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Medical Decision Making among Individuals with a Variant of Uncertain Significance in a Hereditary Cancer Gene and those with a CHEK2 Pathogenic Variant

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Medical Decision Making among Individuals with a Variant of Uncertain Significance in a
Hereditary Cancer Gene and those with a *CHEK2* Pathogenic Variant

by

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A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science in Public Health
with a concentration in Genetic Counseling
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ABSTRACT

Despite national guidelines, women with a *BRCA* VUS or *CHEK2* pathogenic variant are choosing to have risk-reducing surgeries such as bilateral mastectomies which are not aligned with their level of cancer risk based on genetic test results alone. Semi-structured telephone interviews were conducted with 6 women with a *BRCA* VUS and 12 with a *CHEK2* pathogenic variant exploring the factors influencing their decision-making process when considering medical management options. Patients from a cancer registry agreed to a recorded telephone interview. Coding was performed using the main constructs from the Ottawa Patient Decision Guide including: knowledge, uncertainty, values, and support. Iterative analysis was used to identify emerging themes.

Analysis of the interviews revealed overlapping of the four constructs in the decision-making process. The knowledge sought to make medical management decisions was driven by the uncertainty associated with the genetic test results. Participants often contextualized their risk by building on the risk associated with genetic test results with family history, variant re-interpretation, and the knowledge that the risks associated with other genes may be higher. Patients generally made the decision they thought was best for them, even though it was more difficult if that decision was not supported by healthcare providers, friends, or family. When faced with uncertain cancer risks and presented with options for medical management, values were weighed against the negatives of each option. Often mental health was prioritized over the negatives associated with ‘removing body parts’.

These findings offer a look into the decisional needs of patients such as accurate knowledge, certainty, decisional support, and attention to personal values. Better understanding of the unmet needs of these patients and working to rectify them through provider education, outreach, counseling strategies to mitigate uncertainty, and research on how to best address and identify each patient's specific decisional needs can contribute to the goal of risk-appropriate and values-based decision-making. With a better understanding of patients' decisional needs, healthcare providers can better advocate for tailored counseling sessions which explore and address specific patient needs to help them make informed, risk-appropriate, and value-based medical management decisions.

INTRODUCTION

Approximately 10% of all cancer occurrences are hereditary and can be attributed to a pathogenic variant in a hereditary cancer gene. Hereditary cancer genes can be broadly categorized as high, moderate, or low risk by the magnitude of increased cancer risk associated with each specific gene. High risk genes such as *BRCA1* and *BRCA2* are well-known, significantly increase the risk of specific cancer sites, and confer a high enough risk to inform clinical management per national guidelines (Slavin et al., 2015). A pathogenic variant in a *BRCA* gene increase a woman's lifetime risk to develop breast cancer from the general population risk of 12% to up to 80%, and from a 2% risk to up to a 40% risk for developing ovarian cancer (Kuchenbaecker et al., 2017). The magnitude of increased cancer risks associated with pathogenic variants in *BRCA1* and *BRCA2* is high enough to recommend surgical options such as a bilateral mastectomy and bilateral salpingo-oophorectomy to reduce the risk of cancer incidence and mortality (Domchek et al., 2010; NCCN, 2019).

The *CHEK2* gene is considered a moderate risk breast cancer gene, increasing a woman's lifetime risk of developing breast cancer from 12% to 40%, which is not considered high enough to warrant risk-reducing bilateral mastectomy (NCCN, 2019). Pathogenic variants in *CHEK2* are also associated with an approximate 12% lifetime risk to develop colon cancer which is between 2-3 times the general population risks (NCCN, 2018). Given the increased cancer risks, the National Comprehensive Cancer Network (NCCN) recommends increased surveillance including annual mammograms and consideration of annual breast MRI in addition to colonoscopies every 5 years beginning at age 40 (NCCN, 2019). Women with a *CHEK2* pathogenic variant, may be

receiving bilateral risk reducing mastectomy which would only be medically appropriate with significant family history or as a consideration for breast cancer treatment (West et al., 2018). Additionally, risks for other *CHEK2* associated cancers (i.e. thyroid cancer, ovarian cancer, prostate cancer, testicular cancer) are unclear and not increased enough to warrant changes to medical management; therefore, current testing and management guidelines do not exist for these particular cancer risks (AlDubayan et al., 2019; Dong et al., 2003; Näslund-Koch, Nordestgaard, & Bojesen, 2016; Robson, 2010). For many patients, discovering a pathogenic variant in *CHEK2* comes with recommendations that may be unclear and posed more as options for how to manage a moderately increased risk for breast cancer. These loose guidelines may leave patients wondering if new cancer risks or recommendations will be established in the future.

Pathogenic variants are one example of the possible test results that can be received through genetic testing. There is also the chance that genetic testing can result in detection of a Variant of Uncertain Significance (VUS) in one of the hereditary cancer genes. The American College of Medical Genetics and Genomics (ACMG) defines VUS as a gene change which the lab is unable to classify as either pathogenic or benign due to limited data (Richards et al., 2015). The ACMG issued standard guidelines for interpretation of sequence variants which state that VUS results should not be used to inform clinical management recommendations because it is unknown whether it confers increased cancer risks (Richards et al., 2015). Additionally, studies have shown that the majority of VUSs detected, are eventually reclassified as benign variants (Welsh et al., 2017). VUSs present an enormous challenge for patients and genetic counselors especially when informing clinical management recommendations is a main motivator for pursuing genetic testing.

The use of multi-gene panels has become increasingly popular practice among genetic counselors. The multi-gene panel approach allows for testing of multiple genes within one test at one set cost; therefore, this approach can be more efficient in identifying hereditary cancer (Slavin et al., 2015). However, with this new approach, there is an increased chance of finding a VUS in a hereditary cancer gene or a pathogenic variant in a moderate risk gene (Cheon, Mozersky, & Cook-Deegan, 2014; Pederson et al., 2018; Slavin et al., 2015; West et al., 2018).

Even though ACMG guidelines recommend that clinical decisions should not be informed by VUS results in any gene, some individuals with a VUS in one of the *BRCA* genes still choose to proceed with a risk reducing mastectomy and oophorectomy and some non-genetics providers have reported providing the same medical management recommendations for *BRCA* VUS and pathogenic carriers (Kurian et al., 2017; Murray, Cerrato, Bennett, & Jarvik, 2011; Welsh et al., 2017). These women may choose to proceed with these irreversible surgeries despite the uninformative genetic test results and this suggests that uncertainty and gaps in knowledge may contribute to medical management decisions that do not align with the national guidelines.

This qualitative study aimed to explore factors that influence medical management decisions for women with a VUS in a *BRCA* gene or a pathogenic variant in *CHEK2*. Semi-structured interviews were conducted to identify why and how women with a *BRCA* VUS or *CHEK2* pathogenic variant make medical management decisions. By exploring their decisional needs, there is potential for opening dialogue between genetic professionals and other healthcare providers about the pieces of information which are most salient to the patient decision-making process and this may inform how pretest and posttest counseling sessions can better meet the identified needs of these women.

METHODS

Participants

Approval from the Institutional Review Board (IRB) was obtained through the two institutions involved in recruiting and conducting the semi-structured interviews. Participants were selected from a cohort of women participating in a cancer registry who were interested in being contacted for future research opportunities. Individuals were ineligible to participate if they received genetic testing that indicated a pathogenic variant in another hereditary cancer gene. Eligible individuals were English speaking adult women who were willing to be contacted for an interview and had a *BRCA* VUS (n=8) or a pathogenic *CHEK2* variant (n=15). Ultimately, 6 women with an identified *BRCA* VUS (2 *BRCA1*, 4 *BRCA2*) and 12 women with *CHEK2* pathogenic variants were available to be interviewed based on the ability to schedule a time to complete the interview that was available for both the participant and the interviewer. The ideal sample size of a qualitative study is dependent upon the richness of the data collected and the research goal; however, beginning with 8-12 interviews has been reported as good start before evaluation for thematic saturation can be assessed (Guest, Bunce, & Johnson, 2016; Tracy, 2013).

