Understanding and Managing Genomic Uncertainty

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Abstract

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The overall aim of this dissertation was to study how patients understand and manage uncertainty in genomic medicine arising from Variants of Uncertain Significance, a type of genetic test result.

Results from Chapter 2 suggest that, overall, the epistemological source of VUS uncertainty was well recognized by patients and these patients were also accepting of the prevalence of medical uncertainty in general. This acceptance gave them hope that VUS-related uncertainty is manageable would be resolved in future. Patients also identified several issues of VUS-related uncertainty such as implication for family members, and being informed about reclassification. We identified themes representing nearly all issue-related subdomains of Han's taxonomy of uncertainty which demonstrates the wide range of diagnostic, prognostic,

therapeutic and psychosocial difficulties that patients with VUS experience. More importantly however, patients also identified methods for managing VUS-related uncertainty. We organize the various provider and patient level management strategies into a provisional framework of uncertainty management strategies that identify patient and provider level approaches for VUS management. Chapter 3 offers a detailed examination of patients' VUS-related information seeking behavior and its relation to VUS management behavior. We find that more than half of the survey respondents reported seeking VUS-related information and information from health care providers and cancer research organizations were preferred. In accordance with VUS-related management guidelines, most patients did not undergo surgery (61.8%) or screening (62.5%) based on VUS results, and the majority of patients (69.5%) did not check back for a VUS reclassification; 46.7% asked family members to get a genetic test because of their VUS result. Lack of association between information seeking and VUS management may be explained by the unavailability of actionable VUS information. Results from Chapter 4 showed that men and women are equally knowledgeable about genomic sequencing, and report equal frequency of current familial communication of Colorectal Cancer and Polyposis (CRCP) risk and express future intention to share CRCP related genomic test results with family members. Factual genomic knowledge explained only a small proportion of variation in familial communication of CRCP risk. Application of these findings to VUS family studies requires additional considerations. For example, VUS are a particularly challenging group of variants to communicate to family members and two major barriers to communicating VUS test results are – perception that VUS has no genetic or medical implication for family members, and that probands themselves are ambiguous about the result and thus do not feel confident about sharing.

Results from this dissertation add to our understanding of how is VUS-related uncertainty is perceived and managed by patients, how information seeking is used as an

uncertainty management strategy and its relationship with VUS management behavior. One specific VUS management strategy is to participate in family studies of variant reclassification that require familial communication - we explore genomic knowledge and gender as determinants of familial communication of genetic risk.

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CHAPTER 1: INTRODUCTION

> *"Generally, it is considered a weakness and a sign of vulnerability for clinicians to appear unsure. Confidence is valued over uncertainty and there is a prevailing censure against disclosing uncertainty to patients. Experts who acknowledge the full extent of their ignorance may expect to be replaced by more confident competitors who are better able to gain the trust of clients. An unbiased appreciation of uncertainty is a cornerstone of rationality – but is not what people and organizations want. Extreme uncertainty is paralyzing under dangerous circumstances, and the admission that one is merely guessing is especially unacceptable when the stakes are high. Acting on pretended knowledge is often the preferred solution."*
>
> - Daniel Kahneman, Thinking Fast and Slow

Uncertainty is ubiquitous in medicine. Genomic medicine, in particular, is replete with uncertainties because of the amount of genetic code that is yet to be deciphered. As we ride the rising wave of clinical genomics, all stakeholders, including patients and providers will likely experience uncertainty at some point or another and an unbiased appreciation of genomic uncertainty is more important than ever.

Variants of Uncertain Significance

A major source of uncertainty in medical genomics is a type of genomic test result called Variant of Uncertain Significance or VUS. The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) recommends using a five tier classification system that indicates the pathogenicity of a variant – Pathogenic, Likely Pathogenic, VUS, Likely Benign and Benign (Richards *et. al.,* 2015). VUS comprise a residual category that variants default into when they cannot be classified as any of the remaining four categories due to inadequate or conflicting scientific evidence. This type of information thus represents epistemic uncertainty i.e., arising from limitations in the current state of knowledge of the variant (Han *et. al.,* 2013).

Given our embryonic understanding of the human genome, yet increasing use of clinical multi-gene testing, exome and genome sequencing, issues regarding the scale and complexity of VUS classification are compounded and magnified (Feero, 2014). First, VUS are quite prevalent. Currently, the frequency with which VUS are reported is lower in more well studied genes such as *BRCA1/2* where the estimates range between 2% and 4% (Hall *et. al.,* 209), but much higher in less well characterized genes – up to 95% of patients who receive some clinical tests (LaDuca *et. al.,* 2014; Tung *et. al.,* 2015; Maxwell *et. al.,* 2016). Despite sophisticated scientific approaches to validate the functional significance of individual variants, a considerable proportion of variants are classified as VUS. Rates of VUS detection increases proportionately as more genes are tested together (Shirts *et. al.,* 2016; Selkirk *et. al.,* 2014) and as less well studied genes are included in the panel tests (Maxwell *et. al.,* 2016). Second, variant classification is often discordant between laboratories – i.e., the same variant may be classified as VUS in one laboratory while pathogenic/ likely pathogenic or benign/ likely benign in another (Lincoln *et. al.,* 2017; Lek *et. al.,* 2016). Third, VUS reporting rates are disproportionately higher in tests performed in ethnic minorities such as Hispanic and African Americans (Frank *et. al.,* 2002; Weitzel *et. al.,* 2005; Nanda *et. al.,* 2005; Ricker *et. al.,* 2016). Fourth, there is considerable heterogeneity in the content and format of VUS reporting by laboratories (Makhnoon *et. al.,* 2018) which likely contributes to the clinical interpretation of these variants. As the number of patients receiving multi-gene panel, exome and genome sequencing in clinical care, it is expected that the number of VUS will dramatically increase in the coming years (Lek *et. al.,* 2016; Amendola *et. al.,* 2016).

The ACMG-AMP guidelines recommend that “VUS should not be used in clinical decision making” and “efforts to resolve the classification of the variant as pathogenic or benign should be undertaken”. Echoing this recommendation, in oncology, the National Comprehensive Cancer Network (NCCN) recommends basing medical management for individuals with a VUS

result in a cancer related gene on family history (NCCN, 2014). Thus in practice, a patient with a VUS may be given one of more of the following management recommendations: (1) Do not use VUS for medical management such as surgery and screening, (2) Do not test family members for clinical purposes, (3) Check back for updates regarding VUS reclassification, and (4) Consider participating in VUS reclassification study. Yet, these seemingly straightforward recommendations are openly interpreted and subjectively adhered to.

Patient and provider experiences with VUS

There is significant inconsistency in personal interpretation of these VUS-related clinical recommendations among providers (Petrucelli *et. al.,* 2002) leading to discordant clinical recommendations. Previous studies reported that genetic counselors are less confident when discussing medical management options in connection with VUS and are unsure about how well patients understand VUS (Scherr *et. al.*, 2015a; Scherr *et. al.*, 2015b). VUS information can be confusing for providers who have had little experience with interpreting and counseling patients with this new kind of genetic test result (Scherr, 2015; Eccles, 2015; Petrucelli, 2002). Non-genetics specialists who use genetic results are often unsure about the clinical implication of test reports containing VUS (Eccles *et. al.*, 2015). Misinterpretations of VUS and resulting clinical management failures have also been litigated in court (*Williams's v Quest/Athena).*

Negative patient outcomes in response to VUS results have also been reported. These include higher levels of distress about cancer risk (Vos *et. al.,* 2012; O'Neill *et. al.*, 2006; O'Neill *et. al.*, 2009; van Dijk *et. al.*, 2006), misinterpreting the result as a genetic predisposition to cancer (Vos *et. al.,* 2008), and engaging in prevention measures not indicated by their result (e.g., prophylactic surgeries) (Murray *et. al.,* 2011). VUS is reported to have the highest rate of incorrect risk recall among patients (33%) compared to mutations (20%) or no mutations (6%)

(Richter *et. al.,* 2013) and cause of worry and anxiety (Makhnoon *et. al.,* 2017; Solomon *et. al.,* 2017).

Whether or not to clinically report VUS is an area of active discussion because of the potential for harm a VUS can cause and because VUS lacks clinical significance. Not reporting the variant on the laboratory report may give a patient a false sense of security and may expose a laboratory to risk if variant turns out to be causative. On the other hand, reporting a VUS risks the variant being mis-interpreted as important for care and used as a basis for diagnosis, treatment or follow-up tests (Timmermans *et. al.,* 2017). This lack of consensus on whether or not to treat VUS with clinical importance often presents itself in the variant reporting policies used by laboratories – some report VUS, whereas others do not (Makhnoon *et. al.,* 2018). This is problematic as a strict interpretation of the ACMG guidelines (compared to laboratories' own criteria (Anemdola *et. al.,* 2016)) results in a strikingly high prevalence of VUS in everyday clinical care that laboratories, patients and providers are left to grapple with. When laboratories chose to report VUS, there is also heterogeneity in how the VUS is presented in laboratory test reports (Makhnoon *et. al.,* 2018) – further portraying the ambivalence among the genomics community regarding VUS. Taken together, VUS raises a harbinger of ethical and legal issues in medical genomics: Do healthcare providers have a duty to re-contact patients in the case of a VUS reclassification? How can we improve clinical interpretation of VUS and reduce misinterpretation? (Cheon *et. al.,* 2014).

While discordant VUS classification across laboratories are being resolved, variant classification policies are being standardized, and providers are becoming familiar with VUS, thousands of patients are routinely encountering VUS in specialty and primary care clinics. In order to inform best management practices for these patients, it is important to understand exactly why some patients experience so much uncertainty around this particular type of genetic test result. While encountering a VUS is a non-event for many patients, some make radical and

often incorrect medical decisions. While some can proficiently manage their uncertain genomic finding, others experience debilitating worry and anxiety. Currently, it is not known what causes this spectrum for behavior in response to VUS – it is possible that such variation is solely due to variation in patients' ability to deal with uncertainty. However, societal contribution to patients' experience of uncertainty is also likely. Can providers affect patients' experience with VUS? What exactly is confusing about VUS for patients? What coping mechanisms help or hinder in alleviating this uncertainty? How is genetic information communicated to family members of the proband? The overall goal of this dissertation was to help answer these broad questions related to VUS and familial communication.

