yeah, my other aunt had cancer. So we went through, like all the things, and she told me like, what my risk was, and that we deal with the report. She was super great. I forget who I went to, but she just told me, we're gonna do it, we'll get the report. And then we'll figure it out"

Information Regarding Test Process

Communication of details about the test process includes information about sample collection, how long the results take, and how they will be delivered.

“No, no, they asked me to go to the clinic here, lab test for lab tests, then took some blood, and then I got the genetic test report.”

Delivery of Test Results (Who? How?)

How an individual was given their results may also influence their trust in recommendations and their recall of the results. It was also important that the provider delivering the results was knowledgeable about what they meant.

“They did the testing and then someone called me from the company and like had this conversation with me that I really don’t remember but I remember there was something prior but I did not have any conversation with anyone after that I believe.”

Recommendations for Screening or Risk Reduction

Some patients recalled the recommendations that had been made following disclosure of the VUS. These ranged from routine screening for cancers to high-risk screening. Surgical recommendations were made mostly for individuals with significant personal or family histories of cancer and were not a direct result of the VUS. Some individuals stated no recommendations were made, as the VUS was not informative.

“Yep. So I will do I mean, she recommended some things and then also the oncologist But you know, just going to the dermatologist twice a year, getting your eyes checked, I will eventually get my ovaries and fallopian tubes out. And just being kind of cognizant of like pancreatic cancer, and what she had said the genetic counselor had said that, you know, it’s about a 5 to 10% higher risk. And if you don’t have any family history, they’re not as concerned. And that MD and that MD Anderson, I think is the only place that kind of do that. She said that she has clients that use MD Anderson as like a full test of whether you will get it, but also my oncologist said that they would just do screening, you know, once or twice a year for that as well.”

Recommendation for Family Testing

Most participants noted that no recommendation was made for family members to test based on their VUS or history. Some did mention children who were eligible to testing due to cancer history on the other parent's side of the family.

“He said right now it's probably not something they need to get tested for but it's something that we need to keep an eye on to see what develops with this gene and so that's kind of where it was left about 3 years ago and I've not really had any conversations about it since.”

Category: Other Factors Affecting the Testing Experiences

Other factors were noted to have affected the test experience, including cancer treatment and the whirlwind time right after a cancer diagnosis.

Cancer Treatment (i.e., Impact on Memory, Busy Time at the Start of Treatment, Need to Make Surgical Decisions)

Having genetic testing during cancer treatment had effects on the recall of the genetic test information. Individuals who underwent genetic testing at the same time as the start of their cancer treatment noted that it was difficult to recall the process of genetic testing. This may be due to the “chemo brain” phenomenon, or it may also be that individuals were too busy with treatment to process their reaction to the genetic test result. Discussion of the VUS also brought memories of the emotional trauma associated with the cancer diagnosis.

“Like what happens next, because I was, like, fielding calls from insurance companies, and then the surgeon in the hospital and then the plastic surgeon, and it was just like too much, it was just too much.”

“Yeah, I feel my memory is reduced. And especially when I, when I'm talking, it's likely you only can focus for 10 minutes.”

Delayed Cancer Diagnosis

A delayed cancer diagnosis was another factor impacting the experience of having a VUS. It may have decreased the trust in medical providers.

"I first went to the, to my OBGyn, and she was like, well, you're young, it doesn't seem like anything, it felt...like a cyst to be honest. And even when I finally went back, like 5 months later, they still thought it was related to nursing, but it had been so long that they wanted to ultrasound it and that they knew immediately, like I knew, you know, just looking at it, that it's probably cancer, because it had spread to a few lymph nodes in the axilla."

Posttest Experience (From Right After Results Delivery Until Interview)

Category: Feelings About Having a VUS

Participants expressed several different feelings regarding having a VUS, including surprise, curiosity, stress, anxiety, frustration, worry, relief, and uncertainty.,

Surprise

One participant was a geneticist and knew about the possibility of a VUS, but was still surprised when she had this result.

"I don't think you can be prepared. You can't be? No, because like I said, intellectually, I knew, like, I look for those variants, that's what I do for a living. But I don't think it would have changed anything because it's either there or it isn't right? And at the time, I was sure that I probably wouldn't have BRCA as like, Oh, it's fine. It's not going to come to nothing. It's going to be clean. They're just doing it for whatever reason, right? But yes, I was surprised. I'm not gonna lie."

Another participant stated they expected a more definitive result.

"No, I wasn't surprised. I didn't really? I didn't know that there could be a VUS. I thought it would either be positive or negative. Okay."

Curiosity

Curiosity is the reaction of wanting to know how the VUS works or could impact their life. One individual had both professional and personal curiosity about the VUS and carcinogenesis, as they taught biology as biology teacher. This curiosity appears to keep the participants continuously questioning the VUS result and its effect in his and his children's life.

"And so I really wanted to know about the genetics of cancer, because I teach it in general biology to some degree, not, you know, extensively, but I have a lecture on cancer where I talk about colon cancer."

Another person stated they were curious since they didn't completely understand the result.

"Curious as I don't think I fully understood what that variant meant, and what impact it could have on my future."

Negative (Stress, Anxiety, Frustration)

Negative emotions include stress, anxiety, or frustration. One participant had a negative emotional reaction when considering expanding testing to a larger panel.

"A terrible, horrible, probably weeklong, stressful experience, because I was like, Well, I didn't have any, you know, clarity so far. And then I was like reading about all these rare mutations. And I was like, Oh, god, what if I have this thing that causes multiple types of cancers and right syndrome? So then I was just like, you know, what, for my own like, sanity, since it's not going to change, how I am sort of operating with surveillance. And my daughter is 9. I'm not going down that road. So I didn't."

Cancer Worry (for Themselves or Their Family)

Cancer worry stemmed from not knowing if the VUS was pathogenic or benign. Individuals who had cancer or a close family member with cancer were more worried.

"Am I going to be my sister very soon here?"

"I could have 15 VUSs, what worries me is that one or another mutation causes myself to get some other form of cancer or my daughter to get a cancer."

Positive/Relief

Despite the uncertainty of a VUS, a few participants still felt relieved that a pathogenic mutation was not identified.

"I'm relieved, and I will tell you why. I'm relieved that it wasn't a definite, like, the way it was explained to me is that this is kind of nebulous, and it's indefinite, they will continue to test this gene, to see if it's harmful or not. But at least there's no definite, Hey, you have BRCA. Hey, you have this that will definitely or very likely cause you cancer."

Uncertainty

One participant felt it was important that individuals with a VUS understand that there is still a possibility of a pathogenic variant that hasn't yet been identified and that the counseling process should help them understand this.

“And it's, so you know, it's important to talk to them as well, like, people need to know that. Just because they haven't found the gene, that doesn't mean that the gene doesn't cause it, right. We just, we don't know.”

“When you understand these things, you know, that it can be like, I feel like a sitting duck, because I'm like, Well, what if it is pathogenic, and you guys are doing nothing about it?”

“So, I'm just in this very kind of state of...I don't know if I'm saying purgatory?”

Category: Recall and Understanding of Test Result and Its Implications

Recall and understanding of the test result was another area which was important to how a participant felt about the VUS. Additionally, the understanding of its implication for themselves and their family was an important factor.

Recall of Result and Implications

Recall of the result and implications is what the person remembers about the VUS. This is pure memory of what was the test result given to me, not interpretation or understanding.

“The genetic doctor called me to explain the results kind of tell me that there was a little bit of change in my genetic line. That's number one. But I think it's not a big deal for me.”

Understanding of Test Result and Implications for Themselves and Their Family

Participants explained how they understood what a VUS meant to them in a variety of ways. Some compared it to other aspects of life, while those with a science education could describe in more detail what would happen if the VUS was pathogenic.

“You know, it seems to me to be one of those things that you don't talk to your kids about, like sex and finances, you know, and I'm like, but why?...you know, I mean, it's, it's life...it's part of life.”

“PMS2 was, specifically when for men is common colon cancer. So, but then, it may be, may be, may be pancreatic cancer, slightly linked, PMS2 is slightly linked with pancreatic cancer, Also, you see, our upper endoscopy type of testing, or, or maybe when I went through colonoscopy.”

Misunderstanding of the Test Result and Its Implication

Some individuals did not understand what the VUS meant for its implications on cancer risk and screening. One participant felt the VUS explained her cancer diagnosis:

“But I guess for me, it kind of gave me a reason, right? I mean, so wasn't that it just sort of happened. You know, so that was helpful for me. It wasn't, I mean, I wasn't disappointed, or I didn't have any like horrible feelings about it. And I think like I said, just for me, the significance was that it just let me know why this might have happened to me and things that I can do, kind of going forward to be really on top of my health.”

Recall of What Was Done

Recall of what type of test was done could be an indicator of overall recall of the result. One participant does not recall as much about their test and does not differentiate between MGPT and single gene sequencing.

“A panel of them of what? I don't think it was like a full genetic test from what I remember.”

Another participant had tried to do the testing remotely a few times, and the GC needed to facilitate their test as the sample kept failing.

“...sent the sample in and it wasn't getting processed.”

Category: Coping Strategies Used

Participants noted a few different coping strategies that helped them deal with having a VUS. The most common were volunteerism and information-seeking.

Volunteerism

Volunteerism was mentioned by a few individuals and seemed to be a coping mechanism. One participant noted that they volunteered for the study to help others, and it appeared it was a way of showing they are moving on.

Some individuals felt they could use their knowledge and experience with cancer and genetic testing to help others in their age group with cancer.

“And I'm like, you know when I saw this, I didn't know if I should, because I'm still very anti engaging in anything cancer, because I was still dealing with the, you know, the after effects, but I thought, if I'm gonna encourage other people to be a part of these, I need to be a part of this, because there's another woman who's probably been told the exact same thing as me, who doesn't understand this either.”

“So I actually volunteer a lot for other young women with breast cancer. And so I'm using sort of my VUS status to, and obviously, my educational background, I guess, to sort of educate more, and that's one of the reasons I wanted to participate in this is because, you know, if, if my input can somehow help.”

Information-Seeking

Information-seeking includes doing research into what a VUS was and what it means for cancer risk, including about what a pathogenic variant in the same gene would mean. It also includes asking more questions from their HCPs.

“I don't think I had much of a hope or even expectation that was going to happen anyway. I think that they thought I think they, meaning the bioinformatics people at Fox Chase, thought that I was doing something like that, but I really wasn't.”

For some, information-seeking was such an important part of their personality that they couldn't understand anyone not wanting to know more.

“I have a friend... who's got, you know, really lots of family history. And I'm like, have you done genetic testing? And he's like, I don't want to know, I'm like, What? Yeah, really smart person, really, you know, and he just doesn't want to know, and I'm like, wow.”

Some individuals sought knowledge as a team with their partner and used it to determine what their level of concern should be.

“Me and my husband went on to do research to make sure that we knew what we were, you know, focusing on and what I needed to worry about and what I didn't need to worry about.”

Support Groups

Although this individual is speaking about a cancer support group, it is an example of what benefit these groups can provide. It also demonstrates the need for age-appropriate groups.

“I found another...found a support group that I finally fit in for breast cancer. It's an organization that is geared towards young women who have most of the other support groups for like women who had children my age, and none of them have small children. And these women either have no children, or they have very young children. Yeah, so I kind of feel like I found my tribe.”