Participants were sent an e-mail with four to six options for scheduling the interview based on their reported preferred days and times and asking them to confirm their preferred contact phone number. A reminder email was sent the day before the agreed upon day and time. Participants were then called at the agreed upon day and time at their preferred phone number to complete the interview. Participant characteristics and their breast cancer medical management decisions are summarized in Table A1 using randomly chosen pseudonyms to ensure anonymity and confidentiality.

Data Collection

The exploratory qualitative research design allows the participants to express their experiences and their understanding (Beeson, 1997). A qualitative study design was chosen because it allowed for exploration of why such decisions are being made from the patient's perspective in order to assess if these are truly appropriate and well-informed decisions (Sutton & Austin, 2015). A semi-structured interview guide provides the researcher with a framework to ensure the research question is being addressed while allowing for the complexity of the patient's situation to be explored through open-ended questions (Beeson, 1997). The interview guide used for this study was developed based on the Ottawa Decision Support theoretical framework (ODSF) which aims to discover factors that influence patient decisions about cancer risk management and surveillance options and to identify patient's decisional needs (O'Connor, 2006). The Ottawa Patient Decision Guide (OPDG) applies the framework to explore decisional needs based on four main constructs: knowledge, support, values, and certainty. The ODSF patient guide is based on the foundation of social psychology, decisional analysis conflict, personal values, social support, and self-efficacy principles (O'Connor, 2006). This framework was chosen because it specifically allows for the incorporation of the patient's knowledge, values

and support from others in the decision making model and it was a research interest to explore if the framework would be a true way of explain the decision-making process following genetic testing (O'Connor, Jacobsen, & Stacey, 2002; O'Connor et al., 1998). The use of the OPDG has previously been studied in clinical settings which require a decision to be made about clinical care. The OPDG was found to be an acceptable and effective tool when contemplating a decision and when there is the possibility of including others in the decision-making process (Feenstra, Lawson, Harrison, Boland, & Stacey, 2015). The OPDG has also been used to identify the presence of decisional conflict or examine the salience of support throughout decision making in a clinical setting (Arimori, 2006; Pavličević et al., 2015). The use of this framework will provide a basis to contextualize the many facets to medical decision-making for these individuals.

The semi-structure interview guide used for this study was developed for a larger research effort consisting of multiple aims and therefore was based on two main frameworks: the Integrated Behavioral Model (IBM) and the ODSF. The aim of the present research focused on the use of the ODSF because it allows the exploration of the influences on decision-making rather than focusing on the barriers or facilitators that may affect following through with a chosen course of action which is the main focus of the IBM. Open-ended questions and their more specific probes were developed through the collaboration between five researchers, the majority with a clinical genetics and research background.

Interviews for this aim were conducted by a single researcher and each interview lasted approximately 30 to 60 minutes. Questions asked addressed the patient's feelings toward the genetic test result, the recommendations provided by health care providers, the perceived pros and cons about each option, which factors made it easy or difficult to follow through with those recommendations and ultimately how they have chosen to follow-up with their medical management. Specific questions asked related to this study aim are summarized in Table A2.

Procedures

Recruitment of participants occurred through a cancer registry. Participants with a confirmed *BRCA* VUS or *CHEK2* pathogenic variant who previously completed a survey aimed at identifying the facilitators and barriers to medical management were asked to indicate whether they would consent to be contacted for an interview to expand on the medical management process following genetic testing.

All 18 patients who met eligibility requirements and were contacted to participate in the semi-structured interviews were willing and able to be interviewed for the purposes of this study. All interviews were conducted over the phone due to the fact that the participants interviewed were located in seven different states and because this allowed for flexibility when scheduling the interviews. Before recording commenced, verbal consent was confirmed and participants agreed to have the interview audio recorded. Verbatim transcripts of these interviews were completed by a professional transcription service and personal identifiers were removed.

Data Analysis

Coding of qualitative data allows researchers to explore the narratives presented by participants and identify common themes and influences presented by the participants (Sutton & Austin, 2015). The primary researcher for this portion of the study conducted the interviews,

read over the transcripts, and listened to the interview recordings while reflecting on themes expressed through the data using R Qualitative Data Analysis software was used to code the transcripts based on previously defined a priori codes that were created with input from two other researchers using the main four constructs from the OPDG. Additional sub-codes were created by the primary researcher throughout the coding process to help capture participant perspectives and decisional needs as themes emerged. Iterative analysis was used to combine recent literature highlighting patient's risk tolerance and patient values as considerations in the decision-making process and ODSF theoretical framework constructs to examine the codes, add emerging codes, and identify existing themes (Tracy, 2013; West et al., 2018). For example, knowledge of risks and benefits was an established code but throughout the analysis process, seeking knowledge and inaccurate knowledge were added as codes. Support codes originally included whether support was given or received. Throughout the interview and coding processes, codes were altered to capture whether support was received from close relatives or loved ones, providers, or support groups. Iterative analysis allowed the primary researcher to identify emergent themes while reflecting on the data collected while framing it in the context of existing literature and chosen ODSF theory (Sutton & Austin, 2015; Tracy, 2013).

RESULTS

Reflection upon the data gathered through iterative analysis showed how the four constructs were interwoven together within the data. Often, uncertainty led to knowledge seeking and decisions were typically easier to make when patients' personal values were supported by family, friends, and healthcare providers. In some cases patients sought out information or providers that supported their personal values. The following themes related to influences on the decision-making process were identified: contextualization of risk, family and friend support, healthcare provider support or lack thereof, self-advocacy, and weighing values. These themes are expanded upon below and supported through illustrative quotes.

Knowledge and Uncertainty

Contextualization of Risk

For this study, the types of knowledge of primary interest included any facet of the patients' understanding that helped inform their risk perception and medical management decisions. Certainty was expressed primarily as uncertainty regarding future cancer risks including types of cancers and the respective level of risk for each type. Frequently, knowledge and uncertainty were interwoven in the apparent thought process of these participants as they sought to contextualize their risks. Uncertainties lead several patients to seek knowledge to supplement their understanding of their cancer risks and options. The following examples highlight this theme.

All *BRCA* VUS carriers were able to describe the true meaning of a VUS and articulate how it is unknown whether a VUS increases cancer risk. However, they still used other contextual information, such as family history, in addition to their potential genetic risk, to build their own understanding and perception of their personal risk to develop cancer. Meredith used the information that her *BRCA2* VUS was inherited from her father to help inform her cancer risk perception and this ultimately influenced her decision to remain with breast cancer surveillance rather than electing to have a mastectomy. Unfortunately, Meredith's mother was not able to be genetically tested due to previously having lost her battle with breast cancer. Meredith expressed that if it was found that her father did not carry the *BRCA2* VUS and then presumably she inherited the *BRCA2* VUS from her mother, she would have considered surgical preventative measures to reduce her risk of developing breast cancer. When asked about her reaction to receiving the *BRCA2* VUS result, she said:

[The genetic counselor] explained that it [the *BRCA2* VUS] either came from my mom's side or my dad's side, so they wanted to have my dad tested because my mom is no longer living, which we ended up doing and the significant variant came from his side so it wasn't as much of a concern, which made me feel better. (Meredith, 36, *BRCA2* VUS)

Even though Meredith had previously correctly defined a VUS, she was still referring to her VUS as a 'significant variant'. However, knowing it was inherited from the side of her family with no breast cancer diagnoses was comforting for her and provided clarity in her decision making.