Perception and management of VUS uncertainty

A structured analysis of VUS-related uncertainty experienced by patients in genomic medicine may yield insights into why these non-significant variants are so often befuddling for patients. Han *et. al.,* (2017) offers a taxonomy of uncertainties associated with genomic sequencing information that allows us to explore the subjective perception of uncertainty from various perspectives. He identifies three sources (probability, ambiguity, complexity) and issues arising from experiencing these sources of uncertainty (scientific, practical and personal).

Source refers to the "cause of a given uncertainty or the fundamental reason for a specific knowledge gap" and is subdivided into probability (stochastic nature of future outcomes), ambiguity ("the lack of reliability, credibility, or adequacy of information"), and complexity ("features of risk information that make it difficult to understand"). Ambiguity is further subdivided into conceptual, methodological and clinical; and complexity into multiplicity of causes, multiplicity of effects, and effect modification. *Issue* refers to "the specific substantive matter about which an individual lacks knowledge". This can be subdivided into scientific

(diagnostic, prognostic, causal or therapeutic), practical ("lack of knowledge about the structures of healthcare and the processes of healthcare") and personal (psychosocial and existential issues). *Locus* refers to the "the party in whose mind uncertainty resides". The taxonomy identifies various stakeholder including "patients, clinicians, researchers, or other individuals including family members, regulators, payers or health policy makers". A more extensive definition of components of the taxonomy is available in Han, 2017. These three dimensions are not independent of each other but operate in concert. The underlying cause of the specific *issues* of uncertainty may be any of the *sources*. Different loci may identify different sources and issues for the same type of uncertainty, or they may identify different subcomponents of these dimensions to be important contributors to uncertainty. The first aim of this dissertation work is to describe the sources and issues of VUS-related uncertainty from the patient's perspective.

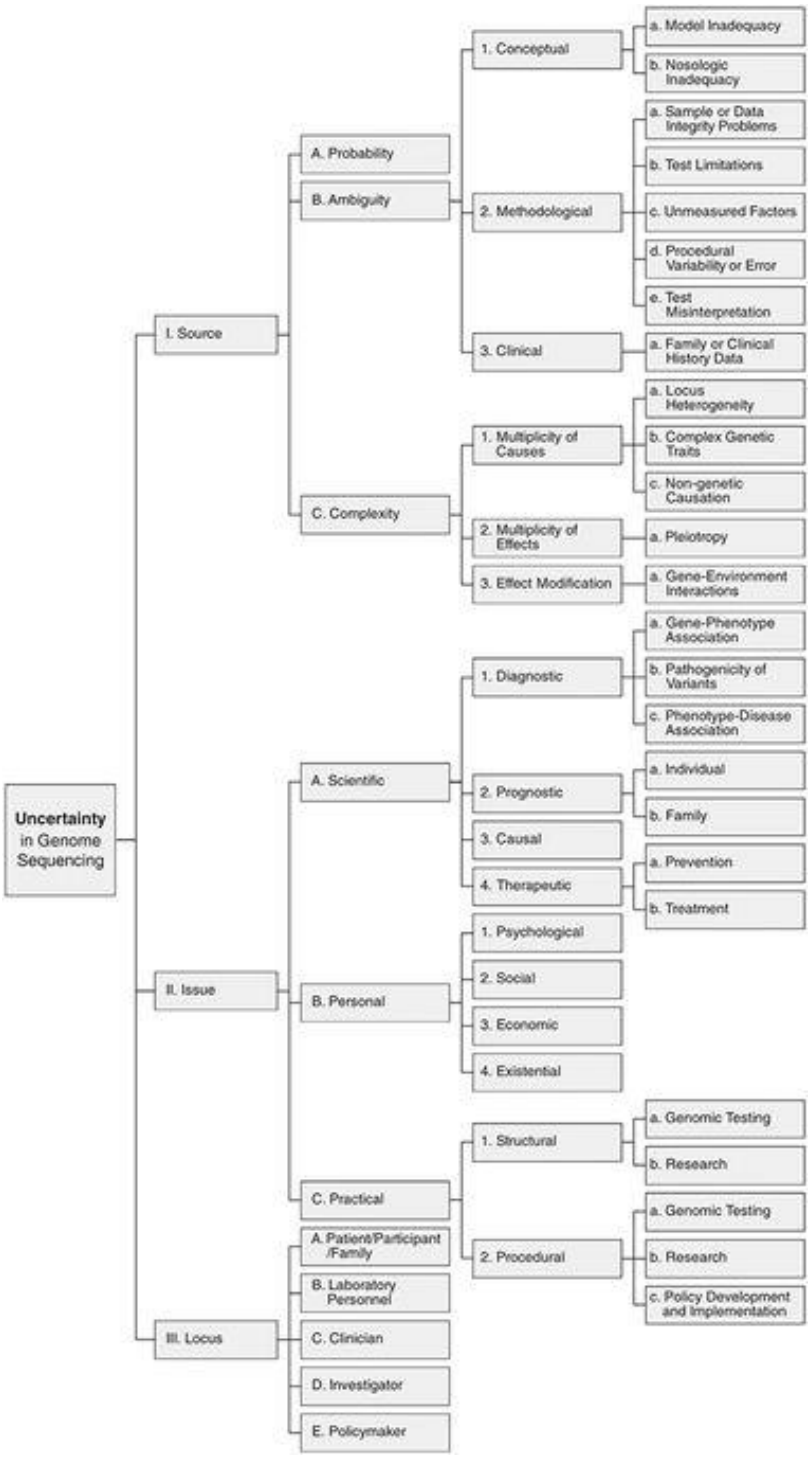


Figure 1: A taxonomy of uncertainty. This is a visual representation of a three-dimensional taxonomy of medical uncertainty in clinical genome sequencing. The three major dimensions are source, issue, and locus (Han *et. al.,* 2017).

Information seeking to guide VUS management

The ability to deal with uncertain genetic test information is likely an important determinant of patients' confidence in subsequent clinical decision making. Patient behavior in response to VUS is varied and often not in line with published guidelines, for example, although, surgical decisions such as mastectomy or colectomy should not be based on VUS results, such decisions are not uncommon (Kurian *et. al*., 2017; Murray *et. al*., 2011). Although Han's taxonomy is useful to understand the source and issues related to genomic uncertainty, it does not offer a framework about how uncertainty is processed or managed – which is offered by another theory called the Uncertainty Management Theory (UMT). UMT suggests that individuals may engage in information seeking to manage uncertainty (Brashers, 2001). In support of this theory, previous studies have shown a positive association between uncertainty level and information seeking in hypothetical (Rains & Tukachinsky, 2015) and applied (Fisher *et. al.,* 2017) scenarios. Therefore, it is likely that VUS related uncertainty is also managed through information seeking but little is known about patients' information seeking behavior in response to VUS test results.

Information seeking may help patients manage uncertainty related to VUS and be important in subsequent clinical decisions. Although a rich body of literature exists in cancer information seeking behavior (Finney Rutten *et. al.,* 2016), studies exploring information seeking in response to cancer genetic test results of any type are limited. A search of the existing literature found that, information seeking was used as a strategy to manage uncertainty among women at-risk for, or carriers of, *BRCA1/2* mutations (Petrucelli *et. al.,* 2002) and to understand the contribution of various health-habits to genetic susceptibility of skin cancer (Hay *et. al.,* 2012). Although information alone does not guarantee healthy behaviors, acquiring adequate information may motivate individuals to make informed changes in their health practices (Meischke *et. al.,* 2005; Shi, Nakamura & Takano, 2004), and is therefore worth understanding.

Thus, VUS-related information seeking may enable patients to deal with VUS information and guide them to making correct clinical decisions. The second aim of this work is to evaluate patients' information seeking behavior after receiving a VUS result, describe patients' VUS management behavior, and explore whether VUS specific information seeking behavior is associated with patient VUS management behavior.

VUS and familial communication

One way to resolve VUS related uncertainty is through reclassification: i.e., reclassifying an uncertain variant to a confirmed pathogenic or benign variant. VUS reclassification may occur through purposefully conducted family based research studies i.e., single family co-segregation analysis (Rosenthal *et. al.,* 2017) or through natural accumulation of evidence that allows the VUS to be reclassified. Family based VUS reclassification research involves gathering genotype and phenotype data from multiple family members of the proband with VUS. With adequate information, a VUS may be reclassified. Currently, reclassification research opportunities are available through genetic testing laboratories as well as some academic research institutions (Garrett *et. al.,* 2016). One method of recruiting family members into these studies is through familial communication via the proband. The proband is required to share their genetic test results with relatives and ask them to participate in variant reclassification research. Familial communication of genetic test result is even more important for communicating confirmed genetic test results that have the potential to improve public health through cascade testing, which rely on index patients to disseminate genetic information to their relatives (Jasperson, 2013).

Familial communication of genetic risk

Familial communication of genetic risk information has been well explored in literature and several systematic reviews offer comprehensive summaries of the known functions and influences of communication of genetic risk (Wiseman *et. al.,* 2010; Gaff *et. al.,* 2007; Nycum *et. al.,* 2009). Familial communication of genomic risk is complex, and often selective and incomplete. To briefly summarize the literature, patients are motivated to share due to feelings of responsibility or obligation towards relatives, desire to prevent disease in relatives, because the family is emotionally close and share information etc. On the other hand, inhibiting influences include being estranged with relatives, proximity of closeness to relative, unable to find a good time etc. (Wiseman *et. al.,* 2010). First degree relatives, especially female siblings, children and parents, are told about genetic results more often than second or third degree relatives (Blandy *et. al.,* 2003; Julian-Reynier *et. al.,* 2000; Wagner *et. al.,* 2003). Probands tell relatives about 'facts and recommended topics' from genetic counseling sessions (Finlay *et. al.,* 2008; Hughes *et. al.,* 2002) and prefer to communicate these information in person or at a 'good time' during normal socializing (Ormondroyd *et. al.,* 2008; Peterson *et. al.,* 2003). In addition, research shows that genetic knowledge and gender are important determinants of familial communication of genetic risk information.