Personality

A person's view of adversity plays a significant role in their reaction to a VUS. One person notes that both they and their family take a very fluid stance when dealing with adverse or uncertain events.

“Roll with the punches with it, essentially.”

Other individuals were optimistic and felt that being alive itself was enough, so they were not bothered by uncertainty.

“As long as you're breathing, you've got more things going right for you than wrong. So I'm good.”

Category: Communication With Family Members

Communication with family members in the posttest period included sharing of test results, discussion of recommendations, family testing, and further discussions about family history. This category also includes codes pertaining to the reactions or feelings about family communication, such as the family not being able to understand, concern for family, protecting certain family members from the information, and frustration with the family's response.

Method of Sharing the Result

This participant noted the genetic counselor provided them with a letter for their family. Others noted using verbal and electronic communication methods.

“My genetic counselor gave me a letter that I could send to them which I've sent to them.”

Openness With Family

A previous history of being open about medical information was important to communicate with family members. This participant describes sharing the test results through email and having discussions with family members, encouraging them to test.

“I'm not reporting on my gynecologist. That type of stuff. Yeah, for sure. Yeah, definitely. Um, because it could potentially span the whole family and affect, you know, all five of us, my parents, my sister and my brother. So no, I emailed them. My genetic lab results, my mom did the same. So you know, we have this like, family chain, and that was definitely like, you know, take a look at this, consider it.”

Family Wouldn't Understand

A family member is less likely to be informed of the VUS if the participant didn't think they would understand the information. Interestingly, if a person was thought to not be able to understand the genetic test information, it was usually a male family member. It was unclear if the concern was with comprehending a VUS or understanding a potentially higher risk of “female” cancers.

“And I also know that no one is going to remember everything of what I say. So I have to tell more than one person, I have to seed it. Right, make sure they have planted a seed.”

“Oh, I didn't tell my brother or my father, because they just, like, can't understand these things.”

Concern for Family

A motivation for communication with family about the VUS was a concern for their health.

“Of course, the genetic testing became important to me for that reason, because of her, her well-being because she had it on both sides.”

“Now, if my results indicated it was hereditary, then I think I would go back and pressure the grandkids a little bit.”

Protecting Family

One participant described a need to protect her mother from knowing she had biopsies, because she didn't want her to worry unnecessarily. Her mother had been very stressed by a sister's cancer diagnosis.

“I didn't know that I did not talk to my mother about my biopsies, which is related but different. I did not talk to her about that because it was just no, no, no, exactly. Especially when I got the results that they were benign.”

Although in this case the participant is protecting her mom from worrying about a possible cancer diagnosis, the same mechanism can lead to an individual protecting a family member from worrying about a VUS. Another participant describes being very careful about discussing genetic testing around their mother, as it was causing the mother increased stress.

“My mom has had, like, it's very stressful for her. So my sister, my sister and I were talking about it, and my sister was warning me she, she saw the geneticist before me, and the geneticists originally recommended that my mom have more testing. Before we did, and my sister, you know, was warning me that mom's really worried that means that she might have something and you have to tell her that it's just for, for information for us. So my mom has a lot of anxiety around it. But she's willing to talk about it. But yeah, we're treading lightly.”

The Effects of the Communication (i.e., Family Members Testing/Sharing of New Results)

Some participants noted that family members got genetic testing or cancer screening because of their discussions about the family history and the VUS, while others noted that nothing happened as a result. Sometimes barriers existed (such as not having access to care), while other times no behavior change was needed.

“So there's some distance between us. We...I communicate with some of them. When I was diagnosed with prostate cancer, I sent out a message to all of my

cousins and said, Hey, this may be hereditary, make sure you get your PSA regularly and everything. And even then, some of my male cousins didn't follow up on her; now they have passed away because of prostate cancer."

Family Testing

Family members testing, either as part of a reclassification study or a separate genetic test, was one outcome of communication.

"My mother ended up with the exact same VUS and her sister ended up with the exact same VUS."

Frustrations at Family's Response

A few patients were confused and frustrated with family members who did not act on the family history. One saw new cancer diagnosis in the family as a result of this inaction.

"A bit irritating that my dad's side of the family hasn't done anything."

Category: Communication With HCP (Including GC)

Communication with HCPs posttest includes both frustrations or barriers and supports. Other codes in this category include keeping in touch with the genetic counselor, reclassification communication, risk management strategies, surgery, follow-up visits, cancer screening, and further genetic testing.

Frustrations or Barriers

Frustrations or barriers to good communication with HCPs include feeling that the provider was rushed, lack of provider knowledge, and unclear communication.

The perception of PCPs as not having knowledge about genetics, especially a VUS, was common:

"Most of your family physicians or general physicians, they don't go through into these specific items. They are just not knowledgeable enough to comment on it."

Another individual was frustrated that her provider had said the VUS doesn't mean anything, but then said there was still a chance it was pathogenic:

"Why would you tell me that? Like, why would you say you're clear, but then tell me 'Oh, but there could still be cancer?'"

Finally, a participant noted her frustration that her breast surgeon gave her the wrong information about the VUS:

"If you're my breast surgeon, you need to know what this means for me, because I'm going to come in contact with you before I come in contact with a radiology oncologist or other oncologist."

Racial Bias

At least one woman noted she felt that because she's a Black woman, the physician wouldn't listen to her and just told her what to do, and that the oncologist recommended an aggressive course of treatment based on the VUS. She switched her care to a new team and described how it made her feel more comfortable with her care.

"Then this was a team that really understood me. And they cared about me. And I also... it also made me think about physicians that I choose, that are going to understand me, especially the bulk of the health disparities that we see. Yeah. And I chose an African American oncologist, I chose a woman breast surgeon, I chose people that I knew what their client base looks like, and that they were open and diverse. Because you can't treat me like you treat someone else with a different cancer."

Supports

Factors that support good communication with HCPs include clear communication and providers appearing knowledgeable. This participant felt that the way the genetic counselor communicated implied a high level of knowledge:

"And I can still just hear certain phraseology that she utilized, I was like, ah, she knows what she's doing."

Keeping in Touch/Checking in With GC

A few participants had called their GC to update family histories, check in on reclassification, or to discuss further testing. These individuals felt the GC was approachable regarding check-ins.

“Actually, no, I thought it went really well. I really liked my genetic counselor, and I thought she was very open with me and I was happy with it. Okay. It’s very helpful. I mean, she, she got my mom, you know, she, my mom was able to contact her. And then she set everything up for my mother. And my mom was in her 70s. So she was very patient with my mom, as far as going through this process. I really thought it went well.”

Reclassification Communication

Almost all the individuals knew about reclassification as a possibility, but only a few had a reclassified VUS. One participant described receiving the information:

“I’d have to, I don’t know, one of them. I got like information that it had, like moved from uncertain significance to likely not significant, but likely benign, or, yeah, one of them.”

Another noted that when she was notified of the reclassification, she was worried the VUS had become pathogenic.

“And so that, that was, and they might even recently... like get a note that something had changed in my report. And I was scared that that was going to turn into an unknown, and I was worried it was gonna go the other way.”

Category: Risk Reduction/Management Strategies Used

Risk reduction or risk management strategies include surgery, follow-up, cancer screening, and further genetic testing.

Surgery

Individuals with a personal or family history may consider surgery, and occasionally the added uncertainty of a VUS influences that decision. One person discussed their increased anxiety when screening over the past year, and therefore is considering prophylactic surgery.

“This past year has really kind of turned up the fire for me, and it made me honestly consider a preventative mastectomy.”

Others described a need to remove the body parts that are cause for concern:

“So it worries me a little bit, but then I was so kind of caught up in the emotion of, we need to get, I need to get rid of this. Like...what are we doing next?”

Others did not want to have prophylactic surgery, given the inherent uncertainty of the VUS.

“And I'm going no, I'm not looking to remove any more parts of me, but because of a variant.”

Follow-Up Visits

Some of the participants noted that they were getting screened often, due either to a personal or family history of cancer that made them high risk.

“I see a provider so often, because I have either a mammogram or an ultrasound every 6 months.”

Some participants hand-picked a specialist who they liked, who would do their cancer screenings.

“And now I have a GI doc right, so that I went out and searched for those specialists and then share this information with them.”

Others noted that follow-up was associated with their cancer diagnosis, and therefore caused them to remember the negative emotions from that time of their lives.

“And I immediately burst into tears. And what was interesting about that is, that's when I realized, Ah, I've got some trauma here.”

Follow-up also caused some individuals to think about their genetic test result.

“But other than that, no, and I'm not obsessing on it on a daily basis, I really am not, but around appointment time I start rethinking about it, or you know, breast cancer, or Breast Cancer Awareness Month in February.”

Cancer Screening

Some individuals were considering high-risk screening, such as with breast MRI. Insurance coverage for these screenings without a pathogenic variant was a point of confusion for both the individuals and their healthcare providers.

“Yes, definitely MRI to answer your question. That is one of the things that has been on the table, there has been some confusion about coverage and how much that would cost.”

Others noted that having a VUS didn't alter their screening plans. In some cases, participants were satisfied with continuing the average-risk screening. Others, like the individual quoted below, wanted to pursue higher risk surveillance.

“It's not changing how I'm going to continue surveillance. Also, definitely not going to change what I intend to do, you know, with my daughter way earlier than myself, like, I started at 36 because of my mom's diagnosis, but like, I'd love to start with my daughter, like, in her 20s, you know, so.”

Further Genetic Testing

One participant had their initial genetic testing to a larger panel. Another had additional genetic testing, which identified a clotting disorder.

“So fast forward then to 2018. That's when I had the second test genetic test.”

Moving From Findings to Theory

The findings of these interviews provide a rich description of living with a VUS. The participants describe the varied emotions they experienced after learning of their result, and the ways in which they cope with the uncertainty. They described the context in which the VUS is experienced, which cannot be uncoupled from the experience. The findings also describe the key processes that the participants viewed as part of their VUS, and their needs as they continue to live with this uncertain result. These findings set the course to develop a theoretical model to describe the experience of having a VUS, which is described in the remainder of this chapter.

Proposed Theory of Living With a VUS Result for Cancer

What Is the Experience of a VUS?

A VUS result is a genetic test result that carries a high level of uncertainty. How individuals make meaning of it is based on multiple factors, including their personal characteristics, coping mechanisms, and cancer experiences. Communication with family and healthcare providers play key roles in the experience of testing and living with a VUS result that brings so much uncertainty for them and their family members (See Figure 4.1).

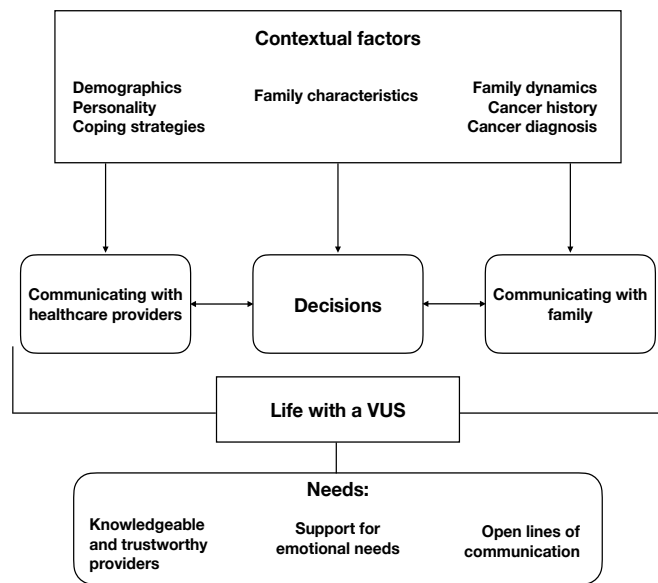


Figure 4.1: A theoretical model of the experiences and needs of individuals with a VUS.