In some cases, when a VUS is received, a healthcare provider may be able to re-interpret the variant by reviewing literature, looking at the location of the variant within the gene, and hypothesizing on how the change might affect the protein function. Christina was a unique case

because she received a re-interpretation of her *BRCA2* VUS from a nearby cancer center's genetics team which performed further research making them more suspicious that her VUS was a disease-causing variant. Christina was retested seven years after her initial testing and re-interpretation and the same variant was still classified as a VUS; however, she held on to the unofficial, unconfirmed re-interpretation. This information, her family history, and her preconception of her cancer risk contributed to her choosing to remove her breasts and her ovaries prophylactically. Of note, from the interview, it appeared that she did not have a family history of ovarian cancer. Christina explains the moment she was informed of her re-interpretation and how that moment resonated with her preconceived risk perception:

Once that I knew that I had a VUS, or the variant, my antenna went up when I found that out from the initial results that I got from my genetic counselor in [my hometown], so that had my attention. When I got the results back from [cancer center in another town], when they explained to me what the results meant, I knew what was happening. I just had this intuitive sense that fate had caught up with me...At one point, when we were talking, I said to the doctor, I said, "Are we putting prophylactic double mastectomy on the table?" And [my surgeon] said, "Yes we are." That was the between the eyeballs moment when I really grasped the gravity of my situation. (Christina, 67, *BRCA2* VUS)

CHEK2 pathogenic carriers also used family history in developing perceptions of risk and seemed to understand how that may factor in to decision making about cancer management. Emma explained her understanding of how recommendations for medical management based on a *CHEK2* pathogenic variant should not be based solely on the results of her genetic testing:

I think it's harder to believe those guidelines are set in stone right there...knowing that there is some, probably, flexibility in those based on own family history and what your own history is as well. (Emma, 35, *CHEK2* pathogenic)

Erica shared how her strong family history of cancer had become a bit of a joke within her family as no one lived past the age of 75 due to cancer. She had always attributed this to behavioral factors such as drinking or smoking and had become a self-proclaimed 'health-nut' to help her chances of not developing cancer. However, learning of her *CHEK2* pathogenic variant changed her perception of her personal risk to develop cancer:

I don't think it [the genetic test results] has lessened any uncertainty but I think it has given a scope to the uncertainty. Like instead of just thinking, 'Gosh, did those people just live crappy?' ... were they just smokers and drinkers? Yes, they were. Was it that they had a gene problem? Probably it was both. It puts a scope to it, there's certainty to the uncertainty. (Erica, 43, *CHEK2* pathogenic)

Erica did decide to proceed with prophylactic bilateral mastectomy for breast cancer risk management based on how her genetic risk changed her perception of possibly developing cancer in the future and also changed her belief that her family's risk may not be solely explained by their lifestyle choices.

CHEK2 pathogenic carriers were also faced with uncertainty regarding which cancers they were at risk for based on their genetic test results other than the established risks for breast and colon cancer and this often led them to seek information from other *CHEK2* pathogenic carriers or their own research. Participants gathered information about other cancer risks after joining social media support groups and meeting other *CHEK2* pathogenic carriers with significant personal and family histories. Some participants used this information to move

forward with other preventative measures such as a bilateral oophorectomy and thyroid ultrasounds or biopsies even though these cancer risks are not established by research or included in the national guidelines. Emma reflected on how she has applied concerns of thyroid cancer risks associated with *CHEK2* pathogenic variants to her own history with thyroid issues:

A while ago, I did have thyroid nodules come up in something well before I knew I had *CHEK2*, and when they did find out I had those, since the thyroid cancer is still being investigated, they do recommend that I do that every few years just because I do have the nodules and last time I checked they hadn't changed, so I think I'm due next year to do another ultrasound with that. (Emma, 35, *CHEK2* pathogenic)

Even though the association between *CHEK2* and thyroid cancer risks has not been proven, Emma is still reflecting on her thyroid surveillance in the context of her genetic cancer risks. When asked how the uncertainty associated with *CHEK2* possibly influenced the decision-making process, Emma responded:

There is a lot of conflicting research out there right now, just based on it. It's not as well-researched as the *BRCA* mutation. I think there is a lot of conflicting information about follow-up care, what the recommendation actually is. I'm on a [social media] *CHEK2* board, so everyone has very different information coming from their doctors and it's interesting to see what the differentiating information is, so I think that's part of it. (Emma, 35, *CHEK2* pathogenic)

Isobel acknowledged the uncertainty that is associated with *CHEK2* pathogenic test results and explains how she handled that by seeking out knowledge through support groups and her own research to better understand the risks:

[I felt] uncertainty, yes, but then I joined a *CHEK2* [social media] support group and did a lot of research on the *CHEK2* and fit what I could fit and then just had to get ... once I knew what the *CHEK2* was going to potentially involve, I was like “well I’m not going to take my thyroid out” so I just get ultrasounds every 6 months. When I found out there was some risk for ovarian cancer, I was able to convince an OBGYN oncologist to do my... I kinda had to work around some rules but I got a hysterectomy [oophorectomy]. And I get an annual colonoscopy and I get an annual or every six-month skin check. You know I can’t take out my colon and I can’t remove my skin. I already got a mastectomy [for treatment] and a hysterectomy [oophorectomy] and I watch the thyroid. That’s really all I can do and those are the top cancers related to the *CHEK2*. (Isobel, 50, *CHEK2* pathogenic)

Although most of these cancer risks are not established to be associated with *CHEK2*, Isobel finds comfort in knowing that she is ahead of the research in case over time these risks emerge as significant.

For Miranda, who is a *CHEK2* pathogenic carrier, learning of her test result motivated actions she perceived as able to help prevent developing another cancer diagnosis. Even though *CHEK2* is not associated with an increased risk of skin cancer, this participant cited living in a location where there is a lot sun exposure as well as an inaccurate belief that *CHEK2* will increase this risk as being the reasons for cancer monitoring:

It [the *CHEK2* pathogenic variant] has made me a little more proactive in getting tested as far as doing colonoscopies, skin testing, that sort of thing. Which again, is a good thing. (Miranda, 68, *CHEK2* pathogenic)

The knowledge that the breast cancer risks were not as high as those associated with a *BRCA* pathogenic variant was another common piece of information used among *CHEK2* pathogenic carriers to contextualize their cancer risk. Monica, who is unaffected but does have a family history of breast cancer described feeling relief when she heard that she does not carry a pathogenic *BRCA* variant by saying, “Not that I was relieved, but in a way, I was relieved that it wasn't *BRCA*”. For Phoebe, who has a personal and family history of breast cancer, she was almost dismissive of the actual result in the beginning and was focused on learning her *BRCA* status:

I actually was expecting to hear worse things, and at the time *CHEK2* not much was known about it. So when I questioned them it was kind of vague. They told me that there were a couple physical areas I had to watch out for, but I actually was more interested to find out if I had the *BRCA* gene or not. (Phoebe, 70, *CHEK2* pathogenic)

It was apparent that the risks associated with *BRCA* pathogenic variants were more well known for these individuals and the knowledge that they had a pathogenic variant in one of these moderate-risk genes seemed to ease their minds about their cancer risks and both ultimately chose to remain with breast cancer surveillance and Phoebe opting to treat her breast cancer with a lumpectomy.

Incorporating knowledge and uncertainty in order to contextualize risk seemed to play an important role in the decision-making process. Common factors that were used to build the context around this uncertain risk included family history, personal history, associations made between the gene and increased risks for various cancers (whether or not these risks have been scientifically verified as a true associations of high enough magnitude to warrant preventive actions), the knowledge that pathogenic variants in other genes would have caused even higher

risks, and in one unique case, a personalized interpretation of the test result. Actions taken based on their contextualization of risk were usually perceived as beneficial by the patient. However, intolerance for uncertainty may also be contributing to decisions, such as prophylactic mastectomy or oophorectomy, which may be unwarranted based on the level of cancer risk.

Support and Values

Family and Friend support

For some participants, values and support influenced decision-making in tandem. Support from family and friends provided reassurance to make value-based decisions about cancer screening. One participant, Miranda, was found to be *CHEK2* positive after her daughter was diagnosed with premenopausal breast cancer. Miranda's mother and daughter were both affected by breast cancer, but Miranda remains cancer free even though she has the same *CHEK2* pathogenic variant as her daughter. Miranda chose breast and colon cancer surveillance through the help of her daughter's example. She reported that going through the screenings together with her daughter was a motivating factor to keep up with the numerous doctor appointments:

My daughter, I think, showed a lot of courage in being proactive, and she is, to this day, and encourages us to be. But it's easy to ... It's easy to get in a rut and say, oh, I'll do that tomorrow. Procrastinate. So she's been a good example for us. Our daughter gives us a little impetus about, you know, you're retired but, get up and take care of yourselves and make sure you get tested. (Miranda, 68, *CHEK2* pathogenic)

Erica found decisional support by seeking information from other women faced with a similar decision, helping her gain perspective to make her own personalized decisions:

That [talking to others] was really useful to me, just to get it first person... talking to persons, like friends of friends, stuff like that was very useful. Not because I'm the same

as those people and not because I would process things the same, but just to understand what the physical reality of something is like, or what they found hard or what they found easy. Stuff like that. (Erica, 43, *CHEK2* pathogenic)

After consulting other women and considering her own values, she decided to proceed with a prophylactic double mastectomy even though this is not what is recommended based solely on her genetic risk to develop breast cancer. Notably, before genetic testing she had attributed her family history of cancer to their behavioral risk factors which she did not adopt. Thus she may have felt her healthier lifestyle choices were protecting her until she discovered that the cancers in her family were probably not entirely related to lifestyle.