Although it is believed that genomic knowledge is important to realize the promise of genomic medicine, the exact contribution of genomic knowledge for specific genomic health outcomes remains to be understood. A commonly reported barrier to familial communication revolves around inadequate knowledge of genomics - fear of not being able to answer relatives' questions about genomics or misunderstanding about inheritance (Adelsward & Sachs, 2003; Finlay *et. al.,* 2008) or benefits that can be gained from the information (Mellon *et. al.,* 2006; Weiseman *et. al.,* 2010). This suggests that those with better genomic knowledge will be more empowered and therefore more likely to disseminate results to family members. However, the

exact contribution of counselees' genomic knowledge on the multifactorial outcome of familial communication remains unexplored and in need for further investigation.

Gender of the counselee has been established as an important determinant of the nature and frequency of family communication of genetic risk. Women generally hold the responsibility for disseminating results within the family and carry out most of the familial communication (d'Agincourt-Canning, 2001; Foster *et. al.,* 2004). Men report informing fewer relatives and often use a female relative as a proxy to disseminate results (d'Agincourt-Canning, 2001; McGivern *et. al.,* 2004). Although the predominant explanation for this gendered activity is the social role of women whereby females are considered to be caretakers of the family and therefore communicators of genomic information, it is possible that other explanations also exist. Women may be more knowledgeable than men about genomics as is often the case for other health domains (Guiné *et. al.,* 2016; Madsen *et. al.,* 2015; Jensen *et. al.,* 2008; Kim, 2013) which makes them more comfortable to disseminate results. There is yet to be a direct examination of gender differences in genomic knowledge.

Given our limited understanding of the effects of genomic knowledge and gender, these factors should be explored for familial communication of genomic risk in general before focusing on a specific type of uncertain genomic risk. Thus, based on prior literature and our conceptualization of familial communication, the third aim of this work is to explore relationships between gender and genomic knowledge; and gender and probands' intention to communicate genomic test result with family members.

Dissertation roadmap:

The specific aims, hypothesis and approaches of this dissertation study are:

Aim 1: Describe VUS-related uncertainty from the perspective of the patient who has a confirmed VUS.

Han's taxonomy of medical uncertainty will be qualitatively applied to patients' VUS-related experience using semi structured qualitative interviews.

Aim 2: Evaluate patients' information seeking and VUS management behavior after receiving a VUS result, and explore association between VUS specific information seeking and VUS management behavior.

Aim 2a: Evaluate patients' information seeking behavior after receiving a VUS result.

Hypothesis: Most patients will seek information about VUS and will utilize a variety of information sources.

Aim 2b: Describe patients' VUS management behavior.

Aim 3c: Assess association between VUS specific information seeking behavior and patients' VUS management behavior.

Hypothesis: VUS specific information seeking behavior will be positively associated with patients' VUS management behavior.

Aim 3: Evaluate the relationship between genomic knowledge, gender and familial communication behavior.

Aim 3a: Evaluate the association between genomic knowledge and current frequency of familial communication about Colorectal Cancer and Polyposis (CRCP) risk and future intention to share CRCP related genomic test results with family members

Hypothesis: Individuals with higher genomic knowledge will have increased familial communication about genomic risk information

Aim 3b: Identify gender differences in genomic sequencing knowledge.

Hypothesis: Females will score higher than males in genomic sequencing knowledge

Aim 3c: Assess the unique contribution of genomic knowledge in the association between gender and familial communication about CRCP related genetic risk.

Hypothesis: Genomic knowledge will explain a minor proportion of the variation in familial communication.

CHAPTER 2: Qualitative application of Han's taxonomy of genomic uncertainty to understand patients' perspectives of variants of uncertain significance

ABSTRACT

Variants of uncertain significance (VUS) are a well-recognized source of uncertainty in genomic medicine. Despite the existence of straightforward clinical management recommendations, patients report feeling anxiety, worry and uncertainty in response to VUS. We use Han's taxonomy of uncertainties in genome sequencing to understand uncertainty related to VUS from a patient's perspective. We conducted in-depth semi-structured interviews with 11 patients to elicit their experiences of receiving VUS, reflections about their result and thoughts regarding implications of the result for themselves and their family members. Patients' primary concern with VUS related uncertainty involved personal and practical issues as they directly inform health care decisions. Patients demonstrated good understanding of the epistemic nature of this uncertainty. However, discordant provider explanations of the implication of this epistemic uncertainty for patients' diagnosis, prognosis, and therapy was a major contributor to the overall experience of uncertainty. Strategies for uncertainty reduction involved periodically checking back for reclassification and receiving concordant and clear recommendation from providers. Other proactive strategies of uncertainty reduction – such as information seeking and reading the genetic test report – were not helpful. Collectively, these findings offer significant insight into patient experiences of VUS related uncertainty which providers can use to manage uncertainty in these patients.

Keywords: VUS, variants of uncertain significance, uncertainty, tolerance, management

INTRODUCTION

Genomic medicine, especially genomic testing is awash with uncertainties – from variant interpretation to communicating results to patients (Han *et. al.*, 2017). Variants of Uncertain Significance (VUS) are genomic variants which cannot be classified as pathogenic or benign because of inadequate or conflicting information. This type of information thus represents epistemic uncertainty (i.e., arising from limitations in the current state of knowledge) (Han *et. al.,* 2013), which often creates a clinical situation that is difficult to manage (Han, 2013). Genetic test results that include identification of a VUS routinely, and understandably, incite uncertainty among patients who receive this result. Patients report feelings of worry and anxiety (Makhnoon *et. al.*, 2017; Solomon *et. al.*, 2017) and higher levels of distress about cancer risk (Vos *et. al.*, 2012; Richter *et. al.*, 2013) upon receiving a VUS result. These variants are also often misinterpreted by patients as diagnostic for disease or genetic predisposition (Vos *et. al.*, 2012), which leads patients and providers to engage in inappropriate clinical measures (e.g., prophylactic surgery) (Murray *et. al.*, 2011). The National Comprehensive Cancer Network (NCCN) recommends basing medical management for individuals with a VUS result in a cancer related gene on family history and offering them research options to help classify the variant (NCCN, 2014). Despite this clear guideline, patients regularly respond to VUS with some degree of uncertainty. However, little is known about why exactly some patients find this particular type of genetic test result so problematic.

Determinants of uncertainty related to VUS results may be related to the unique type of information it represents (complex, genetic and uncertain) and to the context under which patients encounter the information (cancer and anxiety). Some proportion of the total uncertainty experienced by patients with a VUS result may also be explained by disparate provider practices in managing VUS results. Studies suggest that VUS results are not only confusing for patients but for providers who have had little experience with this new kind of genetic

information (Scherr *et. al.*, 2015; Eccles *et. al.*, 2015; Petrucelli *et. al.*, 2002). Given that patients counseled by even experienced providers often make inappropriate clinical decisions (Makhnoon *et. al.*, 2018), it is important to identify and assess the sources and issues of VUS uncertainty from a patient's perspective to determine the best course of action for patients.

Literature on medical uncertainty suggests that differences in patients' VUS-induced uncertainty and responses to this uncertainty likely depend on their psychological propensity to react under conditions of uncertainty. For example, individuals who encounter uncertainty may appraise it to be positive (e.g., hope or optimism), or negative (e.g., danger), neutral (e.g., inconsequential), or mixed (Brashers *et. al.*, 2002). This appraisal, in turn, predicts how individuals manage uncertainty (Brasher, 2001a), for example, lowering their engagement in risk-reducing behavior (Orom *et. al.*, 2017). Patients who perceive VUS uncertainty to be reducible (Brashers *et. al.*, 2002b) may manage uncertainty with information seeking or participation in VUS reclassification research. On the other hand, patients who perceive VUS uncertainty to be irreducible (Brashers *et. al.*, 2002b) may benefit from learning methods to cope with uncertainty. At this time, we lack empirical evidence about specific coping strategies (Politi *et. al.*, 2007; Han *et. al.*, 2011) but some proposed cognitive-behavioral techniques attempts to improve understanding and probabilistic thinking, engage in vigilant self-monitoring etc. (Epstein & Street, 2007).

Han and colleagues have developed a typology of uncertainty to accommodate the unique uncertainties seen in genomic medicine (Han *et. al.*, 2017). The taxonomy also allows investigation of uncertainty from multiple perspectives or loci. The subjective perception of uncertainty necessitates that VUS related clinical uncertainty be explained from the perspective of the experiencer. Of all the various stakeholders who experience it (such as patients, research participants, family members, clinicians, laboratory personnel and researchers), patients are perhaps the most vulnerable and thus have the greatest potential to benefit most from

behavioral interventions to manage uncertainty. We use the Han's taxonomy of medical uncertainty in genomic medicine to describe the sources and issues of VUS-related uncertainty from the patient perspective.

Han's taxonomy of medical uncertainty

The taxonomy divides uncertainty across three dimensions – Source, Issue, and Locus (Han *et. al.*, 2017) (Figure 2). *Source* refers to the "cause of a given uncertainty or the fundamental reason for a specific knowledge gap" and is subdivided into probability (stochastic nature of future outcomes), ambiguity ("the lack of reliability, credibility, or adequacy of information"), and complexity ("features of risk information that make it difficult to understand"). Ambiguity is further subdivided into conceptual, methodological and clinical; and complexity into multiplicity of causes, multiplicity of effects, and effect modification.