Cancer itself is a distressing diagnosis to receive, and having genetic testing right after a cancer diagnosis appears to be distressing and making things even harder to cope with. The cancer treatment itself was described by the participants as causing cognitive impairment, and individuals discussed the trauma associated with that time period. The

stress of that time makes it difficult to process the results of the testing or recall what they were told. Experiences during the cancer diagnosis also affect the subsequent perception of genetic testing and living with a VUS result. For instance, a delay in diagnosis impairs individuals' trust in their HCP, and the participants who described a delayed diagnosis also were more anxious about the possibility that a VUS would be pathogenic.

Context

Understanding the context in which an individual experiences genetic testing and living with a VUS is crucial to understanding the overall experience that ultimately helps the healthcare provider find better ways to serve these individuals. Contextual factors include sociodemographics, personality characteristics, coping strategies, family characteristics, cancer history, cancer diagnosis, and cancer treatment.

Education may play an important role in the understanding of a VUS result and experience in living with the result. Having a science background gives a participant more ability to understand genetics concepts and also a VUS. However, it may also give more curiosity and continuous motivation to search the implications of a VUS result. Having higher levels of education, even in non-science fields, still provided a greater understanding of how to research the VUS.

Insurance coverage has a role both in genetic testing and subsequent experiences. Participants noted that their insurance covered the genetic testing or they were able to pay out of pocket for the test. Later, some had confusion or problems with getting their insurance to cover cancer screenings such as breast MRI. Others were denied coverage from their insurance for second or third rounds of genetic testing.

Geographic location affected the overall testing process. Some individuals had to drive to other cities to have genetic counseling and testing. Others noted that they felt lucky to live in a city with a large medical center where they could easily access all the

healthcare they needed. Geography was also relevant for family communication, as it influenced how the participants shared results with their family, and how useful they thought the information would be. For instance, if relatives were in the United States or Canada, it was expected that they could get cancer screening and genetic testing if needed. If the relatives lived in China or India, it was expected that getting screened would be much harder, and that genetic testing was essentially impossible. In these cases, the VUS and family histories were still discussed, but the participants didn't press their relatives as hard to pursue cancer screening.

Personality characteristics are also an important factor impacting the ability to live with uncertainty. Some participants tended not to worry about things that are out of their control, while others found that lack of control to be very stressful. These perceptions of uncertainty influenced their feelings about the VUS. Some participants were not bothered by having a VUS result due to its lack of effect on their lives when compared to a major life event such as cancer, while others emphasized that they just simply are not bothered by events that are outside their control, or that are not definitely a threat to their health. Individuals who were more anxious about the VUS tended to not be comfortable with uncertainty and preferred to be able to make plans to control outcomes.

Individuals described different coping mechanisms that affected their overall experience during and after the testing. Some individuals pursued information-seeking to feel more proactive toward cancer prevention and early detection; others chose to learn more about the gene itself and the mechanisms of cancer. Individuals who employed information-seeking likely were using this process to gain a sense of control over their health, as were individuals who felt more comfortable with pursuing high-risk cancer screening or prophylactic surgeries.

Family characteristics were important. Family members were not only someone to communicate test results to but also were sources of support. Emotional closeness

provided this support and created a more open environment in which to talk about genetic testing and cancer risk. The demographics of the family members such as educational level, sex, or current place of residency were also important. Female relatives were considered more at risk for breast cancer and therefore more likely informed if there was thought to be a risk for breast cancer, while male relatives were informed of prostate cancer risk. The education level of the family members, as well as their ability to understand the genetic information was also important, as relatives who were physicians or scientists were often treated as the first point of contact.

Individuals who had cancer themselves and a family history of cancer were more concerned that it will be discovered that their VUS is pathogenic, or that there was some other hereditary cause not yet found. Those who noted cancers only in older relatives or were the only person in their family with cancer were not as concerned about the chance of a hereditary risk. Similarly, if the gene where the VUS was identified was not associated with the pattern of cancers in the family (i.e., A VUS in PMS2 but the family history is of breast cancer), then the VUS was not as concerning.

Communication With Healthcare Providers

Communication with healthcare providers is a key component of the experience in both genetic testing and having a VUS result. This communication involves the decision to get tested, preparation for testing, results disclosure, and how they are advised of the implications of the test results such as cancer screening, preventive surgeries, family members need to be tested. In the longer term, this communication occurs during follow-up, when updating their personal or family history, and when learning about any reclassification of the VUS.

Communication with healthcare providers affects all experiences around having a VUS result and appears more complicated than for those individuals with a more

definitive genetic test result. Participants described healthcare providers who appeared uninformed as to what a VUS was, and what the implications were. They noted getting conflicting advice on cancer screening and prophylactic surgeries from different healthcare providers. Other participants, who described their healthcare providers as knowledgeable, noted that they were given clear guidelines on what the implications of the VUS were. Having incorrect or inconsistent information about the VUS and management recommendations decreases the individual's trust in their providers. Considering the nature of a VUS result and lack of guidelines in the management of these cases, it is important to make clear that the limitations are with the science of genetic testing, and not the provider.

Participants were more comfortable with healthcare providers they perceived as knowledgeable and trustworthy sources of information. If the HCP was seen as untrustworthy or not knowledgeable due to confusing communications, then the participant did not trust their recommendations and had more anxiety or worry. When an individual received incorrect or inconsistent information about the VUS from their provider, this reduced the trust in that provider

Racial and gender issues were mentioned in the communication with HCPs. One participant, a younger Black woman, noted she felt that her first oncologist didn't listen to her needs or questions about her genetic test and what was needed for her breast cancer treatment. She noted that this physician was an older white man who did not give her options. After experiencing severe complications from an aggressive treatment approach, she decided to transfer to an oncologist she selected, a younger Black woman, who she felt gave her more options and supported the choices she made. She felt that she had been dictated care because she was a young, Black, woman, and that had led to her complications. Her trust in the system had been ruined, and her new care team had to rebuild it.

Good communication is supported when the provider clearly communicates with the patient and is confident in their recommendations, which leads to the patient feeling more comfortable. There were several times when participants noted that a provider appeared to be uncertain in what they were saying, and each of these times the provider was not a specialist in genetics. In contrast, the times where participants stated they felt like they were speaking to an expert, it was a genetic counselor who they were communicating with. One participant even noted that the way the GC spoke made them feel comfortable that they were speaking with an expert. This highlights the need for providers to not only be knowledgeable but also to be confident in their communication of that knowledge. Geneticists or genetic counselors gave the clearest explanations of recommendations, preparing participants for possible results including a VUS, and generally were described as more knowledgeable.

Self-advocacy supported good communication with healthcare providers. This occurred when participants spoke up for themselves and their needs, as providers were seen as rushed or not knowledgeable enough to provide the necessary care. Individuals described asking for specific referrals and tests, and those who didn't expect a provider to be entirely knowledgeable about the VUS seemed more satisfied that they were getting the care they need. Additionally, participants who were able to select the providers they saw for follow-up were much happier with their care.

Finally, the participants stated that they appreciated the follow-up invitation from the healthcare provider who had done their genetic testing; usually this was from a genetic counselor. Some had the opportunity to update their family history with the provider or were involved in helping their family members to be tested. Some only checked in about the status of the VUS, or with questions about medical management. A few participants emphasized the importance of updating the contact information of

patients on a regular basis, to ensure that they receive any news on the reclassification of the VUS result. An alternative suggestion was scheduling a routine follow-up.

Decisions

Decision-making started when participants either sought referral for genetic testing or were recommended to have genetic testing by a provider. Reasons for this decision included determining cancer risks, concern for family, and to support treatment and surgical decisions. Most participants described the frustration with decisions after receiving a VUS test result, including cancer screening, preventive surgery, follow-up visits, and their children's healthcare. Most of the healthcare decisions made were not directly a result of the VUS, but were complicated by the uncertainty or lack of clear guidelines for individuals with a VUS. Some participants described having multiple rounds of genetic testing, due to the need for expanding an initial small gene panel to a larger one. Most accepted further testing; however, one participant chose not to have a third round as the thought of another VUS was causing her too much anxiety.

Cancer screening pursued by participants included mammography, breast ultrasound and MRI, pelvic ultrasound, colonoscopy, and PSA. Many participants were still considered high risk due to their personal or family histories of cancer and were instructed to follow high-risk cancer guidelines, including increased frequency and different modalities of screening. Participants who were currently too young to pursue cancer screening noted that they needed to consider it in the coming years. Of note, a few patients insisted on high-risk screening, regardless of what their guidelines or their provider suggested. The decision to pursue high-risk screening appeared to be a coping mechanism, as it allowed them some semblance of control over an uncertain situation.

Surgical decisions include methods used to treat or remove a known cancer, as well as prophylactic surgery, specifically mastectomy or oophorectomy. In some cases,

the VUS result was used to support the decision for a mastectomy instead of more conservative surgery. Some women were in the process of deciding on a prophylactic mastectomy due to their family history, even though no genetic risk for cancer had been identified. Other women discussed considering surgery in the future when they are past menopause, and still others were not interested in surgery at all unless a genetic risk was identified. Participants were not clear on if their treatments would have been different had a pathogenic result been identified (i.e., the selection of a PARP inhibitor for breast or prostate cancers).

Deciding when to tell a child about the family history of cancer and the VUS was another part of the experience affecting life of individuals with a VUS result. Although participants with younger children appeared not to keep their cancer diagnosis hidden, they tended not to discuss the VUS or potential familial risks with their children. Some participants who had older children had informed them about the test result and encouraged their children to pursue more cancer screening. Others did not try to influence their children's decisions, or said they would only if an actual hereditary risk was identified.

The decision to continue to follow up with a HCP often was a precursor to other decisions to make. For instance, some participants changed their providers or delayed care to see a specific provider to feel more comfortable. Sometimes suggestions that were made at these follow-up visits led to more decisions about genetic testing or screening.

Family Communication

Family communication was both a way of seeking support as well as discussing medical history. It is vital for individuals with personal and family histories of cancer to share this information. Participants in this study frequently noted that finding out about a

family history of cancer started them on their own genetic testing journey. One participant even had her cancer found because of pursuing prophylactic mastectomy after learning about her sister's breast cancer diagnosis. Some of the influences we identified were emotional and relational closeness, perceived importance of the information, a risk to the family member, and openness. Barriers included perceived inability to understand information, a need to protect the family from negative or confusing information, a lack of relatives to discuss the information with, and geographical location or distance.

Emotional and relational closeness was important for communication with family members. Distant relations and those who are not emotionally close were not always informed about the genetic test results. Mothers and sisters were most likely to know about the VUS, especially if the participant was a woman and if breast cancer was part of the family history. In some cases, closeness led to a need to protect the family member from the stress knowing about the VUS might bring, such as cases where information was kept from a parent or child.