Healthcare Provider Support or Lack Thereof

Receiving care from trusted and experienced healthcare providers was a common factor contributing to participants' medical decision making. They often reported following through with their healthcare provider's management plans because they were confident in their healthcare provider's recommendations which seemed to fit the participants' understanding of the associated cancer risks in the context of their genetic test results. Maggie, who completed the interview with the help of her husband, a physician himself, expressed how they relied on her healthcare provider's recommendations:

We have really good doctors, we go to [the local cancer center] for everything. And we just trust them that they're gonna tell us [if there are changes or updates associated with *CHEK2*]. And I think the fact that we knew we had good qualified doctors made the difference. (Maggie, 67, *BRCA2 VUS*)

Once Erica had made her decision to have a prophylactic bilateral mastectomy, the support and acceptance she received from her healthcare providers helped her follow through with this medical management decision that may have seemed unnecessary or unorthodox to the medical community based solely on her test results:

No one said, "Don't do it." No one said this is medically contraindicated. No one was like, "You're completely ..." It wasn't that it was medically contraindicated or that I was doing something completely unnecessary, it was just on the scope of things that were possible, I had picked an option that they were like, "You don't have to do that." (Erica, 43, *CHEK2* pathogenic)

As Erica reports, with her genetic risk, prophylactic surgery was not entirely recommended but it was the direction Erica wanted go with her medical management and the fact that her healthcare providers supported her by not trying to discourage her seemed to help her accept her decision.

On the contrary, some participants reported not receiving decisional support. Some even expressed feelings of stigma related to their choice. Lack of support from providers to follow through with the medical management the patient preferred or feelings of judgment from close friends and family members was never reported as deterring the participants from making the decisions they preferred. However, these circumstances were reflected upon as a factor that made decision making more difficult. This was seen primarily for patients who made surgical and especially prophylactic surgical decisions. Christina felt the genetics infrastructure failed to provide guidance or emotional support for her and her unique story:

Because I was prophylactic, there really didn't seem to be a place for me. I couldn't exactly call myself a survivor because I had not had breast cancer, and I knew I was a previvor. But, there really wasn't, to my knowledge, a group at [the cancer center]. There

wasn't anyone that they put me in touch with who had been through the process themselves...You're kind of out there in left field. You can't rely on the doctors and the nurses to help you through this because, God love them, you're just another patient, really. So there isn't an emotional place for previvors. (Christina, 67, *BRCA2* VUS)

The re-interpretation of her *BRCA2* VUS placed her in a unique and isolating situation wishing she had some emotional support as she implemented this important decision.

Isobel, a *CHEK2* pathogenic carrier, reported shopping around for a healthcare provider who would perform the medical management that she desired. She found and convinced health care providers to follow her with annual colonoscopies, thyroid ultrasounds every six months, skin checks every six months, a bilateral mastectomy which was partially prophylactic, and even a prophylactic bilateral oophorectomy. This participant even disclosed in the interview that she feigned symptoms to get the care she valued.

I am very diligent and passionate about my care. One of the docs was tired of doing my thyroid ultrasounds every year and wanted to switch to something else so I just found a different doctor who would do it every six months or every year like I want. The GI doc with my annual colonoscopy, which I know there are risks for even just the colonoscopy, but he knows me well enough that if he doesn't do mine that I'll just complain of rectal bleeding or just go find a different GI. (Isobel, 50, *CHEK2* pathogenic)

Isobel is passionate about her care and therefore if she does not find support in her current healthcare provider, she will go and find someone who will support her in her medical management decisions.

Another participant remarked that she immediately felt discouraged with the medical plan laid out for her by her oncologist when they dismissed her *CHEK2* pathogenic result. Emma is an unaffected 35-year-old with a family history of cancer. While not receiving different advice from her second healthcare provider, she felt her first healthcare provider did not treat in a manner she respected as illustrated in her quote.

She [previous provider] was very just dismissive of it. It's just like, "Well, environmental factors can give you the same risk," ... That was my first doctor experience after going to the genetic counselor, and that's not exactly what you want a bedside manner to be, so that's why I had switched doctors. I wouldn't say the doctor at [the University] has tons of different things to say. I'd say the information is exactly the same, but the way it's presented and the way, how she handles things, and the way she interacts with me is a much more positive experience than the one at [the previous clinic]. (Emma, 35, *CHEK2* pathogenic)

Emma expressed that she was more likely to take the advice and recommendations from this second healthcare provider based solely on their support and the respect they showed Emma even though they did not provide her with any new information.

Ellis also reported moving on to a second oncologist when her original oncologist was not listening to her medical management preferences and her concerns about managing her risk with medicine.

The first oncologist, she recommended the Tamoxifen. And she recommended the diet. And I saw her every three months to begin with. But I just felt like she was more pushing the medication instead of listening to what it was doing to me physically and mentally. (Ellis, 45, *CHEK2* pathogenic)

Tamoxifen is a common preventative recommendation for *CHEK2* pathogenic carriers based on the high prevalence of estrogen receptor positive breast cancer with *CHEK2* carriers, however, Ellis was adamant that medication gave her strong negative side effects and felt dismissed when she voiced these concerns to her healthcare provider. She eventually sought a new healthcare provider who maintained the surveillance recommendation without pushing Tamoxifen.

Self-Advocacy

Many of the prior quotes also illustrate that when faced with management options and the uncertainty of cancer risks, often participants vocalized their ability to advocate for the care and medical support they desired and felt was necessary. Emma reflected on how she had to become her own self advocate when she started experiencing gastrointestinal issues and how she feels this experience can help other *CHEK2* pathogenic carriers receive value-based medical management:

I think being your own advocate...I think it's just making sure people are their own advocate, if they feel like something's wrong or they feel like they need additional testing, to make sure that you push doctors for that and I think that was part of my thing with the colonoscopy. My stomach's been messed up for years and I want to make sure that I don't go in at 40 or 45 and find out I have Stage III colon cancer...I'd rather push ahead of time...Now I know that there's a baseline at 33, as supposed to waiting until I was 40, 45 and always having that in the back of my head. (Emma, 35, *CHEK2* pathogenic)

Emma made it clear to her healthcare providers that she desired to be followed early and more frequently for colon cancer.

Isobel has also taken on self-advocacy to ensure that she is doing everything she can to detect cancer early or prevent it from developing. As she states it, “we are the research”, and she goes on to explain why she felt she needed to advocate for the care she desired:

You know I am the research. The research showed...some of the geneticists weren't even acknowledging [the risks] for breast cancer and wouldn't indicate a prophylactic mastectomy. Nowadays it is getting more and more prevalent that it is happening, but I was not going to wait until I was on a research paper in five years with multiple cancers to do what I felt needed to be done to prevent further cancer...I am a very passionate advocate; I am totally out of the closet. (Isobel, 50, *CHEK2* pathogenic)

Isobel believes that her medical management choices were justified if she remains part of the research on her terms. She expressed not wanting to be the research by having multiple cancer diagnoses. Instead, she wishes to participate in research similar to this study where she can advocate for the medical management care that she believes in necessary.

Weighing Values

Interestingly, but not unexpectedly, medical management decisions were commonly made when one option was perceived to be better than the other even if the selected option was not the conservative or even a medically necessary management path. Some women discussed weighing the value of body parts, especially breasts, in decision-making. One woman, Christina, described her feelings toward her breasts as being turned negative after learning about the re-interpretation of her *BRCA2* VUS and therefore choosing to surgically remove them before cancer could develop.