Issue refers to "the specific substantive matter about which an individual lacks knowledge". This can be subdivided into scientific (diagnostic, prognostic, causal or therapeutic), practical ("lack of knowledge about the structures of healthcare and the processes of healthcare") and personal (psychosocial and existential issues). *Locus* refers to the "the party in whose mind uncertainty resides". The taxonomy identifies various stakeholder including "patients, clinicians, researchers, or other individuals including family members, regulators, payers or health policy makers". A more extensive definition of components of the taxonomy is available in Han, 2017.

These three dimensions are not independent of each other but operate in concert. The underlying cause of the specific *issues* of uncertainty may be any of the *sources*. Different loci may identify different sources and issues for the same type of uncertainty, or they may identify different subcomponents of these dimensions to be important contributors to uncertainty. This

paper will describe VUS related uncertainty from the perspective of the patient who has a confirmed VUS.

Every patient's experience is unique and therefore this inquiry necessitates the use of qualitative method (Glesne, 2016) to accurately represent the range of factors that influence VUS comprehension. Consequently, we selected qualitative methodology to obtain the rich, narrative description of interpersonal factors that emerge when individuals explore their clinical and personal experience with VUS. Basic qualitative research methodology is appropriate when prior theoretical propositions guide data collection and analysis and the researcher wishes to account for and describe contextual conditions.

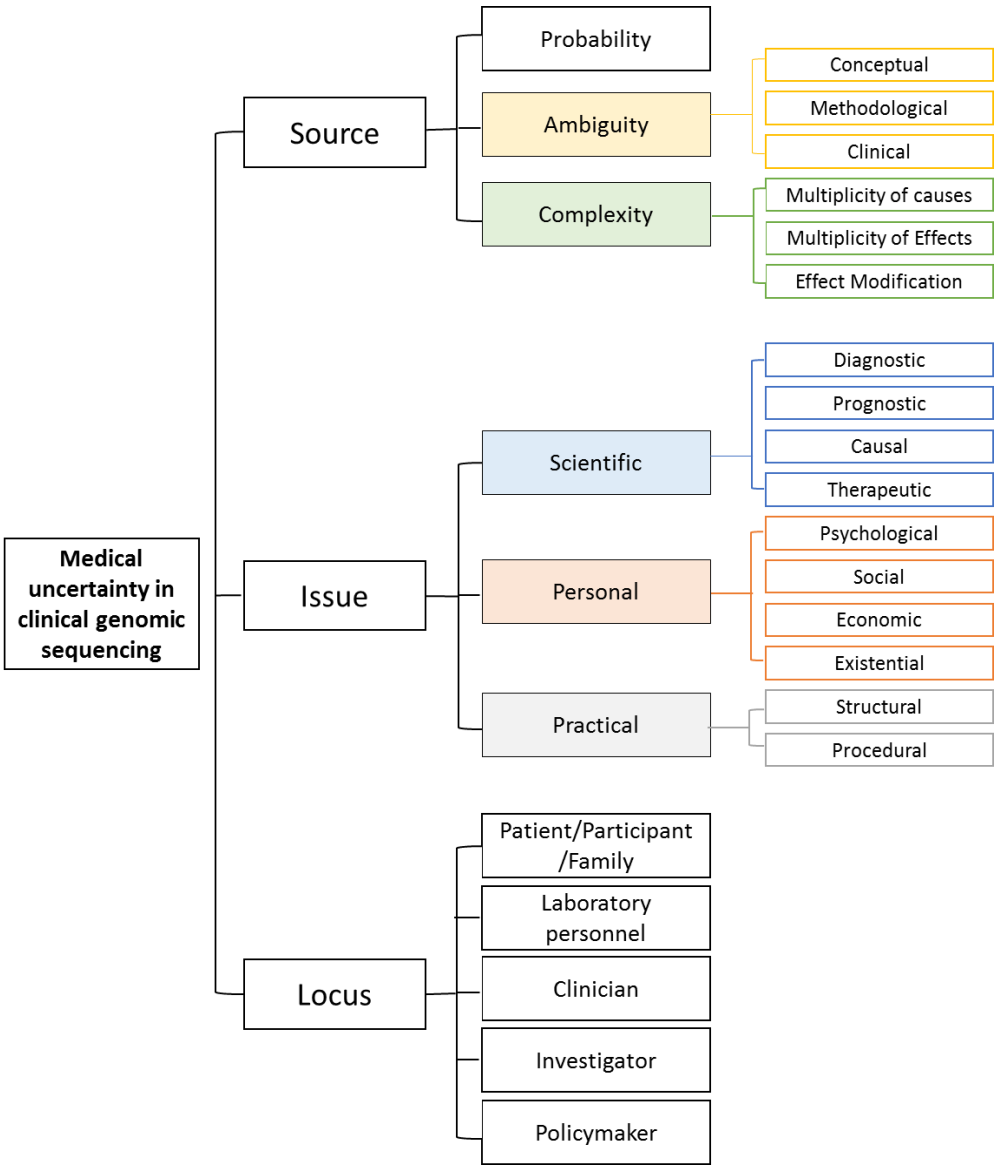


Figure 2: Han's taxonomy of medical uncertainty in clinical genome sequencing (adapted) [reprint permission obtained from author].

MATERIALS AND METHODS

Recruitment: Patients seen at the Seattle Cancer Care Alliance (SCCA) genetic counseling program and/or a genetic oncologist between October 2013 and December 2016 for

Breast Cancer (BC), Colorectal Cancer (CRC), Uterine Cancer (UC) and Pancreatic Cancer (PC) were identified through the clinic database and screened for study eligibility. Patients who met the following inclusion criteria were identified as potential study participants: 18 years of age or older, underwent genetic testing for BC, CRC, UC or PC and received a VUS result as a part of routine clinical care, and speaks English. Eligible patients were contacted over phone with invitation to participate in the study. Ten participants were recruited and interviewed for the study between November 2016 and February 2017. Study information was also sent to 3 genetic counselors in Eastern Washington with request for referrals. One participant was recruited through this method and interviewed for the study in June 2017.

Data collection: Interviews were conducted in person or by telephone using a semi-structured interview guide designed to elicit participants' views of genetic testing, experiences of receiving genetic test results, reflections about their VUS test result, and thoughts regarding implications of their result for themselves and their family members. Each interview lasted between 30 and 60 minutes. All interviews were audio recorded and transcribed, transcripts were de-identified using study numbers to protect confidentiality. The study was approved by the University of Washington Institutional Review Board (STUDY00000175). Study participants were compensated for their time with a $30 gift card.

Data analysis: A hybrid deductive and inductive content analysis was used to analyze the data. Han's taxonomy of uncertainty served as the main framework for this study and its elements served as categories. Therefore a deductive (directed) approach was applied whereby key categories were pre-determined according to the model used. Each interview was read several times by one analyst and themes were condensed and assigned a code which was then placed under a pre-determined category of the taxonomy. The generation of new themes and subthemes not represented in Han's taxonomy represents the inductive approach. All

transcripts were uploaded into the qualitative analysis software Atlas.ti 8 for coding and content analysis.

RESULTS

Participants

Patients interviewed for this study had VUS in 11 different genes (*ATM, BARD1, BRCA2, CDH1, CHEK2, MLH1, MUTYH, PTEN, RAD50, STK11, and TP53)* all of which were cancer risk genes. One participant had 2 separate VUS in 2 different genes, and 4 participants had a VUS accompanying a deleterious mutation in the same or different gene. Participants had an average age of 46 years, and most were highly educated (Table 1). All participants were female, of European ancestry, insured, and genetic test results were disclosed to them by a genetic counselor or genetic oncologist.

Table 1: Participant sociodemographic characteristics (N = 11).

Variable	N	%
Age (N =11)		
Mean age (years)	46	
Range (years)	35-62	
Sex (N =11)		
Female	11	100
Parenthood (N =11)		
Parent	9	81.8
Not a parent	2	18.1
Education (N =11)		
12 years or High school	0	0
Post high school/vocational	1	9.0
Some college	3	27.3
College graduate	5	45.4
Postgraduate	2	36.4
Insurance status (N =11)		
Insured	11	100
Uninsured	0	0

Interview results

Findings from the study are presented under elements of Han's taxonomy of medical uncertainty:

Meaning of VUS:

The word 'uncertain' or 'inconclusive' was commonly used by patients to describe their test result, but what patients meant by an uncertain result differed. Uncertainty was defined as a lack of known relationship between variant and phenotype; for example, although mutations in *ATM* gene have been associated with an increased risk for several cancer types, one participant described her *ATM* VUS in context to her own family history of pancreatic cancer:

> "I had the broken *ATM*…and that was uncertain for pancreatic cancer." (Participant 1)

Three different interpretations of uncertainty were expressed by a patient – (1) uncertainty around the inability of VUS to explain family history of disease; (2) uncertainty around gene of uncertain significance (i.e., a gene that has no strong relationship to the phenotype) and VUS causing the patient to give more importance to the gene than the classification of the variant, and (3) the misconception that ambiguity in clinical testing can be clarified with better and more sensitive follow up tests. When probed, the patient expressed confusion about why she was never offered additional follow up tests:

> "She said that it doesn't mean that the history is not there but she said that it came back inconclusive and that it needed more testing. She said it didn't show history of breast cancer but it did show history of other types of cancer. And that was the test that came back inconclusive and that it needed further testing. And I am also thinking this because we also have a family history of liver cancer, my uncle just had pancreas cancer…So

they were saying that, as far as breast… it came back inconclusive. It came back inconclusive about other types of cancer in my family." (Participant 8)

Another patient could recall the possibility of a non-significant finding, but could not specifically recall the concept of VUS:

"When I chose which panel to do, I knew that I was asking for a lot of other gene mutations that either would be significant or would be nonsignificant. I didn't know there was anything called a VUS. But I knew that there was colon cancer genes and they were doing a broad enough panel that there was other things that might come up." (Participant 6)

Yet another interpretation of uncertainty was a general imprecision about the overall genomic test result. Patients reported the presence of an unusual mutation in their test result implying a seeming non-specificity of genomic tests:

"Something weird showed up, I didn't know it was a mutation. I was just like I got this weird thing that showed up as a variant." (Participant 9)

Participants' views about the source of VUS uncertainty:

(a) PROBABILITY:

Probabilistic uncertainty arises because of a fundamental indeterminacy of the diagnostic test or inability of the VUS to predict the future. Our patients did not report probabilistic uncertainty about the existing cause or source of uncertainty, however, they expressed uncertainty about the likelihood of future pathogenicity of VUS. These probabilistic issues of VUS-related uncertainty from a patient's perspective is reported under the section 'VUS management strategies' below.