Openness was also important. Many participants who had shared their genetic test results were also open about other aspects of their health. Openness also included having a sibling or partner participate in the counseling visits. In these cases, the communication was not just about making sure information was conveyed, but it also provided support for the person being tested.

Partners were often not only informed of the VUS but were also part of the counseling visits. This was especially true if the participant was going through cancer treatment at the time of the genetic test. If the participant had children, their partner was part of the discussion on when or how to inform them about the family history. Partners were also cited as helping with researching information about the VUS.

Not having any closely related family was one reason someone may have not communicated with family about their test results. Close relatives were noted to be

children, siblings, and parents. Sometimes this was extended to aunts or uncles, cousins, and nieces or nephews. When some individuals had only elderly family or distant cousins, they didn't always communicate the results.

Another reason not to share their results or history was due to a perceived inability of the family member to understand the results. This was not clear whether they meant the person couldn't understand cancer-related health issues, genetics, or both. It may also be an emotional inability to cope with the uncertainty. Male relatives were more often noted to be unable to handle the information.

As mentioned previously, the geographical distance was a barrier. First, relatives in a different country were frequently informed through email or phone calls and not in person. Second, many noted they weren't sure the information would be helpful since genetic testing wasn't widely available in the country where their relatives resided.

The perceived importance of the VUS or family history was also key. For instance, if the gene is associated with breast cancer, it is more likely that a female relative will be told, but a male relative might not because of a belief that the genetic information wouldn't impact them. It was less likely to be shared if the test result wasn't viewed as important to someone's medical care.

Needs

Participants noted a need to get their healthcare from a knowledgeable and trustworthy provider. This person does not need to be an expert in genetics. However, they do need to understand the basics of genetic testing for hereditary cancer, how family history impacts cancer risks, and where to seek information when they don't know enough about a given topic. This could be in consultation with an expert or referral to genetics. Participants were appreciative that sometimes the provider needed to do

research before giving them advice. Honesty that the uncertainty of the VUS is a limitation of the current science was also important.

Individuals also needed open lines of communication with their healthcare providers. Patients should feel able to recontact their provider about reclassification, family history changes, or to ask new questions. Some participants appeared to be curious about the new discoveries on the VUS result and interested in learning more about what a VUS result meant for them or their family members. Some were interested in learning more about their children's risks. Life circumstances might also prompt the need for more information such as deciding to have children or children becoming adults. Most participants appreciated when they were given the option to keep in touch with their provider.

Finally, participants needed to have their emotional needs supported. This support can occur at any time but is needed particularly during the pretest decision-making and when the results are delivered. These needs varied among participants, from preparation for genetic test outcomes, to identifying those with higher levels of stress and anxiety after learning about the VUS. Active coping, such as joining support groups or volunteering, was often noted to be a successful way of reducing negative emotions. Other participants appreciated when providers recognized that information-seeking was their way of coping and therefore continued to answer questions or assist them in identifying resources.

Summary/Conclusion

This qualitative, grounded theory study describes the experiences of individuals with a VUS on genetic testing for hereditary cancer risk. We found that many contextual factors, including cancer diagnosis, family history, personality traits, coping mechanisms, and having close relatives influence the key process of communicating with family,

communicating with healthcare providers, and decision-making. The major needs of individuals with a VUS were knowledgeable and trustworthy providers, open communication with healthcare providers, and support for their varying emotional needs. This study shows that the experiences of the individual with a VUS are much more heterogeneous than previously understood and are heavily reliant on the context in which the person learns about and lives with the VUS.

CHAPTER 5

DISCUSSION

The purpose of this grounded theory study was to describe the experiences of individuals with a VUS on genetic testing for hereditary cancer risks. Despite the increased use of multigene testing for hereditary cancer risks and its subsequent increase in the numbers of identified individuals with a VUS, very little is known about the experiences of these individuals. Therefore, it is vital to understand how individuals live with a VUS result and how these individuals can be best supported. We used constructivist grounded theory methods to achieve this purpose. A semistructured interview guide was developed based on the review of literature and past experience, and a total of 20 interviews were conducted. After transcription, several rounds of coding were completed according to Charmaz and Saldaña (Charmaz, 2014; Saldaña, 2021; Vanover et al., 2021) until a satisfactory theoretical framework was developed.

First, this chapter will attempt to answer each research question using the collected data and emerging model of the study, as well as the related literature. Next, we will review the theoretical model, and make recommendations for future research and clinical practice. Finally, we will present the limitations of this study.

Research Questions

To review, this study focused on answering three primary research questions:

1. What does having a VUS result for hereditary cancer susceptibility mean to individuals for themselves and for their first-degree relatives?
2. What is the experience of individuals with a VUS result for hereditary cancer susceptibility in communication with healthcare professionals?
3. What is the experience of individuals with a VUS result for hereditary cancer susceptibility in communication with family members?

We will next discuss the findings as they relate to each individual question.

Meaning of Having a VUS Result for Hereditary Cancer Susceptibility for Individuals for Themselves and Their First-Degree Relatives

The results of this study show that the experience of a VUS is highly individualized and contextual. Some of the most important factors that influence this experience are personal and family history of cancer, individual coping mechanisms and personality, and communication with healthcare providers. Having children or other closely related family members also influences the experience of a VUS. A VUS is often described in terms of an individual's personal interpretation of its associated cancer risks. Additionally, the process of decision-making is central to the experience of a VUS, as the individual decides on healthcare such as testing and risk-reduction strategies, who to communicate with, and how they will do this. In the literature, it was also found that individual characteristics, and not the type of hereditary cancer syndrome, that caused differences in psychological distress and coping (van Oostrom et al., 2007).

In this study, participants weren't always able to state what gene the VUS was in; however, they generally understood that it was not a result that changed their medical management, and that it did not mean they had a hereditary predisposition to cancer. Moreover, a difference existed between recall and personal interpretation of the VUS. Although none of our participants stated they believed they had a hereditary cancer risk, several were concerned due to the combination of histories and the VUS. Few studies in the literature focus on individuals with a VUS result, and these studies focus mainly on knowledge, understanding, and recall of the test result. Giri et al (2018) examined health literacy as an explanation for a lack of understanding but didn't find an association. Other studies also found confusion about what a VUS was (J. G. Hamilton et al., 2019; Tsai et al., 2020). Studies examining knowledge found that while some individuals do have a basic knowledge of genetics, it isn't comprehensive, and most people have no knowledge

about it (Veilleux et al., 2020). Peterson et al. (2018) reported that better genetics knowledge is associated with having higher educational attainment, income, and numeracy skills; being female, a nonsmoker, white, and married; and having a family history of cancer. Reuter et al. (2019) similarly found that recall was better than the understanding of etiology. These findings show that individuals with a VUS result may recall and know that they had a VUS result; however, it may bring many unknowns related to how to use this information for themselves and their families.

A majority of our study participants had a college degree or higher; therefore, compared to the general population, they may have been more likely to have some prior knowledge of genetics. Bartley et al. (2020) found that higher genomic literacy allowed individuals to make more meaning from the VUS. Therefore, it is possible that our population had an experience different from the general population with a VUS. Consideration of genomic literacy and overall education should be included in pretest counseling.

This study describes the importance of context in personal understanding of a VUS, with cancer history and personal characteristics playing an important role. Vos et al. (2008) found that understanding of the VUS was influenced by how it was explained in the context of family history. Reuter et al. (2019) noted that the appraisal of the VUS was done based on the personal and family pattern of cancer. This supports a consideration of context when discussing genetic testing and is an area that needs future research.

We found that individuals with a VUS experienced different emotional reactions, with some participants noting relief that the result was not pathogenic, and others being anxious about the uncertainty and worried about cancer risks. This is consistent with the limited literature, where it was found that individuals with a VUS did have distress related to the result, but many had a decrease in distress or were less distressed than those with a pathogenic variant (Culver et al., 2013; Esteban et al., 2018; Richter et al., 2013). Some

participants, in this study, had various emotional responses including anxiety, worry, neutral, surprise, and relief. Many participants didn't think about the VUS very often. Although Tsai et al. (2020) found that anxiety was related to a misunderstanding of the VUS, in this study anxiety was more related to the uncertainty. Participants in this study who were more comfortable with uncertainty tended not to worry as much about the VUS. While some studies have examined individuals' ability to deal with uncertainty in cancer or genetics (Bartley et al., 2020; Braithwaite et al., 2002; Wonghongkul et al., 2000), most other studies examining emotions about a VUS focused on psychological impact and found either no or low levels of distress after having genetic testing (Peterson et al., 2018). Fear or distress of the unknown can increase negative reactions to a VUS (Carleton, 2016). Although comfort with uncertainty is not a trait that is easily influenced, it is something that should be assessed during the pretest visit.

In this study, we also found that active coping was often employed successfully to manage the uncertainty of a VUS. These coping strategies included information-seeking, volunteering, and making a plan for cancer screening. In their study, Ahadzedah and Sharif (2018) found that changes in quality of life associated with uncertainty were significantly moderated by breast cancer patients' active emotional coping styles. Similar benefits of active coping were found by Guan et al. (2020) among prostate cancer survivors and found benefits from assessing coping strategies in men with prostate cancer. This supports the need for including a discussion of coping during genetic counseling.

Many of the participants in our study were satisfied with their cancer-screening regimen. This is contrary to Makhnoon, Shirts, et al. (2019), who reported that some participants wanted more screening, but aligns with Tsai et al. (2020), where participants thought their medical care was sufficient. Planning for screening was a common method of coping and seemed to provide a sense of control over cancer risks, which is also noted

in Solomon et al. (2017). In this study, some participants wanted to have risk-reduction surgery, and others were not interested in pursuing surgery without a pathogenic variant. The interest in prophylactic surgery was in individuals with personal histories of cancer or cancer in close relatives. Although their concern was compounded by the VUS, it was not solely based on it. Culver et al. (2013) found that all individuals in the study who had a bilateral salpingoophorectomy met surgical criteria based on personal or family history of cancer. This supports the need to better inform individuals of the applicable cancer-screening guidelines, including the recommendation to base screening and risk reduction on cancer history and not the VUS.

The Experience of Individuals With a VUS Result for Hereditary Cancer Susceptibility in Communication With Healthcare Professionals

Communication with HCPs plays an important role in both the understanding of and reaction to a VUS result. Participants who were given clear recommendations and explanations appeared to be happier with their healthcare and less worried about the VUS being pathogenic. Participants who didn't feel their provider was knowledgeable were less likely to trust their recommendations. Aspects of clear provider communication included pretest genetic counseling and clear communication. Participants stated that they appreciated availability of the genetic counselor for questions or follow-up.

Some participants were not interested in general screening guidelines and wanted to pursue higher risk screening as they felt more in control by doing so. This disagreement with the recommendations of the HCP may lead to frustration and possibly searching for a new provider. Makhnoon, Shirts et al. (2019) also noted that participants were frustrated when they felt their concerns were dismissed. J. G. Hamilton et al. (2019) found that having a VUS was related to a decreased satisfaction with care. Most of the individuals in this study understood that having a VUS didn't change management of their follow-up healthcare.

Non-genetics providers, including both primary care and specialists, have been shown to have an incomplete knowledge of genetic testing and its implications. This is visible to patients when communicating with them about any aspect of genetic testing, and this lack of knowledge is especially true when considering communication about a VUS. Training HCPs is therefore a key component of improving the communication with patients who have a VUS. Previous studies of provider preferences for continuing medical education modalities showed interests in workshops, lecture series or rounds, and self-paced learning (Veilleux et al., 2020).