I think a lot of times women are ... this is going to sound stupid, because we're all attached to our breasts, okay? I think we're all attached to our breasts, they're an external

embodiment of our femininity, and I loved my breasts as much as any woman did, but I couldn't trust them anymore. (Christina, 67, *BRCA2* VUS)

Similarly, another participant expressed indifference towards her breasts and acknowledged that this may be a difficult decision to make when women perceive their breasts and ovaries as adding value to their femininity. However, since she never valued her body parts, she felt it would relieve her stress and anxiety to remove them rather than to go back every six months to a breast cancer screening:

Finally, I decided, "You know what, I've never thought my breasts made me attractive or unattractive. I don't care about them" ... They're just creating stress. I don't need them, I don't really want them now. I didn't need them before and now it was like I would be happier without them. I thought, "You know what? That's what I'm going to do." I'm just going to get rid of them and be happier without them. I think if I were a person who had valued my breasts more, then I probably wouldn't have made this decision, or if I was a person who was sort of a calmer, more go with the flow kind of person, I probably wouldn't have made this decision. I feel like it suited me, and I felt really happy about that. (Erica, 43, *CHEK2* pathogenic)

Erica was happy about her decision to have a prophylactic bilateral mastectomy because she no longer felt she needed to stress over the screening and the increased possibility to develop breast cancer one day. Erica valued having or regaining a sense of control over her health so adamantly that she even considered doing nothing over routinely going back for breast cancer screenings and having to worry about cancer:

One of my options that I didn't discuss with anybody but that I considered is doing nothing. I considered that as an option, just because I felt like I am very type A, I am a person who worries about things and I recognize that if I get into a situation where I'm always thinking about something and worrying about something, that's just not healthy either. Maybe it doesn't increase my risk of cancer, but it decreases my quality of life by quite a bit and I'm prone to do that. That's just my psychological makeup is that I'm a controlling person and I worry about things. (Erica, 43, *CHEK2* pathogenic)

Ultimately, she concluded that a prophylactic bilateral mastectomy would be a way to prevent breast cancer and minimize her anxiety and stress.

Ellis described how it was important for her to regain control of her life with her medical management decisions. She described weighing the negatives and consequences of preventative surgery against her desire to stay alive and be present for her family and her son.

Why I chose to do it [prophylactic double mastectomy] is I wanted to live and see my kids graduate, and I was doing it to prolong my ... not to wait and see or do all ... at least get the major, major worry out of the way. (Ellis, 45, *CHEK2* pathogenic)

She felt the worry associated with not doing the surgery would have taken away from her presence in her family's lives and therefore, surgery became the best choice for her.

Women's descriptions of their decision-making process support the idea that they often weigh their values to determine which risk management or cancer surveillance strategy is best aligned with their values and they also determine whether family, friends and providers will support their preferred options. Weighing values is a complex theme because each person will place different value to each option which varying weight. Commonly the weighing was described to be between living with anxiety, stress, or worry versus enduring a surgery. Patients were prone to value their mental health and psychological needs above any physical harm that would result from surgery.

DISCUSSION

This study identified themes related to decision-making about cancer risk management and surveillance options for women with uncertain cancer risks following the identification of either a *BRCA* VUS or pathogenic variant in a moderate-risk breast cancer gene called *CHEK2*. Themes of support, self-advocacy, and values in decision-making were interlaced with themes of uncertainty and knowledge. If risks were clearer and outcomes were more certain or if recommendations were not loosely given as considerations, the decision making process may have been characterized differently and been more straightforward. As it is, uncertainty appears to have caused this group of women to use the limited (and sometimes inaccurate) understanding they could glean from their genetic test result, family history, healthcare providers, online support organizations and other informational sources to construct their perceived cancer risks. In addition to seeking information, many sought support or motivation from friends, family, and healthcare providers in order to help make or justify their desired cancer risk management or surveillance decisions. Women also reported weighing the pros and cons of each option against their level of worry and desire to eliminate worry or take back control over their lives. Those women who expressed significant worry often elected surgical options in order to circumvent the need to think about cancer every time they underwent cancer surveillance through MRI or mammography. Other women who recognized their risks were lower than for people with pathogenic mutations in high penetrance genes such as *BRCA1* or *BRCA2* or those who trusted their healthcare provider and cancer center completely were able to release some of their worries and pursue ongoing cancer surveillance.

Study Strengths and Limitations

This is the first study to our knowledge to report qualitative data highlighting experiences in decision making related to cancer risk management and surveillance for women with *BRCA* VUS results and *CHEK2* pathogenic variants. The novelty of the study findings and efforts taken to enhance study method quality strengthen the study and these should be considered alongside the study limitations. For example, credibility was established through presentation of illustrative quotes to support the identified themes and review of data with other researchers. Nevertheless, having a second data coder could further enhance credibility by establishing inter-coder reliability (Sutton & Austin, 2015). Another limitation is that theoretical saturation was not met because interviews continued to contribute new findings to a category (Glaser & Strauss, 1967). Nevertheless, several useful and consistent themes were characterized. Additionally, the sample of women participating in this study lacked ethnic, racial, and socioeconomic diversity and therefore any cultural differences that may exist within a value-based decision-making process could not be identified.

The OPDG may not be the best, most comprehensive framework to use when evaluating the decision-making process for *BRCA* VUS and *CHEK2* pathogenic carriers. Additional interview data exists that were not reported here because they were not captured using codes related to the OPDG. This additional data can and should be coded and evaluated because it will highlight some of the barriers and facilitators to implementing their medical management decisions. Such barriers include financial burden, transportation, and scheduling constraints which did not fit cleanly into this framework and were outside the scope of this thesis, but highlight a major potential area of exploration for future research.

Finally, given that qualitative research calls on the participants to reflect on past experiences, many of the participants involved in the present study had to take pause and remember back to when they received their genetic test results and made some of these decisions. Reflection by both the participant and the researcher, introduces the possibility of bias and subjectivity into the research (Sutton & Austin, 2015). Research looking at real-time decision making may therefore identify additional or different salient themes than the current study which was focused on retrospection about previous decisions and behaviors.

Practice Implications

Despite these study limitations, results may help facilitate discussion among the genetic counseling and medical community regarding the salience of a patient's personal values and contextualization of risk when deciding on medical management following genetic testing when results may carry some uncertainty. This study highlights the importance of tailored medical care. This should begin with using the patient's whole history, including their genetic risk, to inform their personal cancer risks and continue through to the consideration of their mental health status.

There exists the concern that a proportion of these women are choosing irreversible medical management decisions which are not aligned with the national recommendation guidelines (Kurian et al., 2017; Murray et al., 2011; Welsh et al., 2017; West et al., 2018). Although some healthcare providers and researchers have considered that such decisions may be based on personal reasons and in the context of a strong personal and/or family history of cancer they may sometimes be appropriate, there have been no studies which explored why these medical management decisions are being made from the patient perspective. The present study

shed light on the decision-making process of the patient and may help ignite conversations among healthcare providers to ensure quality medical management decisions are being made.

Previous studies have established that cancer risk should be informed by genetic test results, family history and other risk factors (West et al., 2018). The present study shows that participants are using these factors and, in addition, they are using other factors, such as fear, worry and uncertainty, to inform their medical management decisions. Whether or not patients are adequately guided as to how best to use the supplemental information to understand their cancer risks and make decisions is uncertain and raises concerns that genetic testing may be leading to over treatment in some cases. Due to this concern, we recommend that healthcare providers who are disclosing genetic test results also incorporate a discussion of how the patients contextualize the genetic test result with other information and explore issues of anxiety and uncertainty when discussing medical management. The goal will be to ensure that other options for dealing with anxiety and worry have been explored before the patient seeks out surgical interventions that may not be aligned with actual cancer risks.