(b) AMBIGUITY:

Conceptual ambiguity: Patients' accounts of the conceptual ambiguities surrounding VUS were not technical but provided a broad and accurate overview of the source of VUS uncertainty. They readily recognized that broadly, the source of VUS uncertainty was a lack of scientific knowledge about the genetic variant:

> "There's a lot of diseases out there and there is a lot of things that they haven't had the time or the money to explore and research on, I just don't think they fully comprehend what it is, what it does, and how to cure it. They extent to which this might play a role in someone's health." (Participant 9)

> "I understand it means you know that just they simply don't have enough data on that variant to know if it makes any difference or not." (Participant 2)

Methodological ambiguity: Methodological ambiguity was not commonly reported as a source of VUS uncertainty by patients. However, one patient who self-identified as a trained geneticist doubted that there were not more than one VUS in her result, thereby questioning the methodological accuracy of genomic testing:

> "I just thought it was a pretty big gene panel that there should have been more of 'I don't know what to do with that variant'. But I didn't have a very good reason to believe that. I don't know how many gene variants are in a normal person, or like what their cut offs are for reporting them, I kind of felt like, this one was above the threshold to include on their report, even there were others that they didn't report and I was sort of curious how they were making the decisions about reporting. That I was expecting, a priori, I expected to have multiple uncertain variant. So there was only one, so I was like…European ladies look like the reference." (Participant 5)

Clinical ambiguity: Patients never identified family or clinical history as a contributing source that affected their VUS uncertainty. In fact, patients were appreciative of how thorough and detailed family histories were taken from them.

> "Well they asked a lot of questions, like about family history, my mom's side and my dad's side." (Participant 7)

> "Genetic counselor… are very interested in… family history. She was very thorough, I came in with my history already prepared. And up to my great grandparents, and we, she talked a little bit about the process, was mostly focused on gathering information from me. She was very nice, very helpful" (Participant 11)

(c) COMPLEXITY:

The intricacy of genetic information was acknowledged with apprehension by patients and was indicated as a source of VUS uncertainty. The difficulty in understanding complex genetic information almost surely contributed to patients' feelings of VUS uncertainty:

> "I don't wrap my arm around genetics stuff because I think…there is just this fine line… kind of like playing God and you knowing just enough to make it dangerous..." (Participant 6)
>
> "I think genetics is a pretty tough thing to understand." (Participant 7)

Despite the trepidation about genetics, having a nuanced understanding of medical science seemed to help patients be more tolerant of VUS uncertainty:

> "I know there are some people who believes that you know the medical world is full of answers. And I get and fully understand that there is still a lot that is unknown." (Participant 2)

Participants' views about the issues of VUS-related uncertainty:

(a) SCIENTIFIC

I. Diagnostic

The intricate concepts of genotype-phenotype association and pathogenicity of variants were combined in patients' minds to produce simplified personal interpretations of VUS. Although patients understood that VUS has no diagnostic significance, somewhat confusingly, they had intuitions about the variant-phenotype relationship:

> "In the family it would have something to do with the breast obviously but they don't know what significance it would have with it." (Participant 2)

Patients also expressed frustration at not having a definitive diagnosis:

> "I thought that was the point of doing this was…that they knew what it was. It was a little frustrating to have them say that we don't know what it is…" (Participant 9)

II. Prognostic

Uncertainty regarding the future consequences of VUS was frequently mentioned as an issue – for both the patients themselves as well as their family members. Patients expressed uncertainty about the personal health implication of VUS in the event that the VUS remained unclassified (i.e., a VUS) and if it was reclassified (i.e., to pathogenic):

> "I do wonder if it's going to, if this is something that is going to keep recurring in the future…and if I am going to have to keep going back for treatment. Or if this is going to resolve into something else, that's going to cause me problems later?" (Participant 9)

However, there was also recognition of the general uncertainty in cancer care as a whole and that VUS is only a drop in the ocean of uncertainty:

> "I don't think it was hard for me…it kind of is square one. Really, no one ever knows if they are 100% going to get breast cancer so, I was really no better off or worse off". (Participant 7)

Although uncertainty about individual prognosis was an important problem, patients also noted how VUS uncertainty effects their family members. Patients were unsure about how the VUS may impact their family members in future:

> "It would be nice to know if it had any significance for my daughter" (Participant 2)

III. Causal

The lack of causality for VUS was more frustrating than uncertainty provoking for patients. Patients understood why causality cannot be established for VUS and that causality in genetics is often probabilistic and multifactorial.

> "…I am kind of curious as to why it was me. Why is the variant in me when we [siblings] are all from the same parents? I would want to know why it was me and why how come no one else is affected by this? I don't know if it is my environment [or] my lifestyle Quite honestly my other siblings are a little on the heavier side, I don't know if that has something to do with as well, right?" (Participant 9)

IV. Therapeutic

Uncertainty around the contribution of VUS to health consequences such as disease prevention and treatment is highly dependent on contextual factors such as presence of an accompanying pathogenic variant in the test result or having a cancer diagnosis. Patients who had VUS as well as a pathogenic variant or had been diagnosed with cancer felt less uncertain about their VUS. This was because these patients were already eligible for aggressive cancer screening and/or

treatment, which they felt 'covered' the VUS. One patient with an *ATM* pathogenic mutation and *BARD1* VUS, reported:

> "In the course of testing, *BARD1* [VUS] will be covered because I will be getting mammograms more often than I would if I didn't have this. And, I and then other thing…is that pancreatic cancer, so I will be screened more for that. So, you know I feel like my screening will be covering…they are checking me out for my ovarian and my uterine… you name it and they are checking me. And so, I feel like all of those things will be looked at as far as *BARD1* [VUS] comes along. It will be covered." (Participant 11)

A different patient reported that her *RAD50* VUS does not affect her disease treatment or prevention because she has already had a mastectomy:

> "I had a double mastectomy so I don't anticipate it [VUS] having any effect on me whatsoever" (Participant 2)

Straightforward and explicit interpretation and recommendation of VUS reduced some patients' experience of uncertainty:

> "For some reason between her [genetic counselor] and my oncologist, I got the impression, correctly or incorrectly that my VUS didn't really matter. Or I shouldn't pay attention to it" (Participant 6)

(b) PERSONAL

I. Psychological

Few issues regarding patients' psychological well-being was described by patients with a VUS result. One patient described the initial astonishment of receiving such a result:

> "I was expecting Lynch, and I got something that I totally wasn't expecting at all. So it was like oh, huh! It was just kind of like a shock." (Participant 11)

Another patient described her inability to psychologically cope with uncertainty:

> "It just feels dangerous and very uncertain to me…I am the kind of person that if I think, if I hear something about my future, if its not certain, it would really stress me out. [If I had been tested 21 years ago] I wouldn't have made a decision to do anything drastic about it without certainty; so for 21 years I would have been a wreck". (Participant 7)

II. Social

In addition to impacting an individual's future well-being, VUS related uncertainty was also reported as an issue for the family's well-being. One patient reported that sharing uncertain genetic information with family members has the potential to harm people who are not capable of handling such information:

> "I have a 7 year old girl… a 12 year old girl… 16 year old boy and an 18 year old girl. So it's [VUS] really a powerful piece of information. Depending on the person and situation it can do a lot of harm, it may be able to do some good. I feel like it has the potential to do a lot more harm than good in certain situations." (Participant 6)

III. Economic – no theme representing this domain was observed in the study sample.

IV. Existential

VUS uncertainty introduced several existential issues in patients – i.e., issues related to patients' sense of meaning in life.

> "Getting cancer was unfair, not knowing the reasons why is unfair-ish." (Participant 4)

(c) PRACTICAL

a. Structural

Patients in our sample did not report lack of knowledge about institutional facilities and resources of health care system as a contributor to VUS uncertainty. However, lack of knowledge about referral and follow-up systems used in genomic medicine was reported as a source of frustration by one patient:

> "I tried to talk to my oncologist about it [VUS] and he actually said, 'no, talk to the genetic counselor'. And…it really bothered me because… first of all you recommended, you referred me to this and you thought it was urgent, and you are my oncologist. I am getting a letter back from a genetic counselor who has an MS, an MS! And she is recommending that I have double mastectomy... I think that's a recommendation that should come from a physician…I am fine with being of unknown significance at this point. Really, I think the research has to take place. I am not fine with my oncologist saying "I don't know, go talk to somebody else" (Participant 11)

Complexities of the healthcare delivery system and the inter-related roles various genetic and non-genetic providers play may have contributed to the patient experience of uncertainty around VUS.

b. Procedural

Procedural issues of VUS uncertainty were directly identified by patients. Several patients noted the process of healthcare delivery surrounding VUS as problematic. Post-test genetic counseling over phone was reported as an imperfect medium for receiving uncertain information such as VUS. Patients reported that in-person counseling could have given them the chance to fully understand the complex information, and ask follow-up questions that could help reduce VUS uncertainty:

> "If I had known there was a VUS thing, I might have wanted more of an in person. Just because it was that uncertainty. So you have that phone call and well that doesn't mean anything. It's kind of a weird conversation over the phone call." (Participant 10)

> "We spoke on the phone and she talked to me [about]… the area of non-significance, variance, which was the *BARD1*. And so that was a less easy to understand on the phone, and I really got no information on if there has been any associations with *BARD1* with any type of cancer, so I didn't really hear that part." (Participant 11)