Participants in our study who saw a genetic counselor were particularly pleased with their knowledge and their confidence in communicating that knowledge. Peterson (2018) found that patients are more satisfied with genetic counselors than a PCP, and that longer clinical visits were also more satisfactory. Our data supports this, as several participants noted that PCPs seemed rushed or lacking genetics knowledge. The literature supports the benefits of counseling by a provider trained in genetics, especially a genetic counselor (Conway et al., 2020; Senter & Hatfield, 2016).

Racial bias had detrimental effects on communication with HCPs. Our study showed that not listening or providing treatment regimen choices was experienced by a woman of color from a white provider. When she changed to a provider who was also a person of color, she felt she was listened to and given more options. In the literature, implicit racial bias from genetic counselors was associated with less individualized information (Lowe et al., 2020). Chapman-Davis et al. (2021) found that 39.1% non-Hispanic Blacks met one or more criteria for genetic testing prior to their own cancer diagnosis. They also noted that non-Hispanic Blacks and Asians had higher rates of VUS compared to non-Hispanic whites and Hispanics (Chapman-Davis et al., 2021). This signals that racial biases still influence who gets genetic testing and the

recommendations they receive. Further training for HCPs in recognizing and resolving these disparities is crucial, as is training a more diverse healthcare workforce.

In our study we did not find negative emotional outcomes from telehealth or telephone encounters; however, individuals were more likely to mention how they were given the results if it was an actual scheduled visit versus just a phone call and/or a results letter. It was noted in the literature that non-in-person results delivery was associated with negative outcomes (Giri et al., 2018; Makhnoon, Garrett, et al., 2019). Prioritizing in-person or face-to-face discussions (such as video calls) was recommended by (Veilleux et al., 2020). Participants also appreciated summary letters and letters they could share with their family, which is supported by the findings of (Makhnoon et al., 2021). Ensuring that the patient receives a summary letter explaining the results, implications, and recommendations is one way of supporting clear communication between patient and providers. This not only gives them something as a memory aid, but they can also share the letter with their healthcare team when seeking cancer screenings.

The Experience of Individuals With a VUS Result for Hereditary Cancer Susceptibility in Communication With Family Members

In this study, most of the participants told their genetic test results to their family members. Participants who hadn't shared their test results with family members noted that they didn't have any close relatives to share them with. This is consistent with J. G. Hamilton (2019), Solomon et al. (2017), and Cypowj et al. (2008), who also found that most participants would share their results with family. Li et al. (2018) also noted a willingness to share based on closeness and a feeling of duty, as did Young et al. (2019).

A major barrier identified was when individuals lived in other countries where genetic testing was not readily available. They may have told some relatives about the VUS and family history, but in some cases thought that doing so would be pointless. Li et al. (2018) also found that sharing had not occurred if the information was not seen as

useful. This indicates a need to establish the importance of the information for family members and, if appropriate, to assist in making connections for genetic testing in other countries. In some cases, a barrier was the perception that a family member couldn't understand or handle the information. This is similar to what Makhnoon, Shirts, et al. (2019) found in their study, where individuals did not share the information when they thought it was too hard to explain or could cause more harm than good.

When individuals did share the information, it seemed to be supported by emotional closeness. Some participants noted they are very open with their family about their health. One participant had their sibling attend the genetic counseling visits, and others had their partners participate in the process. In the literature, Young et al. (2019) found that the family culture influenced communication. Additionally, family presence during genetic counseling was studied by Gilbar and Barney (2018), and while shown to mostly provide emotional and informational support, there were some situations in which the family member would try to exert influence on the decision-making process or might be participating for their own benefit. Family communication can be influenced by providers (Young et al., 2019), and the presence of family can be encouraged as long as the patient's autonomy is respected. However, Rodriguez et al. (2016) did not find that closeness influenced communication in their study of sharing family cancer history information, but instead found that cohesion was a more important factor.

In some cases, the participants shared information on the family history and the VUS with the expectation or hope that their relatives would seek testing or cancer screenings. Especially in the case where children were young adults, participants stated they hoped to influence their health behaviors and get them to screen early and often. This is consistent with Cypowj et al. (2008), who noted a belief that the family members also needed tested or increased surveillance resulted in sharing the information with family members. Young et al. (2019) also found that a feeling of responsibility existed to

protect family, especially children. However, we did not find that parental guilt impeded communication as they did. This indicates that parents may need particular support in communicating with their children, as well as assistance with coping with the fear of having given their child a risk of cancer.

The participant's family was often noted to be a source of emotional support. This is consistent with Ahadzede and Sharif's (2018) study of breast cancer patients, where familial support helped patients cope with the burden of cancer. Our study found that partners, siblings, and adult children assisted participants in researching information about their VUS and developing a plan for medical care. We did not find the alienation of male partners of women undergoing testing that Peterson et al. (2018) noted in their study. Individuals could be encouraged to seek this support as a means of coping with the VUS.

Relevant Existing Theories

Uncertainty Theories

Mishel's Uncertainty in Illness theory (UIT) is a framework that describes how uncertainty affects psychosocial outcomes (Zhang et al., 2017). This theory has been applied to individuals with a variety of diagnoses, from cancer to multiple sclerosis. The framework describes how uncertainty can be appraised as either a threat, leading to negative emotions, or an opportunity, which leads to action and better coping. The antecedents of this appraisal are the "stimuli frame," or how different or incongruent the symptoms of the illness are; and the "structure providers," which are credible authority, support, and education (Zhang et al., 2017). Although the UIT and our model have a lot in common, the one main difference is that individuals with a VUS do not have symptoms. The VUS is not an illness; it will not likely even cause an illness. It also does not account

for the unique communication needs of individuals with a VUS. Therefore, we cannot apply the UIT in this population.

Brasher's Uncertainty Management Theory (UMT) was based on the UIT (Rains & Tukachinsky, 2015). The major difference is that uncertainty can stem from a variety of sources, not just illness-related symptoms, which is likely why it has been used in asymptomatic genetic testing. In this model, appraisal is dichotomous as either hope or danger. Appraisal can be predicted by how incongruous the level of certainty is with the individual's personal goals (Rains & Tukachinsky, 2015). This model incorporates a reassessment of uncertainty levels after information is obtained (Rauscher et al., 2018). The UMT is useful in understanding the appraisal of uncertainty, but it does not meet our needs for describing the entire experience of a VUS.

Communication Theory

Brown and Levinson's Politeness Theory is a model of communication that helps to explain why providers who are not knowledgeable about a VUS may try to appear as if they are and may end up making incorrect recommendations (Bylund et al., 2012). In this model, the provider is trying to present a "good face" to the patient and be accepted. Meanwhile, the patient may be trying to maintain their autonomy in decision-making, which Brown and Levinson describe as a "negative face." While this theory is important to consider in describing pieces of provider communication, it is by no means comprehensive enough to understand the whole process of communication.

Feldman-Stewart's proposed model of patient-provider communication is a comprehensive description of the process. It includes the interaction between patient and provider, the environment in which the communication takes place, the goals of both patient and provider, and external influences on each (Feldman-Stewart et al., 2005). This model is useful in describing how outside factors, such as lack of knowledge, could

influence communication for each party, as well as how the goals of each may not align. If the goal of our model were focused solely on communication, this would be an excellent model.

Social network theory is one way of looking at family communication. The network is a series of nodes and connections, where the nodes are people. The outcomes are not due simply to the individual people but are due to the attributes of the connections between them (Koehly et al., 2003; Wright, 2016). This theory is being used more frequently to understand family communication about cancer risks.

Proposed Theoretical Model

This study employed the grounded theory design that aims to expand upon our understanding of living with a VUS result for hereditary cancer susceptibility by identifying the key elements of this experience and describing the relationships of those elements. The proposed theory (see Figure 4.1) developed from the results describes how individuals live with a VUS result that carries a high level of uncertainty; how individuals make meaning of it depends on contextual factors, including their personal characteristics, coping mechanisms, and cancer history. Key elements in this experience are communicating with family, communication with HCPs, and making decisions on healthcare. The needs of individuals with a VUS include knowledgeable and trustworthy providers, open lines of communication, and support for emotional needs.

Implications

Clinical Practice

Multigene panel tests (MGPT) are increasingly used for individuals with personal or family cancer histories in order to identify those who have a genetic risk for disease. With the expansion of some cancer panels to include 80 or more genes, the odds of getting a VUS are close to 50%. Given this increase in the number of individuals

undergoing genetic testing for hereditary cancer risks, and the chance of getting a VUS, it is critical that providers understand this result and are able to support individuals with a VUS result through this process, including helping individuals understand the implications, supporting their emotional needs, and supporting communication with family.

Genetics and hereditary disease risks play an integral part in providing holistic nursing care. Although the focus of precision health is often the identification of pathogenic variants that cause a predisposition to certain diseases, an often-overlooked aspect is supporting the individuals and their families as they go through the testing process and beyond. As demonstrated by the lack of literature identified in our scoping review, there is even less knowledge about how to support individuals with a VUS. This study has identified several factors that impact the experience of a VUS, including personality characteristics, coping mechanisms, and communication with HCPs. Therefore, as providers work with individuals who have a VUS, they should help the person identify how they best cope with the uncertainty, and not rely on one-size-fits-all solutions.

Genetic counseling focuses not only on the transmission of information about the genetic test being performed, but also on identifying how the individual and their family will be impacted by different possible results. This includes a discussion of the testing, its possible results, and their implication for individuals tested and their families. As a VUS result is becoming common among tested individuals, the genetic counseling process should include a possible VUS result, its implications, coping strategies, and how the individual responds to uncertainty. All providers need to understand the nature of having a VUS result and how to improve coping strategies and reduce the stress around uncertainty for the patients and their family members. Personalized health must be about caring for the whole individual, not just identifying their genetic risk.

In order to ensure clear communication and avoid confusion, providers who are working with those who have a VUS result for cancer must have a basic understanding and knowledge in genetic testing and implications of the possible test results, and therefore training must be provided. For practicing clinicians, this can be accomplished through specialty-specific professional development. In order to increase the knowledge of new clinicians (including nurses and physicians), genetics training should be incorporated into the curriculum, with a particular focus on helping individuals through the testing process and understanding their results.

Research

Several areas for further research have been identified. First, more research is needed regarding the effects of personality and personal coping strategies on the experiences of having genetic testing, particularly focused on the uncertainty of having a VUS. The results of this study show the importance of individual characteristics on the reactions and experiences of receiving a VUS, which can be used to support those with a VUS result and their families. The literature so far discusses emotions as an outcome only, and does not look at coping, personality influences, or emotional state during testing. Future studies should focus on developing an understanding of how individual context influences the experiences of a VUS.

Although we did not specifically aim to understand experience based on delivery method, outcomes in the literature differed based on delivery methods (in-person vs. telephone or telehealth). Given the increasing use of telehealth since the start of the pandemic, more research is needed into possible differences in outcomes, as well as methods of mitigating those potential differences. Future studies could also focus on what delivery methods are best suited for pre- or posttest counseling.