Research has shown that women who already struggle with some mental health concerns such as anxiety, stress, and depression may be at a higher risk to experience the psychological burden of genetic testing and a cancer diagnosis. Researchers have noted that receiving an uncertain or inconclusive result experience similar levels of stress as women with a high genetic risk to develop cancer (Lerman, Croyle, Tercyak, & Hamann, 2002; Vadaparampil, Wey, & Kinney, 2004). Some of the women in the present study expressed making their medical management decisions based on the value they placed on their mental health. The choice they made was largely influenced by their desire to minimize or control the stress and anxiety related to their genetic risk to develop cancer. A medical management choice which would have been

viewed as unnecessary or perhaps even contraindicated by the medical community was chosen because the patient prioritized their mental health over the consequences of preventative surgery. These findings pose the question of when should healthcare providers prioritize their patient's mental health and in turn support the patient in a medical decision that is not absolutely necessary from the sole standpoint of reducing cancer risks. Additionally, questions remain as to when the psychological burden of decision making may go beyond the scope of practice for genetic counselors and other healthcare providers leading to the need for a mental health professional to assist in the process.

The present study also highlights the important influence healthcare providers may have in the decision making process and that trust and good communication between the patient and healthcare provider may sometimes alleviate worry and motivate ongoing cancer surveillance. If the patient felt that their needs were not being addressed or that they were not being taken seriously, they frequently sought out the care they desired from other healthcare providers. Therefore, another consideration for healthcare providers could be to explore ways to establish patient trust and confidence especially when uncertainty is necessary to communicate. In situations where confidence in their healthcare provider was attained, the patient was comfortable with following the recommendations which the healthcare provider felt were most appropriate for the patient. It would be important to investigate strategies to explain the uncertainty associated with a VUS or a *CHEK2* pathogenic result without losing the patient's confidence.

Research Recommendations

Expansion of this study is indicated to incorporate a larger sample size in the hopes of including more diversity to account for different cultural perspectives and reaching theoretical saturation whereby no new themes are emerging (Glaser & Strauss, 1967). It would also be imperative to investigate coping strategies to assist these women with the existing uncertainty that is associated with these particular test results and to reduce the associated worry and anxiety that goes along with cancer surveillance strategies such as breast MRI and mammography. If efficient and effective strategies are identified, this may save women from making drastic and irreversible medical management decisions based on anxiety or desire to be in control of their health. As always, further research to clarify the associated cancer risks with a *CHEK2* pathogenic variant is encouraged and may also help to mitigate the uncertainty and concerns about risks for other less common cancers. In that same pursuit, communication and research among genetic testing laboratories is desired to better clarify and reclassify VUS results to help alleviate some of the uncertainty.

CONCLUSIONS

Through this exploratory qualitative study, important influences on value-based decisions regarding cancer risk management and surveillance options was highlighted extensively for both *BRCA* VUS and *CHEK2* pathogenic carriers. An individual's risk to develop cancer, and even their perception of their risk, is informed by more than just genetic test results. Healthcare provider support and acknowledgement of the patient's whole history is vital to gain the patient's confidence and adherence to risk-appropriate, national practice recommendations. Dismissal of a part of the patient's history which they find important may cause them to seek out different care from other providers. The psychological burden of decision making and a predisposition to develop cancer is salient to the patient and as so, warrants further attention by healthcare providers in this context. This study did not capture data from a diverse population nor was theoretical saturation attained. However, it presents a foundation for further research into the decision-making process through the use of more comprehensive frameworks and among populations not represented in this study.

REFERENCES

- AlDubayan, S. H., Pyle, L. C., Gamulin, M., Kulis, T., Moore, N. D., Taylor-Weiner, A., ...
Lessel, D. (2019). Association of Inherited Pathogenic Variants in Checkpoint Kinase 2 (CHEK2) With Susceptibility to Testicular Germ Cell Tumors. *JAMA Oncology*.
<https://doi.org/10.1001/jamaoncol.2018.6477>
- Arimori, N. (2006). Randomized controlled trial of decision aids for women considering prenatal testing: The effect of the Ottawa Personal Decision Guide on decisional conflict. *Japan Journal of Nursing Science*, 3(2), 119–130. <https://doi.org/10.1111/j.1742-7924.2006.00062.x>
- Beeson, D. (1997). Nuance, Complexity, and Context: Qualitative Methods in Genetic Counseling Research. *Journal of Genetic Counseling*, 6(1), 21–43.
<https://doi.org/10.1023/A:1025659701805>
- Cheon, J. Y., Mozersky, J., & Cook-Deegan, R. (2014). Variants of uncertain significance in BRCA : a harbinger of ethical and policy issues to come? *Genome Medicine*, 6(12), 121.
<https://doi.org/10.1186/s13073-014-0121-3>
- Domchek, S. M., Friebel, T. M., Singer, C. F., Evans, D. G., Lynch, H. T., Isaacs, C., ...
Rebbeck, T. R. (2010). Association of Risk-Reducing Surgery in BRCA1 or BRCA2 Mutation Carriers With Cancer Risk and Mortality. *JAMA*, 304(9), 967–975.
<https://doi.org/10.1001/jama.2010.1237>

- Dong, X., Wang, L., Taniguchi, K., Wang, X., Cunningham, J. M., McDonnell, S. K., ... Liu, W. (2003). Mutations in CHEK2 Associated with Prostate Cancer Risk. *The American Journal of Human Genetics*, 72(2), 270–280. <https://doi.org/10.1086/346094>
- Feenstra, B., Lawson, M. L., Harrison, D., Boland, L., & Stacey, D. (2015). Decision coaching using the Ottawa family decision guide with parents and their children: a field testing study. *BMC Medical Informatics and Decision Making*, 15(1), 5. <https://doi.org/10.1186/s12911-014-0126-2>
- Glaser B.G., & Strauss, A.L. (1967). The discovery of grounded theory. New York, NY: Aldine de Gruyter.
- Guest, G., Bunce, A., & Johnson, L. (2006) How many interviews are enough? *Fields Methods*, 18(1), 29-82.
- Kuchenbaecker, K. B., Hopper, J. L., Barnes, D. R., Phillips, K.-A., Mooij, T. M., Roos-Blom, M.-J., ... Olsson, H. (2017). Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*, 317(23), 2402–2416. <https://doi.org/10.1001/jama.2017.7112>
- Kurian, A. W., Li, Y., Hamilton, A. S., Ward, K. C., Hawley, S. T., Morrow, M., ... Katz, S. J. (2017). Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer. *Journal of Clinical Oncology*, 35(20), 2232–2239. <https://doi.org/10.1200/JCO.2016.71.6480>
- Lerman, C., Croyle, R. T., Tercyak, K. P., & Hamann, H. (2002). Genetic testing: Psychological aspects and implications. *Journal of Consulting and Clinical Psychology*, 70(3), 784–797. <https://doi.org/10.1037/0022-006X.70.3.784>

- Murray, M. L., Cerrato, F., Bennett, R. L., & Jarvik, G. P. (2011). Follow-up of carriers of BRCA1 and BRCA2 variants of unknown significance: Variant reclassification and surgical decisions: *Genetics in Medicine*, *13*(12), 998–1005.
<https://doi.org/10.1097/GIM.0b013e318226fc15>
- Näslund-Koch, C., Nordestgaard, B. G., & Bojesen, S. E. (2016). Increased Risk for Other Cancers in Addition to Breast Cancer for *CHEK2* *1100delC Heterozygotes Estimated From the Copenhagen General Population Study. *Journal of Clinical Oncology*, *34*(11), 1208–1216. <https://doi.org/10.1200/JCO.2015.63.3594>
- National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian (Version 3.2019).
https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed March 8, 2019.
- National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2018).
https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed March 8, 2019
- O'Connor, A. M., Jacobsen, M. J., & Stacey, D. (2002). An Evidence-Based Approach to Managing Women's Decisional Conflict. *Journal of Obstetric, Gynecologic, & Neonatal Nursing*, *31*(5), 570–581. <https://doi.org/10.1111/j.1552-6909.2002.tb00083.x>
- O'Connor, A. M., Tugwell, P., Wells, G. A., Elmslie, T., Jolly, E., Hollingworth, G., ... Drake, E. (1998). A decision aid for women considering hormone therapy after menopause: decision support framework and evaluation. *Patient Education and Counseling*, *33*(3), 267–279. [https://doi.org/10.1016/S0738-3991\(98\)00026-3](https://doi.org/10.1016/S0738-3991(98)00026-3)