Procedural issues of VUS uncertainty also involved confusion about what would happen in the event of VUS reclassification. Patients were unsure about whether providers would notify them about reclassification or if they should check in about updates:

> "The only other real piece of information I wanted and I guess I don't 100% really remember is like hey if it changes, and if you determined that *RAD50* mutation has an inherent risk…genetically, like for my daughters…to get breast cancer if that is something they should be tested for, you know would I be notified of that". (Participant 2)

In the event of VUS reclassification, providers promised to inform patients of the new classification status. This promise for future re-contact and achieving certainty was welcomed by patients and helped reduce VUS uncertainty:

> "[The genetic counselor said] 'As time goes on, if something pops up, I will be reaching out to you.' Which was, I don't know if that was standard or not standard but I felt great about that" (Participant 10)

In addition to being appreciative of the provider's promise, patients also recognized that this was a lot of responsibility for providers:

> "I mean that would be nice but that just feels like a lot of expectation, responsibility on you. And it's my result and I should… I mean if you guys come back, whenever it is five or ten years from now and you can try and locate me [laughs] then it would be great." (Participant 6)

The option to participate in VUS reclassification research was misunderstood by some patients as a condition for being notified of VUS reclassification. One patient was under the impression that if she and her family participated in VUS reclassification research studies, they would be notified about reclassification, but if they chose not to participate or were unable to participate, then they may or may not informed about reclassification:

> "It wasn't quite clear to me whether or not they would let me know. It sounded to me like they were saying, yes, like if you are involved, if you go further and… bring more into the mix, it kind of sounded like yeah, maybe. If you don't have other family members do it, you may or may not hear from them. Possibly it would be their intention to contact you but they could miss you and forget about it. That's kind of the impression I got." (Participant 2)

Themes not specified in Han's taxonomy:

In addition to the themes identified in Han's taxonomy, providers' role in patient experience of VUS uncertainty stood out as an important theme. These themes are likely moderating factors in the genesis of many types of basic uncertainty, but was an important theme identified by our participants.

Discrepancies in how VUS was explained to the patient and whether VUS specific management recommendations were made by the providers contributed to VUS uncertainties reported by patients. Patient satisfaction with providers appeared to decrease uncertainty, whereas discrepant explanations of VUS appeared to maintain or increase uncertainty. One patient who felt confident about her ability to manage VUS uncertainty reported satisfaction with genetic counseling and confidence in her provider's abilities:

> "She [genetic counselor] gave me a ton of time in my consultation before I made the decision. She… made it easy for me to get the blood test done, she gave a me a realistic expectations about when the result would be back and then she called and gave me all the time in the world when she gave me the results, and was patient, and explained everything and every question I had and totally asked me to contact her with any questions" (Participant 6)

Trustworthy providers were seemingly able to prepare patients for the possibility of future uncertainty. Providers prepared patients for VUS that may result from their genomic testing, and discuss their ability to cope with such uncertainty. Patients reported this to be a beneficial experience:

> "My practitioner did a very good job of asking questions about ability to live with uncertainty. Both what my expectations were, how I would cope with the result either way, if we found something, if we did not find something. And what turned out to be very important this ability to live to uncertainty if you don't actually know what it means. So that counseling experience was good I think. It was broad sweeping but it was very helpful" (Participant 1)

On the other hand, uncertainty was worsened when providers provided discrepant interpretations of a VUS to patients. One patient reported that her oncologist and genetic

counselor at the same institution suggested vastly different proportions of disease risk as an interpretation of her genetic test result (she had a pathogenic variant as well as a VUS):

> "The percentage that my oncologist gave me was higher than what [the genetic counselor] told me. The percentages were much lower." (Participant 7)

Strategies for VUS-related uncertainty management:

Patient-centered strategies: Several strategies for uncertainty management was mentioned by patients:

Being unprepared or ill-prepared to receive an uncertain result may have contributed to patients' VUS uncertainty. Despite having undergone pre-test genetic counseling, several patients demonstrated limited awareness of the possibility that an uncertain result may result from the genomic test. One patient who should have been informed about the possibility of VUS reported not remembering that particular detail of the counseling process:

> "I don't remember that, but she [the genetic counselor] may have [mentioned VUS]." (Participant 6)

Sometimes patients could not recall the pre-test genetic counseling altogether, so maybe discussion of possibly forthcoming uncertainty would only benefit certain people:

> "I know I talked to somebody after the result came in, but I can't remember the other [pre-test counseling], may have been since I was at cancer care that somebody may have come in and talked to me during one of my doctor's appointments". (Participant 3)

Uncertainty reduction was attributed to the ability to understand risk information and capacity to think analytically. For example, one participant described her cognitive comfort with risk information which she believes helped reduce VUS uncertainty:

> "[It is] just my predilection and where my brain fits. I think about risk assessment, I like to read medical stuff, I like to talk about the stuff, I am interested in it, and so, I had a language and an understanding of the language, before I even started on a journey of thinking about my genetic testing and my, as well as my broader risk categories" (Participant 10)

Another patient described her analytical thinking skills which may have helped her understand complex VUS information, thus reduce VUS uncertainty:

> "I deal with the analytical stuff and…data, so maybe that helped" (Participant 4)

A few other themes regarding proactive methods of uncertainty management used by patients were collected from the transcripts: information seeking, checking back for reclassification, and reading the genetic test report.

Information seeking: In addition to the themes identified specific to sources and issues of VUS uncertainty, we identified other important themes not directly linked to Han's taxonomy of genomic uncertainty. For example, patients mentioned information seeking as a strategy for managing VUS uncertainty. Information sources utilized by patients included internet (non-specific google search), scientific databases (e.g., PubMed) and family members:

> "I looked up just to see if there was anything on the internet specific about the *RAD50*. Just to see if there were, if there were papers published or whatever, that might be out

there that I could read. That might have insight onto what is known about it thus far. I understand they cannot say that it is a genetic marker of predisposition but that does not mean they don't have some data on it." (Participant 2)

"I did a quick PubMed search actually." (Participant 5)

"I have someone in my family that I can call and say, 'Dad, I don't know what this means. Can you help me out with those stuff?" (Participant 10)

However, these information sources did not prove useful. Often there were too much information, irrelevant information, or information patients did not have free access to. Thus, it is likely that information seeking did not reduce VUS uncertainty in patients:

"I…totally looked it up. There is not necessarily a lot of information [that I was] able to find… and most of it is in the medical journals... and [I] have no access. So it…landed me exactly where the documentation that the genetic counselor [had provided]" (Participant 10)

"It couldn't just be something easy? It couldn't just be something that I could go read about in google?" (Participant 11)

Checking back for reclassification: Awareness of reclassification possibilities and acting upon that awareness by checking back for updates about VUS reclassification was a method of uncertainty management reported by patients:

"So it's [VUS] something that is always in the back of my mind, and whenever I come to my six month appointments it's one of the questions that I ask. Is there anything new on it?"(Participant 4)

Reading the genetic test report: Patients remembered receiving their genetic test report but very few read the report. The few who skimmed the report, did not find it particularly informative:

> "You know this is kind of sad but the paperwork that I got sent, I never once looked at it. I just trusted that I was told everything on the phone that was of significance. And that my oncologist would see it, that I never even looked at the paperwork…I mean it even wasn't even in my consciousness to look at it. Didn't feel like that was an important thing to do." (Participant 6)

> "I got a printed copy of it. Probably in a file with a whole lot of other things… but you know it doesn't give you a whole lot of information really. It just tells you positive or negative, and all the things they tested." (Participant 2)

> "I don't think it [the report] was very thorough. I remember it talked about the variant but I there wasn't a lot for me to read" (Participant 3)

> "I did thumb through it at home, and it was a little bit hard to understand but I don't remember that as vividly, and it is in my file cabinet somewhere. And I looked through it, I remember seeing one that was inconclusive and…that was about it." (Participant 4)

> "…eventually I got the report… it was quite lengthy…" (Participant 11)

Providers-centered strategies: Providers also played a crucial role in uncertainty management. An important strategy genetic counselors used to decrease VUS uncertainty was to explain the likelihood that a VUS would prove to be benign in future. It is estimated that most reclassified VUS are benign and not pathogenic (estimates range between 80 and 95% [16, 17, 18]). Although this should be a generally reassuring statistic for patients to hear from their

providers, one patient could not recall what the 95% exactly meant but quoted notes she had taken during genetic counseling:

> "'PTEN gene'…'variant of uncertain significance'… '95% of the time they are normal'… don't know what that means…'not enough population to test on'" (Participant 6)

The 95% estimate was also cognitively processed by participants to mean a very small risk of being pathogenic. When asked to describe the genetic test result, one patient cautiously remarked:

> "[T]here is like a 2% chance… or less [of being pathogenic], because they weren't sure, because they were studying it. But that there was a possibility." (Participant 1)

DISCUSSION

Collectively, these findings provide unique insight to better understand patients' perspectives on VUS uncertainty, offer possible reasons for differences in patient responses to VUS, and describe strategies of uncertainty management used by patients. This is the first study, to our knowledge, that qualitatively explores VUS uncertainty among patients using Han's taxonomy (Han *et. al.*, 2017). We find that a patient's primary concern with VUS uncertainty involves personal and practical issues as they directly inform health care decisions. Patients in this study demonstrated good understanding of the epistemic nature of VUS uncertainty. However, discordant provider explanations of the implication of this epistemic uncertainty for patients' diagnosis, prognosis, and therapy was an important contributor to the overall scientific issue of uncertainty. These findings are supported by results from a several other studies which also observed variation in practices of reporting, disclosure and clinical management of patients with VUS (Murray *et. al.*, 2011; Han, 2013). Patient-provider interaction was not a part of the original taxonomy, but was an important theme in our sample for e.g., who explains VUS, what

recommendations are provided, and how these recommendation are given to patients. For several domains of the taxonomy, we identified factors that exacerbated VUS uncertainty for patients (such as discordant explanations of VUS from providers) as well as strategies patients use to tolerate and manage VUS uncertainty (such as information seeking, monitoring for reclassification). We believe, together, these themes explain a significant proportion of the total variability in patient experience of VUS uncertainty, and may have practice implications. Based on our study findings, we offer a provisional framework for VUS-related uncertainty management strategy that may offer clinically actionable methods to manage VUS (Figure 3).