Finally, more testing of the model developed in this study is needed to fully capture the experiences and areas to improve during and beyond the testing process for those with a VUS result. More information regarding styles of HCP communication and measurements of provider knowledge should be collected to better understand the barriers in this area. Similarly, future studies should focus on gathering more information on personal characteristics with regard to coping and personality traits. Finally, prospective studies should be conducted to gather this information as individuals progress through the genetic testing process, which will alleviate some of the issues with recall bias that exist in a retrospective study.

Limitations

The small convenience sample used in this study, while of an acceptable size for a qualitative study, limits generalizability of the results. Much of the sample had a higher level of education than is the average for the United States, which may have led to a stronger motivation to participate in research. The sample demographics did not also include any participants who stated that they were nonbinary or Hispanic/Latino.

Recruitment and data collection for this study were conducted via remote methods during the ongoing pandemic. This did allow for a nationwide sample. However, it may have excluded individuals who did not have access to the recruitment messages or didn't feel comfortable with the technology used to participate. Remote interviews may also cause a change in the style or interpretation of nonverbal communication, especially when conducting audio-only interviews.

This study was retrospective in nature. The varying time periods since results disclosure may have led to differences in recall of the genetic testing process.

Conclusion

The purpose of this grounded theory study was to describe the experiences of having a VUS, from the viewpoint of the individuals with this result. Additional focus was given to communication with HCPs and family members. In the literature review, we found that the limited available studies showed that a high level of uncertainty and misunderstanding existed about the VUS result for cancer. Communication with HCPs was often described as frustrating and, although the studies show that individuals communicated with their family, there is no description of how the communication occurred or what they communicated. Our qualitative findings supported the themes of personal characteristics, emotions, communication with family, and communication with HCPs. These themes are seen across all the time categories in this study, which were pretest, testing, posttest, and long term. The theoretical model developed from this study describes a contextualized experience of having a VUS, with the context influencing the processes of decision-making, communicating with HCPs, and communicating with family members. The needs of individuals with a VUS described in this study include knowledgeable and trustworthy providers, support of emotional needs, and open lines of communication.

APPENDIX A

LITERATURE REVIEW TABLE

Sample characteristics and main findings of the articles included in the scoping review.

Reference and country	Aim	Test result of the population	Population	Assessment and measurements	Methods	Results
Bredart et al. 2019 France, Germany, Spain	To evaluate changes in psychosocial problems before and after genetic testing and prospectively compare between genetic test results in women tested for breast or ovarian cancer genetic	Any result on BRCA 1/2	752 women eligible for breast cancer risk testing, unaffected or affected with a non-metastatic BC. 646 (86%) were assessed after the initial genetic consultation, of which 460 (61%) were assessed again after receiving the test result	Genetic test results, Clinical data PAHC measuring personal, family and social issues, emotions, familial and personal cancer worry, and children-related issues Assessment: pre-test and 2 months after the genetic test	Observational prospective study.	Individuals with a VUS result decreased more in psychosocial problems related to hereditary predisposition and familial/social issues after receiving test result. The receipt of psychological help after testing was associated with higher problems in the 'emotions' domain.
Chern et al., 2019 USA	To compare the cancer risk management decisions of patients with	VUS or negative BRCA1/2	Women 18-90 years who had BRCA1/2 test; participants with a VUS were	Risk reducing breast surgery and RRBSO uptake, Surgical pathology	Chart review study.	Women with a VUS result were more racially diverse, and less likely to be privately insured. There was no significant

Conley et al., 2020 USA	VUS to those of patients with definitive negative genetic testing results	To analyze patterns of results disclosure in young Black breast cancer survivors	Any result from the study provided BRCA1/2 test	matched by age and date of test to a negative test result; 99 women with a VUS test result were included	149 Black women living in Florida, diagnosed with invasive breast cancer before age 50	Disclosure of results to family 12 months after having genetic testing	Quantitative, cross-sectional study.	Disclosure to female relatives was higher, except for those with a PV, who were less likely to disclose to daughters. Other results did not predict disclosure. Concern for family was most common reason for disclosure.	difference in personal history and in rate of RRBSO uptake.
Culver et al., 2013 USA	To compare surgical decisions, risk perceptions, cancer distress, and opinions about GT process in those with UN vs VUS	To compare surgical decisions, risk perceptions, cancer distress, and opinions about GT process in those with UN vs VUS	VUS or UN in BRCA1/2	785 women with a personal or family history of breast cancer, enrolled in City of Hope registry from 1997-2010	Surgical decisions, Risk perception, Cancer distress, perception of GC/GT. Assessment: 2 year follow up survey with questions regarding recall of surgery and cancer risks, cancer concerns, utility of GC; medical records review	Surgical decisions, Risk perception, Cancer distress, perception of GC/GT. Assessment: 2 year follow up survey with questions regarding recall of surgery and cancer risks, cancer concerns, utility of GC; medical records review	Case control design with pre- and post-test assessments.	There was no significant difference in surgical decisions for VUS vs negative result. All BSO in VUS group met guidelines. BC risk recall was 75% for both groups. OC risk recall was 56%. 15% with VUS and 10% with UN believed they were high risk. The VUS group reported significant change in concerning thoughts with 92% reporting a decrease	

Elsayegh et al., 2018 USA	To evaluate predictors of CPM in individuals who had MGPT and determine whether predictors of CPM differ by gene or result type	Any PV or VUS on MGPT	314 women from a MD Anderson registry with breast cancer who had MGPT from 2014-2017	regarding surgery to determine appropriateness of surgery	CPM uptake	Analysis of existing registry data.	in frequency. A majority of both groups saw GC as helpful. All of the VUS patients who were dissatisfied with GC stated that it didn't provide new knowledge. 10.6% of VUS carriers elected CPM. PV carriers are more likely to elect CPM than those with a VUS. In the VUS group receptor status was not associated with CPM election but age was.
Esteban et al., 2018 Spain	To seek patient opinions and preferences regarding results disclosure and to analyze the psychological impact of multigene and cancer testing	Any results on the 25 gene panel	187 participants diagnosed with cancer from a parent study, who either met NCCN criteria for HBOC or Bethesda criteria for LS.	Psychological impacts of testing; patient's opinion and preference for what is disclosed of the genetic test result; MICRA, IES, CWS; Medical information and GT genetic test results; Assessments: Questionnaires	A comparison of two cohorts using quantitative measurements at 3 time points.	CWS scores did not change over time and it did not differ depending on GT result. IES did not differ depending on results and there's no statistically significant long-term change. Patients with a PV had higher distress than patients with negative or VUS result. There was a tendency among patients with high	

<p>Giri et al. 2018 USA</p>	<p>To understand men's needs regarding genetic testing for inherited prostate cancer and evaluating their knowledge of cancer risk and personal results</p>	<p>Any PV or VUS</p>	<p>109/200 participants from the GEM parent study A significant difference between responders and non-responders was that 80% of those with HCS responded to the survey vs 44.8% without HCS</p>	<p>were self-administered after the pre-test visit, and 1 week, 3 months and 12 months after results disclosure</p> <p>Knowledge of cancer risk and genetics, Understanding of personal test results</p> <p>Baseline assessment followed by GC (either in person or by telehealth) and genetic testing,</p> <p><i>Assessments:</i> medical history, lifestyle, risk factors, knowledge of prostate cancer risk, genetic literacy. Participants received post-test survey by mail.</p>	<p>Quantitative surveys using a pre- and post-test design.</p>	<p>penetrance PV to report that they understood their options better. Most patients wished to be disclosed VUS and moderate penetrance PV.</p> <p>101 participants responded that they definitely understood their test results, 88 of which responded correctly regarding the test results and 13 responded incorrectly answering that they carry a mutation when they did not. 12/13 who responded incorrectly had at least 1 VUS. Having a VUS result was significantly associated with reporting incorrect test results. Phone or telehealth disclosure were also associated with misunderstanding of results</p>
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<p>Hamilton et al., 2019 USA</p>	<p>To characterize the genetic testing experiences, medical management, and psychosocial adaptation of individuals living with CDH1 variants</p>	<p>CDH1 PV or VUS</p>	<p>57 individuals identified through the PROMPT registry with a CDH1 PV or VUS</p>	<p>Understanding of result, Nomenclature of variant, Personal and family history, Impact of MGPT, Adapted Carolina Genomic Knowledge scale, Adapted NCI risk measure, Decision Regret Scale; Emotional distress-MICRA and Worry about discrimination question, QOL, family communication <i>Assessment:</i> Survey completed online 0-4 years after results disclosure</p>	<p>Cross-sectional design using a quantitative online survey.</p>	<p>8 cases had conflicting lab classifications; 1 discordant LP/P vs VUS and 7 VUS vs LB/B. 12/56 self-report discordant with 3 participants reporting PV and actual result VUS 45.6% recalled pretest information about the possibility of a VUS. Those with VUS reported significantly lower CDH1 knowledge and less satisfaction with HCP knowledge. Both VUS and LP/P groups reported cancer risks at scale midpoints. Most had shared result with family. VUS group more likely to be concerned about scaring family. VUS less likely to have family interested in testing. 69.2% of VUS had breast MRI. 92% of VUS had mammogram at least yearly. 6% of VUS group had upper endoscopy at least yearly.</p>
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Li et al., 2018 Singapore	To explore facilitators and barriers to sharing information with family	Any BRCA 1/2 result	24 women in Singapore who had GT for HBOC	Family communication assessed by semi structured interviews	Qualitative grounded theory design with inductive thematic analysis.	Willingness to share is based on closeness and feeling the duty to inform. If the participant thought the family member could handle genetic information, they were willing to share. Individuals who shared wanted to influence outcomes for family. Some did not share because they wanted to avoid misunderstanding and false alarm.
Miron et al., 2000 USA	To present the spectrum of BRCA 1/2 mutations and the reactions of women after results disclosure	BRCA 1/2 VUS or PV	In the main study, testing was offered to 221 probands and 110 relatives. In this study, 213 probands accepted, relatives were incomplete at time of publication	Randomly assigned 2 forms of written materials about HBOC and GT. All were offered free GC prior to decision to test. <i>Assessments:</i> Baseline survey attitudes, knowledge about cancer genetics, GT, and risk perception. Follow up surveys after test decision, results disclosure, and posttest GC	Quantitative surveys completed pre- and post-free GC and testing.	Subject's self-estimate and the calculated estimates differed significantly from each other. 15/25 who were interested in RRM before GC and testing and received a negative test result were no longer interested in surgery 3/4 VUS also changed minds on RRM. BSO decisions were less changed by test results.