- Pavličević, I., Škrabić, S., Malički, M., Merćep, A. H., Marušić, M., & Marušić, A. (2015). Decisional conflict and vaccine uptake: cross-sectional study of 2012/2013 influenza season in Croatia. *Archives of Medical Science : AMS*, *11*(4), 788–795.
<https://doi.org/10.5114/aoms.2015.53299>
- Pederson, H. J., Gopalakrishnan, D., Noss, R., Yanda, C., Eng, C., & Grobmyer, S. R. (2018). Impact of Multigene Panel Testing on Surgical Decision Making in Breast Cancer Patients. *Journal of the American College of Surgeons*, *226*(4), 560–565.
<https://doi.org/10.1016/j.jamcollsurg.2017.12.037>
- Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., ... Rehm, H. L. (2015). Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, *17*(5), 405–424.
<https://doi.org/10.1038/gim.2015.30>
- Robson, M. (2010). CHEK2, breast cancer, and the understanding of clinical utility. *Clinical Genetics*, *78*(1), 8–10. <https://doi.org/10.1111/j.1399-0004.2010.01444.x>
- Slavin, T. P., Niell-Swiler, M., Solomon, I., Nehoray, B., Rybak, C., Blazer, K. R., & Weitzel, J. N. (2015). Clinical Application of Multigene Panels: Challenges of Next-Generation Counseling and Cancer Risk Management. *Frontiers in Oncology*, *5*.
<https://doi.org/10.3389/fonc.2015.00208>
- Sutton, J., & Austin, Z. (2015). Qualitative Research: Data Collection, Analysis, and Management. *The Canadian Journal of Hospital Pharmacy*, *68*(3), 226–231.

- Tracy, S.J. (2013). *Qualitative research methods: Collecting evidence, crafting analysis, communicating impact*. Chichester, West Sussex, UK: John Wiley & Sons.
- Vadaparampil, S. T., Wey, J. P., & Kinney, A. Y. (2004). Psychosocial aspects of genetic counseling and testing. *Seminars in Oncology Nursing*, *20*(3), 186–195.
<https://doi.org/10.1053/j.soncn.2004.04.005>
- Welsh, J. L., Hoskin, T. L., Day, C. N., Thomas, A. S., Cogswell, J. A., Couch, F. J., & Boughiey, J. C. (2017). Clinical Decision-Making in Patients with Variant of Uncertain Significance in *BRCA1* or *BRCA2* Genes. *Annals of Surgical Oncology*, *24*(10), 3067–3072. <https://doi.org/10.1245/s10434-017-5959-3>
- West, A. H., Blazer, K. R., Stoll, J., Jones, M., Weipert, C. M., Nielsen, S. M., ... Olopade, O. I. (2018). Clinical interpretation of pathogenic ATM and CHEK2 variants on multigene panel tests: navigating moderate risk. *Familial Cancer*, *17*(4), 495–505.
<https://doi.org/10.1007/s10689-018-0070-x>

APPENDICES

Appendix A: Tables

Table A1. Participant Characteristics

Pseudonym	Age	Gene	Result	Race & Ethnicity	Personal History of Cancer	FDR with cancer	Breast Cancer Surgery	Mammogram in 2017/2018	Breast MRI in 2017/2018
Meredith	36	<i>BRCA2</i>	VUS	NHW	None	Yes	No Surgery	Yes	No
Christina	67	<i>BRCA2</i>	VUS	NHW	None	Yes	Prophylactic bilateral mastectomy & oophorectomy	No	No
Lexie	47	<i>BRCA1</i>	VUS	Asian	Breast	No	Unilateral Mastectomy	Yes	Yes
Joanne	50	<i>BRCA2</i>	VUS	NHW	Breast. Skin	Yes	Bilateral mastectomy (partial prophylactic)	No	No
Maggie	67	<i>BRCA2</i>	VUS	NHW	Thyroid, Colon, Skin	No	No Surgery	Yes	Yes
Amelia	42	<i>BRCA1</i>	VUS	NHW	Colon	Yes	No Surgery	Yes	No
Isobel	50	<i>CHEK2</i>	Pathogenic	NHW	Breast	No	Bilateral mastectomy & oophorectomy	No	No
Miranda	68	<i>CHEK2</i>	Pathogenic	NHW	None	Yes	No Surgery	Yes	Yes
Catherine	73	<i>CHEK2</i>	Pathogenic	NHW	Breast	No	Bilateral mastectomy	No	No
Adele	55	<i>CHEK2</i>	Pathogenic	NHW	Breast	Yes	Unilateral mastectomy	Yes	Yes
Ellis	45	<i>CHEK2</i>	Pathogenic	NHW	None	Yes	Prophylactic bilateral mastectomy	Yes	Yes
Rachel	59	<i>CHEK2</i>	Pathogenic	NHW	Breast	No	Bilateral Mastectomy	No	Yes
Monica	57	<i>CHEK2</i>	Pathogenic	NHW	None	Yes	No Surgery	Yes	Yes
Phoebe	70	<i>CHEK2</i>	Pathogenic	NHW	Breast	Yes	Lumpectomy	Yes	Yes
Emma	35	<i>CHEK2</i>	Pathogenic	NHW	None	Yes	No Surgery	Unknown	Yes
Erica	43	<i>CHEK2</i>	Pathogenic	NHW	None	Yes	Prophylactic bilateral mastectomy	Yes	Yes
Janice	55	<i>CHEK2</i>	Pathogenic	NHW	Breast	No	Lumpectomy and removal of lymph nodes	Yes	No
Lorelai	68	<i>CHEK2</i>	Pathogenic	NHW	Breast, Uterine, BCC ⁵	Yes	Bilateral Mastectomy	No	No

¹ Results were either *BRCA1* variant of uncertain significance (VUS), *BRCA2* VUS, or *CHEK2* pathogenic

² Non-hispanic White (NHW) or Asian

³ First Degree Relative (FDR) refers to parent, sibling, or child

⁴ Unless otherwise labeled as prophylactic, surgery was for treatment of a breast cancer diagnosis.

⁵ Basal Cell Carcinoma (BCC)

Table A2. Select questions used during interview and the respective ODSF construct

Construct	Questions
Knowledge	How did you feel after receiving your genetic test results?
	Describe the medical management recommendations given to you after receiving your genetic test results and which healthcare provider told you about them?
	What did they tell you or recommend to you about medical management?
	What information made it easier or more difficult to decide on your chosen medical management?
Certainty/ Uncertainty	Did you feel any uncertainty with your genetic test results?
	Did the medical management recommendations make sense based on the information given to you about your genetic test results?
	Did you feel confident in the recommendations made by your healthcare provider?
Support	Did you receive support from any family, friends or providers at this time?
	Did your healthcare providers support your medical management decision?
	Did you receive any guidance or advice?
Values	What were the benefits of the recommended medical management?
	What were the negatives of the recommended medical management?
	Did you feel you had options for medical management?

Appendix B: IRB Approval Letter



RESEARCH INTEGRITY AND COMPLIANCE
Institutional Review Boards, FWA No. 00001669
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11/26/2018

Deborah Cragun, PhD.
Global Health
3720 Spectrum Blvd Suite 304
Tampa, FL 33612

RE: Expedited Approval for Initial Review

IRB#: Pro00037381

Title: GeneCARE: A Follow-Up Package for Gene-Based Care for Women At Risk for Inherited Cancer

Study Approval Period: 11/24/2018 to 11/24/2019

Dear Dr. Cragun:

On 11/24/2018, the Institutional Review Board (IRB) reviewed and **APPROVED** the above application and all documents contained within, including those outlined below.