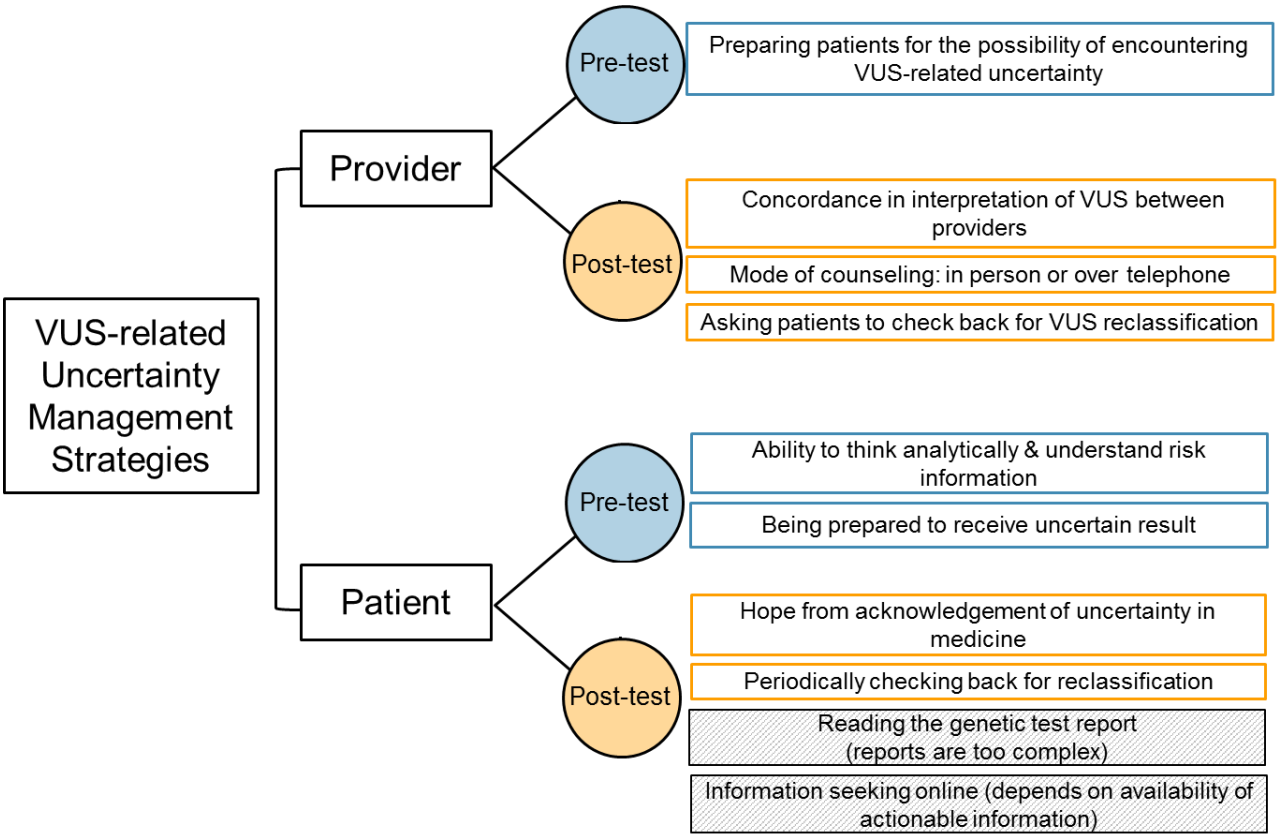


Figure 3: Framework for VUS-related uncertainty management strategies in clinical genome sequencing. Unshaded solid boxes represent effective management strategies, solid boxes shaded grey represent ineffective management strategies.

Preparation for the possibility of receiving a VUS result from a genomic test through pre-test genetic counseling appeared to help patients become more tolerant of VUS uncertainty. The effectiveness of framed health messages on behavior is well known (Rothman & Salovey, 1997); indeed, patients who knew to expect inconclusive genetic variants and were prepared to cope with the resulting uncertainty, were eventually more understanding of VUS uncertainty (Biesecker *et. al.*, 2014). Yet, despite the preparatory counseling, some patients confused VUS with 'inconclusive genes' or genes that are not directly related to the patient's indication for testing. The percentage of gene tests resulting in a VUS is only expected to increase when the extent of sequencing increases to include untranslated and deeper intronic regions and when tumor testing becomes routine (Lek *et. al.*, 2016). Thus preparing patients for the possibility of VUS through pre-test genetic counseling will continue to be important so that patients can learn to grapple with scientific uncertainty of VUS and benefit fully from shared decision making. Further research is needed on what type of preparatory discussion of VUS uncertainty will be most beneficial to patients and how the discussion of uncertainty may be best incorporated into the current conversation. One tangible solution may be to state the expected prevalence of VUS from genomic tests so that patients realize the concrete and real possibility of receiving inconclusive variants.

The epistemic uncertainty around VUS was well explained by the experienced genetic providers in our study, and consequently well understood by patients. Skilled providers used various counseling strategies to help patients manage their VUS uncertainty – e.g., mentioning

that there is a 95% probability that the VUS would be reclassified as benign (Lincoln *et. al.*, 2017; Thomson *et. al.*, 2013; Easton *et. al.*, 2007) was helpful. Providers who gave clear clinical recommendations in response to VUS seemed to help reduce patients' VUS uncertainty. Conversely, discordance of VUS interpretation between providers exacerbated VUS uncertainty for patients. On one hand provider discordance could represent ambiguity, specifically arising from provider explanations of VUS, but we believe that the theme did not represent any of the 3 subcategories as defined in the existing taxonomy– conceptual, methodological or clinical. In addition, the discordance arises from a three-way interaction (between 2 providers and patient) which, we believe represents a novel domain. Educating providers about VUS recommendation and interpretation may be easier than educating patients. Provider's promise of re-contact in the event of VUS reclassification was reassuring to patients and helped with uncertainty management. Han's taxonomy does not specify a provider's role in patient's uncertainty experience but this newly identified source should be confirmed using future qualitative studies and quantitative studies to determine how it fits into the existing taxonomy.

Several domains of Han's taxonomy were not observed in our study. Understandably, patients identified complexity as a general characteristic of genomic testing rather than specifying the underlying concepts (multiplicity of causes, multiplicity of effects, and effect modification). Economic issues were not identified in our sample, but coverage and reimbursement of genomic testing is a known problem that limits uptake of genomic testing among patients who are offered testing (Prince, 2015; Spoonamore & Johnson, 2016; Makhnoon *et. al.*, 2018). No structural issues were identified in this study perhaps because patients who have a VUS result have already navigated and successfully completed the steps that are often necessary to get a genomic test. The absence of these domain-specific themes

indicate that the relative importance of domains within the taxonomy vary by the nature of uncertainty under discussion.

VUS-related uncertainty may be reduced by participating in VUS reclassification research. Thus suggesting a follow-up process that have the potential to reduce uncertainty is valuable. However, unintentionally giving the impression that re-contact, in the event of VUS reclassification, is contingent on research participation is problematic as research participation should not be coerced. Although not reported by our study participants, it is possible that participation in VUS reclassification studies would also aid uncertainty management for patients as has been suggested previously (Solomon *et. al.*, 2017). Providers could assist patients with other methods of uncertainty management – such as learning strategies to cope with uncertainty. For many patients the only option is waiting and periodically checking back for reclassification. These patients may specially benefit from discussions about strategies to cope with uncertainty.

Patients reported two proactive strategies of uncertainty reduction, internet searches and periodically checking back with providers; however, neither were ultimately useful. Among the highly educated study participants, those who attempted internet searches there was little success; there was not any actionable information about VUS, patients were unable to understand the complex information, or the information was not freely accessible. The recommended practice of periodically checking back for VUS reclassification was used by some patients and seemed to be beneficial for uncertainty management. This finding is similar to that of a prior study which found that information seeking about VUS was not associated with patient behavior in response to VUS (Makhnoon *et. al.*, 2017). Most patients did not attempt to read the genetic test report that they were given because they trusted their providers to read and

interpret the report for them. The few who skimmed the report, found it to be unhelpful. These observations about readability and patient utility of genomic test reports have also been identified in prior studies (Makhnoon *et. al.*, 2018; Haga *et. al.*, 2014).

Study limitations: This is the first structured exploration of patients' experiences of VUS uncertainty but is not without its limitations. The main limitation of the current study is the lack of generalizability of these findings to all clinical settings as the sample was almost exclusively composed of patients from a specialized cancer hospital system. In addition, the lack of viewpoints from a diverse group of patients with VUS results also affected generalizability. However, these findings demonstrate that even patients counseled by skilled genetics providers experience various VUS uncertainties and may need assistance coping with uncertainty. Uncertainty related issues raised by highly educated sample of patients is likely to be even more profound in less educated populations. All participants in this study were selected because of their VUS result, but specific clinical and personal circumstances may have varied across patients. The patients encountered various counseling experiences from different types of genetic providers (genetic counselors, and genetic oncologists) and non-genetic providers (surgeons).

Conclusion: This study illustrates several contributors to cancer patients' VUS uncertainty. Han's organizational framework can help other stakeholders reach a greater understanding of VUS uncertainties in patients' minds; providers can understand patient perspectives of uncertainty and counsel patients accordingly. Patient interviews highlight the importance of giving clear and concordant VUS-based clinical recommendations – VUS results should not be used for medical care, and have no direct implication for family members. Providers should take

care that the offer of research participation is not interpreted as a condition for being informed about reclassification.