Reuter et al., 2019 USA	To assess patient understanding of a VUS identified on MGPT and factors that may influence recall, reaction to, and interpretation	Any VUS in the absence of a PV	10 female, 1 male who had a VUS on MGPT	that included specific questions on risk estimates, interest in prophylactic surgery Factual recall, perceived significance, response to result, expectations and motivations for testing <i>Assessment:</i> semi structured interview in person or via phone 5-13 months after results disclosure	Qualitative study, analysis used an iterative approach with both inductive and deductive coding.	2 participants could not recall having a VUS. There was variation in describing results. Participants generally understood that a VUS doesn't impact medical management. Some did not understand that a genetic etiology was still possible. Emotional responses varied. Most do not report frequent thoughts about VUS
Solomon et al., 2017 USA, Canada	To describe the experiences of individuals who had a VUS result on genetic testing for LS	Any VUS on LS panel	21 females 6 males who had testing for LS due to a personal or family history of cancer.	Recall, uncertainty, appraisals, expectation of reclassification <i>Assessment:</i> semi structured interviews, most within 1 year of results disclosure	A qualitative study Codes were developed based on concepts of interest and the interview guide, and data were coded in an iterative	23 recalled having a VUS. 27 connected their result to their history. 13 did not know about the possibility of a VUS pretest. Responses ranged from relief to shock. 23 conceptualized VUS as uncertain. 10 self identified as having LS. 7 said they did not have LS. 17 appraised VUS as a

Cypowyj et al., 2009 France	To describe subjective understanding of BRCA1/2 VUS and explore communication of results to family	BRCA1/2 VUS	30 women being followed by the clinic in France	CESD and IES; CancerGene probability calculated; Researcher-developed questionnaire on transmission of info to families and risk perception <i>Assessment:</i> Two years after results disclosure Data collected from geneticist regarding	A mixed method, cross-sectional study Qualitative data was analyzed using thematic analysis.	7 women recalled a PV, 9 recalled a negative result, 14 were uncertain. 76% had communicated test results to their family within the 2 years after the test. Individuals in the uncertain group found it difficult to explain the information to families because it was unclear. Participants also included comments about what their physician told them. Most of the women who thought they were positive	threat, 17 appraised as an opportunity. Participants often repeated what providers told them. Mobilizing was most common coping strategies 17 reported having a plan for screening. 15 communicated with family. 6 sought information. 14 expected reclassification. There was a perceived benefit from following a surveillance and management plan	process.
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Garcia et al., 2014 USA	To describe decision making and follow up in women with VUS vs PV	BRCA 1/2 PV or VUS	374 women followed by Kaiser Permanente after genetic testing.	medical history and risk assessment Rates of RRSO, RRM, surveillance, time to reclassify	Chart review.	told their family because they thought they would need screening. VUS group had lower rates of RRM RRSO than PV group Rates of surveillance were low for both groups and dropped every year.
Makhnoon, Garrett, et al., 2019 USA	To explore the experiences of patients with a VUS result who were seeking reclassification	VUS	25 female and 1 male eligible for screening based on family history	Motivations for reclassification, VUS interpretations, understanding of screening recommendations, emotional responses Assessment: Semi-structured phone interviews	A qualitative study. Semi-structured interviews were analyzed using inductive thematic analysis.	Individuals were motivated by history and prevention. Uncertain VUS interpretations understood but lacked guidance on how to move forward. Some individuals wanted more screening and family testing; most misunderstood management recommendations. Negative affects occurred after disclosure. Individuals expressed frustration with providers and felt their worries were dismissed. Some felt relief or indifferent about the VUS. A majority were more concerned for their family. Post-test counseling via telephone described as "imperfect".

Makhnoon, Shirts, & Bowen, 2019 USA	To understand why some individuals have difficulty after a VUS result.	VUS in genes associated with breast, colorectal, uterine, or prostate cancer.	11 women identified through a clinic registry	Emotions, understanding, views of process Assessment: Semi-structured in-person or phone interviews	A qualitative study. Hybrid deductive content analysis of semi-structured interviews using the framework of Han's Taxonomy of Uncertainty.	Uncertainty regarding future pathogenicity of VUS and prognostic concerns. Ambiguity related to complexity of information. Participants were aware of environmental etiology of cancer. They did not want to share with family if it causes more harm than benefit. Participants expressed frustration and concerns about GT process. Emotional outcomes were better when providers discussed coping strategies for VUS prior to test. Those who were unprepared for VUS had more uncertainty.
Richter et al., 2013 Canada	To compare individuals with different types of results regarding comprehension, perceived risk, cancer worry, and surveillance/risk reduction; also, to determine	Any BRCA 1/2 result	144 women who had been seen at a breast cancer clinic	Recall and significance, risk perception, cancer specific worry, adoption of surveillance and risk reduction, Trask Worry Score Assessment: mailed surveys GCs were also	A quantitative, cross-sectional design with survey data collected from individuals who had genetic testing, GCs, and	VUS group had the highest rate of incorrect recall (36%). VUS and negative groups both reported decreased perceived risk. VUS had intermediate levels of worry. GC would make recommendations based on histories for those with VUS MDs said they would refer a family of a proband with a

Vos et al., 2008 The Netherlands	practices and perceptions of VUS among clinicians	VUS in BRCA1/2	24 women with breast and/or ovarian cancer who had received their results from one of two Dutch cancer clinics	asked about practice patterns, counselee worry, and comprehension. Physicians were asked about practice patterns	physicians.	VUS for testing.
	To examine possible differences between recall and interpretation in individuals with a VUS using the distorted perception hypothesis			Understanding, perception of GC, expectations of a VUS, uncertainty about the possible genetic cause of family cancer history assessed by interviews. <i>Assessment:</i> Likert style questions and open-ended interview questions. Data about genetic counseling was collected from GC summary letter.	A mixed-method study which was part of a larger study where GT was offered to unaffected relatives of probands with a VUS.	67% recalled the VUS as uninformative. 79% interpreted VUS as pathogenic; 21% interpreted it as uninformative. The disclosure of the VIS was described as neutral. The mean life change score was low. Large life changes were mentioned in the interview. 7 had a mastectomy due to VUS. No difference in surgery choices between those who recalled result as PV or VUS.

APPENDIX B

FLYER

HAVE YOU HAD AN UNCERTAIN GENETIC TEST RESULT FOR HEREDITARY CANCER RISKS?

We are conducting a study of individuals with a Variant of Uncertain Significance (VUS) in order to learn more about their experiences and needs in understanding the test result for themselves and their family members. Additionally, we are trying to understand the process of communication with their first-degree relatives and healthcare providers about genetic risk and risk management. Participation is expected to take 80 minutes in total.

You may be eligible participate in this study if you:

- Are over age 18
- Are able to speak English
- Can participate in an interview via telephone or video chat
- Had a variant of uncertain significance (VUS) on a genetic test for hereditary cancer risks

If you are interested in learning more about this study, please follow this link: <link to qualtrics> or scan the QR code below:



UMassAmherst
College of Nursing

Contact the study team:

Danielle Gould, PhD Candidate
Daniellegoul@umass.edu
413-545-9922

APPENDIX C

RECRUITMENT EMAIL

Email messaging:

Dear <name of community contact> ,

I am currently seeking participants for my dissertation study at The University of Massachusetts Amherst, titled "The Experiences and Needs of Individuals With a Variant of Uncertain Significance (VUS) on Genetic Tests for Hereditary Cancer Syndromes: A Grounded Theory Study" (IRB protocol 2477). This study seeks to further our understanding of the experiences and needs of individuals with a certain genetic test result, called a "VUS", on genetic testing for hereditary cancer risks.

To be eligible, participants must:

- Be over age 18
- Be able to speak English and connect via telephone or video chat
- Had a Variant of Uncertain Significance (VUS) on a genetic test for hereditary cancer susceptibility
- Has access to or recall of the result nomenclature

Participation is expected to take 80 minutes in total. If any members of your community are interested, they can find more information by following this link: <qualtrics link to consent and survey>. Any questions can be directed to me via email daniellegoul@umass.edu. Thank you for your time and assistance to disseminate this information

Sincerely,

Danielle Gould MSN, APRN, FNP-C
PhD Candidate
University of Massachusetts, Amherst
College of Nursing

Social media (Twitter, Facebook, Instagram, discussion boards/forums):

I am currently seeking participants for my dissertation study at The University of Massachusetts Amherst (IRB protocol 2477), which seeks to further our understanding of the experiences and needs of individuals with a certain genetic test result, called a "VUS", on genetic testing for hereditary cancer risks. Participation is expected to take 80 minutes in total. For more information and eligibility criteria, please follow this link <qualtrics link to consent and survey>.

APPENDIX D
IRB DETERMINATION LETTER

UMassAmherst

Human Research Protection Office

Mass Venture Center
100 Venture Way, Suite 116
Hadley, MA 01035
Telephone: 413-545-3428

LETTER OF EXEMPT DETERMINATION

Date: December 4, 2020
To: Professor Memnun Seven and Danielle Gould, College of Nursing
From: Professor Lynnette Leidy Sievert, Chair, University of Massachusetts Amherst IRB

Protocol Title: *The Experiences and Needs of Individuals With a Variant of Uncertain Significance (VUS) on Genetic Tests for Hereditary Cancer Syndromes: A Grounded Theory Study*

Protocol ID: 2477

Review Type: EXEMPT -NEW

Category: 2

Review Date: 12/04/2020

No Continuing Review Required

UM Award #:

The Human Research Protection Office (HRPO) has reviewed the above named submission and has determined it to be EXEMPT from the federal regulations that govern human subject research (45 CFR 46.104)

Note: This determination applies only to the activities described in this submission. All changes to the submission (e.g. protocol, recruitment materials, consent form, additional personnel), must be reviewed by HRPO prior to implementation.

A project determined as EXEMPT, must still be conducted in accordance with the ethical principles outlined in the Belmont Report: respect for persons, beneficence, and justice. Researchers must also comply with all applicable federal, state and local regulations as well as UMass Amherst Policies and procedures which may include obtaining approval of your activities from other institutions or entities. All personnel must complete CITI training.

Consent forms and study materials (e.g., questionnaires, letters, advertisements, flyers, scripts, etc.) - Only use the consent form and study materials that were reviewed by the HRPO.

Final Reports - Notify the IRB when your study is complete by submitting a Close Request Form in the electronic protocol system.

Serious Adverse Events and Unanticipated problems involving risks to participants or others - All such events must be reported in the electronic system as soon as possible, but no later than five (5) working days.

Annual Check In - HRPO will conduct an annual check in to determine the study status.

Please contact the Human Research Protection Office if you have any further questions. Best wishes for a successful project.

APPENDIX E

CONSENT FORM

Consent Form for Participation in a Research Study
University of Massachusetts Amherst

Researcher(s): Danielle Gould MSN, APRN, FNP-C, PhD Candidate
Memnun Seven PhD, RN, Assistant Professor and Faculty Sponsor
Study Title: The Experiences and Needs of Individuals With a Variant of Uncertain Significance (VUS) on Genetic Tests for Hereditary Cancer Syndromes: A Grounded Theory Study

1. WHAT IS THIS FORM?

This form is called a Consent Form. It will give you information about the study so you can make an informed decision about participation in this research. We encourage you to take some time to think this over and ask questions now and at any other time. If you decide to participate, you will be asked to sign this form and you will be given a copy for your records.

2. WHAT ARE SOME OF THE IMPORTANT ASPECTS OF THIS RESEARCH STUDY THAT I SHOULD BE AWARE OF?

- 1) Consent is being sought for research and participation is voluntary.
- 2) The purpose of this research is to further our understanding of the experiences of individuals who have had a Variant of Uncertain Significance, or VUS, on genetic testing for hereditary cancer susceptibility.
- 3) Your participation will involve completing an online questionnaire which will take 15-20 minutes and an interview via telephone or video call, which will take approximately 45-60 minutes.
- 4) If you are not comfortable with being recorded, you should not participate in this study.
- 5) There are minimal risks expected from participating in this study. However, there is a risk of psychological distress or negative emotions due to the discussion of experiences related to genetic testing.
- 6) There are no direct benefits to you. However, by participating in this research you will be contributing to science and the improvement of health care.