Approved Item(s):

Protocol Document(s):

[USF proposal](#)

It was the determination of the IRB that your study qualified for expedited review which includes activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the categories outlined below. The IRB may review research through the expedited review procedure authorized by 45CFR46.110 and 21 CFR 56.110. The research proposed in this study is categorized under the following expedited review category:

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Your study qualifies for a waiver of the requirements for the informed consent process as

outlined in the federal regulations at 45CFR46.116 (d) which states that an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Your study qualifies for a waiver of the requirement for signed authorization as outlined in the HIPAA Privacy Rule regulations at 45CFR164.512(i) which states that an IRB may approve a waiver or alteration of the authorization requirement provided that the following criteria are met (1) the PHI use or disclosure involves no more than a minimal risk to the privacy of individuals; (2) the research could not practicably be conducted without the requested waiver or alteration; and (3) the research could not practicably be conducted without access to and use of the PHI. A waiver of HIPAA Authorization is granted for this study. Pursuant to this waiver, the USF study team is allowed to obtain PHI of subjects who provide their signed HIPAA Authorization during the informed consent process conducted by the lead site, Vanderbilt University.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with IRB policies and procedures and as approved by the IRB. Any changes to the approved research must be submitted to the IRB for review and approval via an amendment. Additionally, all unanticipated problems must be reported to the USF IRB within five (5) business days.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,



Melissa Sloan, PhD, Vice Chairperson
USF Institutional Review Board

Appendix C: Informed Consent Form

Institutional Review Board
Informed Consent Document for Research

Principal Investigator: Tuya Pal, M.D. Revision Date: 11/15/18
Study Title: GeneCARE: A Follow-Up Package for Gene-Based Care for Women At-Risk for
Inherited Cancer
Institution/Hospital: Vanderbilt University Medical Center

This informed consent applies to adult women living in the United States who are at-risk for hereditary cancer with a documented pathogenic mutation or variant of uncertain significance (VUS) in a gene associated with hereditary cancer.

Name of participant: _____ Age: _____

The following is provided to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you are given the opportunity to download a copy of this informed consent form for your records.

You do not have to be in this research study. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. If you are a Vanderbilt patient, your medical record may contain a note saying you are in a research study. Anyone you authorize to receive your medical record will also get this note.

1. What is the purpose of this study?

You are being asked to take part in this new research study (conducted through Vanderbilt University Medical Center and in partnership with collaborators from the University of South Florida) that is enrolling adult women who are at-risk for hereditary cancer and have a known pathogenic mutation or VUS in a gene associated with hereditary cancer. The purpose of this study is to better understand access to follow-up care recommended by a healthcare professional after genetic testing and how patients go about sharing their genetic test results with family members. About 500 people will take part in this study.

2. What will happen and how long will you be in the study?

If you agree to be in this study, we will ask you to take an online survey. This will take about 10-15 minutes of your time. At the end of the survey, we will ask if you would be willing to take part at a later time in an in-depth phone interview that will be recorded.

If you agree to take part in the phone interview and are selected for this second part of the study, we will schedule a later time and date for your interview. At that time, a

member of the study team from Vanderbilt or the University of South Florida will call you and ask you more questions over the phone. This phone interview will be recorded and will take about 30-60 minutes of your time.

After the phone interview, the study team from Vanderbilt may contact you to ask you to contact up to five of your blood-related adult family members (18 years of age or older) to ask their permission to share their contact information with the study team so they may receive information about inherited cancer. You will need to contact these family members and ask for permission to share their contact information with the study team. Once we receive this information and permission to contact, we will mail or phone them to provide general information about hereditary cancer services and where they can get more information about inherited cancer. We will also provide them with contact information of the study team if they want more information.

3. Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

4. Side effects and risks that you can expect if you take part in this study:

Questionnaire and Interview:

This study only involves a brief online survey (all participants), and a phone interview and follow-up contact (up to 100 selected participants), therefore the risk of injury or personal harm due to this study is very low. There is always the chance that some of your private information may be accidentally released. The study team will do everything possible to reduce these risks. All study staff have received required training on how to keep information private.

Family Contact Information:

If you are one of the 100 participants selected for the second part of this study, we will ask you to identify up to five blood-related adult family members and share their contact information with us after getting their permission. Strong steps will be taken to keep this information private, and it will not be used for any purpose outside of this study. You have the right to not provide information about your family for this research. We understand that family members may react differently towards sharing this type of information for the purposes of research.

5. Risks that are not known:

There may be risks that we do not know about at this time. If we find any other risks we will let participants know.

6. Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance

will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury. There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating any illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

7. Good effects that might result from this study:

a) The benefits to science and humankind that might result from this study: This study may help to increase our overall knowledge of access to follow-up care recommended by healthcare professionals after genetic testing and how patients share genetic test results with family members. This knowledge can help to develop strategies to improve follow-up care and family sharing among those at risk for inherited cancer.

b) The benefits you might get from being in this study: None.

8. Other treatments you could get if you decide not to be in this study:

This is not a treatment study. You may decide not to be in the study and nothing about your healthcare will change.

9. Payments for your time spent taking part in this study:

If you enroll online and complete the online survey, you will receive a \$10 gift card. If you are selected for and complete the in-depth phone interview, you will receive a \$50 gift card to reimburse you for your time.

10. Reasons why the study doctor may take you out of this study:

You may be taken out of the study if you request it. If you are taken out of the study for any other reason, you will be told why.

11. What will happen if you decide to stop being in this study?

Being in this study is your choice. You can choose to stop being in this study at any time. Any routine care you receive will not change if you choose to participate or if you choose not to participate in this study. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. If you decide to stop being part of the study, you should contact the study team. At that time, we will stop gathering information about you, however the data that is already part of the study will be kept.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Tuya Pal, M.D. C/O the GENECARE Study Team at [REDACTED]

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at [REDACTED] or toll free at [REDACTED].

13. Confidentiality:

If you agree to take part in this study, all information collected by Vanderbilt University Medical Center and the University of South Florida during the study will be kept strictly confidential. In accordance with federal law, we will keep the study records private by storing them in a locked area or on a password-protected computer. Your identifying information, such as your name and contact details, will be kept separately in a secure location, so that only the study team can access it. When we use data collected in the study, the information that identifies you will not be used. Instead, we will give you a study identification number that no one else can use to identify you. Your name or other information that would allow someone outside the study to identify you will never be used in study publications or reports. Your study record will be kept separately from your regular medical record and insurers will not have access to your study records. If insurance companies, employers, or others obtain genetic information about you from this research, it has the potential to affect your insurability or employability. This is why we will do our best to ensure that privacy of all identifiable study records will be protected to the full extent provided by law.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Pal, and her staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

Because this study is funded by the National Institutes of Health (NIH), it is conducted under a Certificate of Confidentiality. This Certificate keeps us from sharing your identifiable sensitive information (which is information gathered during the course of research that might identify you) gathered for research purposes unless you allow us to do so. It also keeps us from being forced to release your study information as part of a court, legislative, administrative or other proceeding.

There are times when the Certificate cannot be used. For example, we cannot refuse to give information to government agencies that oversee or fund research, such as the NIH, Department of Health and Human Services (DHHS) or Food and Drug Administration (FDA). The Certificate also does not stop us from giving information to local government agencies, law enforcement personnel or others if we suspect you or someone else is in danger or if we are required to do so by law.

The Certificate does not keep you from giving out information about yourself and your treatment in this study. We will allow the release of some study information, such as lab

test results, if you wish us to do so and you give us permission in writing. If you have any questions, please ask the study doctor or study staff.

14. Authorization to Use/Disclose Protected Health Information:

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies by Vanderbilt and research collaborators at the University of South Florida that can be traced back to you. Using or sharing (“disclosure”) such data must follow federal privacy rules. By signing the consent for this study, you are agreeing (“authorization”) to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Vanderbilt University Medical Center may share questionnaire data, the results of your study and/or non-study linked genetic results, as well as parts of your medical record, to the groups named below. These groups may include our research partners at the University of South Florida, the Federal Government Office for Human Research Protections and the Vanderbilt University Institutional Review Board. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be destroyed. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact the study team in writing and let them know that you withdraw your consent. The mailing address is:

GeneCARE Study Team [REDACTED] Vanderbilt University Medical Center Nashville, TN 37212

At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment, or enrollment in any health plans or affect your ability to get benefits. You will be given the opportunity to download a copy of this informed consent form for your records.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date

Signature of patient/volunteer

Consent obtained by:

Date

Signature

Printed Name and Title

Time