3. WHY ARE WE DOING THIS RESEARCH STUDY?

We are conducting this research study to explore the experiences and needs of individuals who had a variant of uncertain significance result (VUS) in genetic testing for hereditary cancer susceptibility. We plan to focus specifically on their experiences and needs in the interpretation of the test result for themselves and their family members. We also plan to examine the process of communication with healthcare providers and their first-degree relatives about genetic risk and risk management.

4. WHO CAN PARTICIPATE IN THIS RESEARCH STUDY?

You can participate in this study if you:

- Are over age 18
- Able to speak English and connect via telephone or video chat
- Had a variant of uncertain significance (VUS) on a genetic test for hereditary cancer risks

University of Massachusetts Amherst-IRB Protocol #: 2477 IRB Signature: <i>Nancy C. Swartz</i>
--

- Have access to a copy of your test result or can recall the specific result

You cannot participate in this study if you:

- Did not have a VUS result in a cancer-related gene
- Are not able to complete the interview via phone or video call.

5. WHERE WILL THIS RESEARCH STUDY TAKE PLACE AND HOW MANY PEOPLE WILL PARTICIPATE?

Interviews for this study will be conducted remotely via telephone or video call, therefore participants can be in any location. We expect to enroll 40 participants.

6. WHAT WILL I BE ASKED TO DO AND HOW MUCH TIME WILL IT TAKE?

If you agree to take part in this study, you will complete an online questionnaire regarding your demographics, family history of cancer, and scheduling preferences for the interview; this should take less than 20 minutes. Then, you will complete an interview which will last approximately 45-60 minutes. In total, it is expected that your participation will take less than 80 minutes in total. In each step, you can skip any questions that you are not comfortable with. You will not be contacted after your participation is completed.

7. WILL BEING IN THIS RESEARCH STUDY HELP ME IN ANY WAY?

You may not directly benefit from this research; however, we hope that your participation in the study may advance our knowledge and understanding of the experiences of individuals with VUS results and therefore improve health outcomes in this population.

8. WHAT ARE MY RISKS OF BEING IN THIS RESEARCH STUDY?

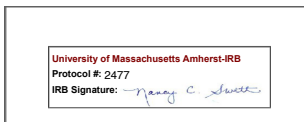
We believe there are minimal risks associated with this research study.

This is a research study that involves questions related to sensitive topics such as your feelings and coping strategies with having a VUS test result that may cause emotional or psychological distress. You always have the option to skip distressing questions or end the interview. As researchers, we do not provide mental health services and we will not be following up with you after this study. However, we want to provide every participant in this study with contact information for available clinical resources, should you decide you need assistance at any time. Mental health resources can be found at <https://findtreatment.samhsa.gov/> or by calling 1-800-662-HELP. In a serious emergency, remember that you can also call 911 for immediate assistance.

There is also a risk of breach of confidentiality and we have taken the steps to minimize this risk as outlined in section 9 below.

9. HOW WILL MY PERSONAL INFORMATION BE PROTECTED?

Your privacy and confidentiality are important to us. The following procedures will be used to protect the confidentiality of your study records. Study records will be stored only in electronic format. All electronic files (including audio recordings, transcripts, notes, survey responses, and databases) containing identifiable information will be password protected. Any computer hosting such files will also have password protection to prevent access by unauthorized users. Only the members of the research staff will have access to the passwords. We will use secure cloud storage called Box.net for file sharing between researchers, which is password protected and encrypted. A transcription service will be used, which



employs transcription in transit and storage to keep data secure, and does not access any individual data. At the conclusion of this study, the researchers may publish their findings. Information will be presented in summary format and you will not be identified in any publications or presentations.

Your privacy will be protected by conducting study procedures in a private location and only allowing authorized research team members to meet with research participants. Signed consent documents will be stored securely and separately from the research data.

10. WILL MY INFORMATION (BIOSPECIMENS OR PRIVATE INFORMATION) BE USED FOR RESEARCH IN THE FUTURE?

Identifiers will be removed and the de-identified information may be used for future research without additional informed consent from you.

11. WILL I BE GIVEN ANY MONEY OR OTHER COMPENSATION FOR BEING IN THIS RESEARCH STUDY?

You will not receive payment for participation in this research study.

12. WHO CAN I TALK TO IF I HAVE QUESTIONS?

Take as long as you like before you make a decision. We will be happy to answer any question you have about this study. If you have further questions about this project or if you have a research-related problem, you may contact the researcher(s), Danielle Gould and Dr. Memnun Seven by email (daniellegoul@umass.edu, mseven@umass.edu) or telephone (413-545-9922).

If you have any questions concerning your rights as a research subject, you may contact the University of Massachusetts Amherst Human Research Protection Office (HRPO) at (413) 545-3428 or humansubjects@ora.umass.edu.

13. WHAT HAPPENS IF I SAY YES, BUT I CHANGE MY MIND LATER?

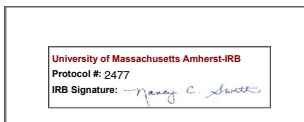
You do not have to be in this study if you do not want to. If you agree to be in the study, but later change your mind, you may drop out at any time. There are no penalties or consequences of any kind if you decide that you do not want to participate.

14. WHAT IF I AM INJURED?

The University of Massachusetts does not have a program for compensating subjects for injury or complications related to human subjects research, but the study personnel will assist you in getting treatment.

15. SUBJECT STATEMENT OF VOLUNTARY CONSENT

(Check here if you agree) I understand that the interview will be either video or audio recorded and



agree to this recording.

When signing this form I am agreeing to voluntarily enter this study. I have had a chance to read this consent form, and it was explained to me in a language that I use. I have had the opportunity to ask questions and have received satisfactory answers. I have been informed that I can withdraw at any time. A copy of this signed Informed Consent Form has been given to me.

Participant Signature:

Print Name:

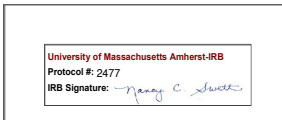
Date:

By signing below I indicate that the participant has read and, to the best of my knowledge, understands the details contained in this document and has been given a copy.

Signature of Person
Obtaining Consent

Print Name:

Date:



APPENDIX F

QUALTRICS SCREENING SURVEY

Q1 Before you officially enroll in this research study, I will be asking you to complete a screening questionnaire. It should take you no more than 5 minutes to complete. If you are determined to be ineligible to participate, your completed questionnaire will be destroyed. If you are determined eligible to participate, the completed questionnaire will become part of the study materials, and we will protect your information as confidential and safeguard it from unauthorized disclosure. Only research personnel will have access to the information contained in your screening questionnaire. If the screening questionnaire indicates that you are eligible to participate, we will proceed to obtaining your written informed consent for participation in the study.

Q2 In this study, we are looking for individuals with a Variant of Uncertain Significance (VUS) for any cancer type in order to learn more about their experiences and needs in understanding the test result for themselves and their family members. To determine if you are eligible to participate, please write in or share an image of your test results with your personal information not visible.

Q3 Enter test results here if not uploading an image:

Q4 How are you recalling these results?

- Direct- I am looking at a copy of the results
- From memory- this is how I remember the results
- Other _____

Q5 If you are eligible for the study, can you participate in the interview via video call (Zoom, Facetime, etc) or telephone call?

- Video call
- Telephone call
- Neither

Q6 Can you communicate verbally in English?

- Yes
- No

Q8 Where did you learn about this study?

- PROMPT
- Twitter
- Facebook
- Other _____

Q7 How would you like to be contacted?

- Email _____
- Phone _____

APPENDIX G
DEMOGRAPHIC SURVEY

Please read the following consent form. If you agree to participate in this study, you will be asked to provide a signature and will then be taken to a survey which will collect some basic information.

Please click this link to read the consent:

[Click here for consent form](#)

I understand that the interview will be either video or audio recorded and agree to this recording.

Yes

No

When signing this form I am agreeing to voluntarily enter this study. I have had a chance to read this consent form, and it was explained to me in a language that I use. I have had the opportunity to ask questions and have received satisfactory answers. I have been informed that I can withdraw at any time. A copy of this signed Informed Consent Form has been given to me.

Yes

No

Please sign below to indicate your consent to participate in this study.

Please enter an email address where we can send you a copy of this consent:

Please fill in the following questions to the best of your ability. You may skip any question you do not want to answer.

What was your age on your last birthday?

What gender do you identify as?

- Male
- Female
- Transgender Male
- Transgender Female
- Other/ not listed _____
- Prefer not to say

What was your assigned sex at birth?

- Male
- Female
- Prefer not to say

What race you identify as?

- White
 - Black or African American
 - American Indian or Alaska Native
 - Asian
 - Native Hawaiian or Pacific Islander
 - Other
-

Do you identify as Hispanic/Latino?

Yes

No

What is your highest level of education completed?

Less than high school (elementary or junior high school)

Did not finish high school

High school diploma

Some college or 2-year degree

Bachelors/ 4-year college degree

Graduate school/advanced degree

What is your employment status?

Working, full time

Working, part time

Unemployed, looking for work

Unemployed, not looking for work

Disabled

Retired

What is your health insurance status?

- I have private health insurance
- I have insurance through the military or VA
- I have health insurance through Medicare or Medicaid
- I am covered by another country's health insurance program
- I do not have health insurance

Does your insurance cover genetic testing?

- Yes
- Not sure
- No

Do you have a personal history of cancer?

- Yes
- No

Personal history of cancer:

	Age at diagnosis	Treatment	Age at recurrence (N/a if none)?
Cancer type 1:			
Cancer type 2:			
Cancer type 3:			
Cancer type 4:			

Family history of cancer (i.e., son, daughter, brother, sister, mother, father, grandmother, grandfather):

	Cancer type(s)	Age at diagnosis
Family member kinship (i.e., son, daughter, mother, father)		
Family member kinship (i.e., son, daughter, mother, father)		
Family member kinship (i.e., son, daughter, mother, father)		
Family member kinship (i.e., son, daughter, mother, father)		
Family member kinship (i.e., son, daughter, mother, father)		
Family member kinship (i.e., son, daughter, mother, father)		
Family member kinship (i.e., son, daughter, mother, father)		
Family member kinship (i.e., son, daughter, mother, father)		

Contact preference

- Text (enter phone number):
- Email (enter email):
- Phone (enter phone number):

Preferred interview method

- Zoom
- Google Meet
- Skype
- Facetime
- Telephone
- Other

Is there anything else we should know?

APPENDIX H
INTERVIEW GUIDE

How would you describe your genetic testing process?

- How did you decide?
- Who did you see?
- Were you referred?
- What prompted it?

What does it mean to you to have a VUS?

- How do you feel about having VUS result?
- How has it affected your life?
- How did it impact any decisions for treatment, screening for yourself?
- How have you coped (strategies)?
- How do you feel about your medical management?

How did you talk to your family about the GT? Did you tell them ahead of time/ after?

- How did you decide to do this?
- Who in your family know about the test result? (children, siblings, parents etc.)
- Which information did you include in your communication?
- Are there relatives you excluded?
- How did it impact any decisions for treatment, screening among your family members?

What do you recall being told about cancer risks?

- Who gave you this test result?
- Which information were you given?
- How did you feel after having this result?
- Do you see anyone for follow-up?

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