CHAPTER 3: Dealing with Uncertainty: Information seeking to guide VUS management

ABSTRACT

Ability to deal with uncertain genetic test information is likely important determinant of patients' confidence in decision making. Management of variants of uncertain significance (VUS) is known to be challenging for patients. We hypothesize that, information seeking may help patients cope with their VUS result and be important in subsequent clinical decisions.
We describe patients' VUS information seeking and management behavior using a cross-sectional survey of 46 patients with a clinically confirmed VUS result. The survey instrument consisted of 3 sections: (1) demographics, (2) use and trust of VUS information sources, and (3) VUS related health behavior. 52.4% of patients reported seeking information about VUS after receiving test results; health care providers and cancer research organizations were preferred and trusted information sources. Most did not undergo surgery (61.8%) or screening (62.5%) based on VUS. 46.7% asked family members to get genetic test because of their VUS result but 69.5% did not check back for VUS reclassification. Few VUS patients encouraged relatives to undergo clinical testing for VUS and. Information seeking was not associated with these behaviors. We did not find evidence to support the hypothesis that VUS related information seeking is effected through demographics, belief, direct experience and mediated through Utility as predicted by the comprehensive model of information seeking.

Keywords: Information seeking, management, variants of uncertain significance, VUS,

INTRODUCTION

Ability to deal with uncertain information is an important determinant of patients' confidence in decision making (Lee & Dry, 2006; Edwards *et. al.*, 2012). People use information seeking as a means of dealing with the psychological challenges of uncertain information in general (Brashers, 2001). Health information seeking behavior relates to the ways in which individuals go about obtaining health information, health promotion activities, risks to one's health, and illness (Lambert & Loiselle, 2007). Information seeking refers to active and deliberate searching and gathering of information outside of the normal patterns of exposure to mediated and interpersonal sources (Atkin, 1973; Griffin et al., 1999). "This definition includes any non-routine media use or interpersonal conversation about a specific topic outside the normal flow of conversation" (Niederdeppe *et. al.*, 2007; Wong, 2012). This coping mechanism is likely to occur and be potentially helpful when faced with uncertainty in genomic medicine as well (Han *et. al*., 2017). In genomic medicine, Variants of Uncertain Significance (VUS) are an increasingly common type of test result (Maxwell *et. al*., 2016) that patients and providers have difficulty using for medical decision making (Mishel, 1999). A variant is classified as VUS if the variant does not fulfill criteria for pathogenic or benign classification, or the evidence for benign and pathogenic classification is conflicting (Richards *et. al*., 2015). The seeking of additional information about a specific VUS may help patients cope with their VUS results that may be important in subsequent clinical decisions, e.g., whether or not to get more frequent mammograms due to a *BRCA1* VUS result. It is worth understanding factors that correlate with VUS related information seeking behavior, and the relationship between patients' information seeking behavior and VUS management so that we can consider implementing interventions that help achieve optimal health outcomes for patients with a VUS.

The National Comprehensive Cancer Network (NCCN) recommends basing medical management for individuals with a VUS result on family history and offering them research

options to help classify the variant (NCCN, 2014). Therefore, patients with a VUS result are given one or more of the following VUS management recommendations: (1) Do not use VUS for medical management such as surgery and screening, (2) Do not test family members for clinical purposes, (3) Check back for updates regarding VUS reclassification, and (4) Consider participating in VUS reclassification study. However, there is inconsistency in personal interpretation of these clinical recommendations among providers (Petrucelli *et. al*., 2002), and perhaps consequently, anxiety and misunderstanding among patients (Makhnoon *et. al.*, 2017).

Patient behavior in response to VUS is varied and often is not in line with published guidelines. For example, although, surgical decisions such as mastectomy, colectomy should not be based on VUS results, such decisions are not uncommon – for e.g., 24%-50% surgeons managed patients with VUS the same as pathogenic mutations (Kurian *et. al*., 2017; Murray *et. al*., 2011). However, little is known about how patients behave in response to the remaining VUS management recommendations such as decisions to change screening frequency, such as mammography or colonoscopy. The goal of this study is to describe patients' behavior in response to clinical VUS results. We limited our study to the first three management behaviors only as the fourth management behavior of participating in reclassification studies is just offered as a suggestion, not a strong recommendation. Additionally, some patients may be ineligible to participate in such studies or a study may not be available to them.

Information seeking may help patients manage uncertainty related to VUS. According to Mishel's theory of uncertainty, unresolved uncertainty can trigger anxiety and fear or resignation, if there appears no way to resolve uncertainty; or it may trigger hope, if new information reframes people's experiences (Mishel, 1999). Indeed, various affective responses

are expressed by patients who receive VUS in clinical settings – positive, negative, neutral and combined (Solomon *et. al.*, 2017; Makhnoon *et. al.*, 2017). The Uncertainty Management Theory (UMT) suggests that individuals may engage in information seeking to manage uncertainty (Brashers, 2001; Han *et. al*., 2017). In support of this theory, previous studies have shown a positive association between uncertainty level and information seeking in hypothetical (Rains & Tukachinsky, 2015) and applied (Fisher *et. al*., 2017) scenarios. Therefore, it is likely that VUS related uncertainty is also managed through information seeking but little is known about patients' information seeking behavior in response to VUS test results.

Although a rich body of literature exists in cancer information seeking behavior (Finney Rutten *et. al.*, 2016), studies exploring information seeking in response to cancer genetic test results of any type are limited. A search of the existing literature found that, information seeking was used as a strategy to manage uncertainty among women at-risk for, or carriers of, *BRCA1/2* mutations (Petrucelli *et. al*., 2002) and to understand the contribution of various health-habits to genetic susceptibility of skin cancer (Hay *et. al*., 2012). Although information alone does not guarantee healthy behaviors, acquiring adequate information may motivate individuals to make informed changes in their health practices (Meischke *et. al*., 2005; Shi, Nakamura & Takano, 2004), and is therefore worth understanding. Information seeking in response to VUS as a mechanism for uncertainty management is likely due to three main reasons. First, feelings of anxiety, confusion, helplessness, and worry are known reasons for and predictors of information seeking following a medical appointment (Li *et. al*., 2014) and these feelings have been well documented among VUS patients (Solomon *et. al*., 2017; van dijk *et. al*., 2006; Makhnoon *et. al.*, 2017). Second, we know that individuals who engage in information seeking demonstrate the capacity to obtain, process, understand and use genomic information for health decision making – for example, they endorse multifactorial beliefs about

cancer (Waters, Wheeler & Hamilton, 2016) and prefer a collaborative role in treatment decision making (Davison & Breckon, 2012). Since VUS management recommendations are often challenging for patients (Solomon *et. al*., 2017; Kurian *et. al.*, 2017), information seeking may also aid health decision making in response to VUS. Third, dissatisfaction with a physicians' performance is another motivator for information seeking (Hay *et. al.*, 2012) and there is some evidence of provider distrust following receipt of VUS results (Makhnoon *et. al*., 2017). These suggest that health information seeking is a likely coping mechanism patients use to deal with VUS information. To our knowledge, information seeking in response to VUS results has not been objectively studied. We aim to describe patients' VUS specific information seeking behavior after receiving a VUS result.

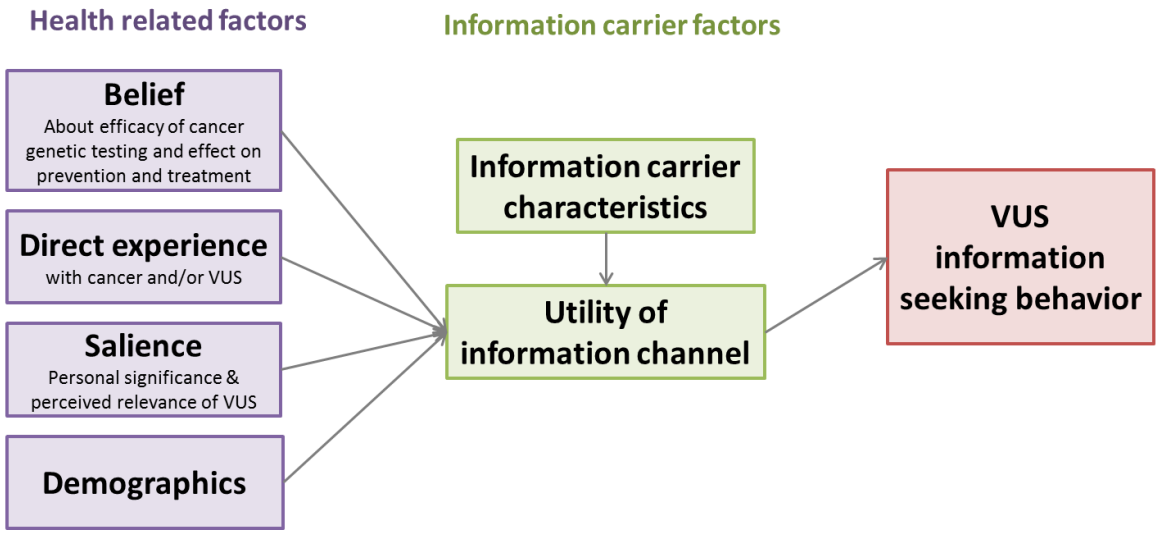
The socio-demographic and situational factors that predict health information seeking behavior in health settings, may also be common among people who undergo genetic testing and receive VUS result. Some socio-demographic factors that predict health information seeking include White race, female gender (Czaja *et. al.,* 2003), younger age (Muha *et. al.,* 1998), higher educational attainment (Czaja *et. al.,* 2003), presence of health insurance coverage, and high eHealth literacy. These socio-demographic factors are also common among patients who undergo genetic testing. The commonalities rationalize using a general health/cancer information seeking model to understand antecedents of information seeking among VUS patients. We will use the Comprehensive Model of Information Seeking (CMIS) to understand the motivational antecedents of VUS specific information seeking in patients.

Information seeking model: CMIS

One widely used model that allows us to explore antecedents of information seeking is the Comprehensive Model of Information Seeking (Johnson and Meischke, 1993). Variables

contained in CMIS are organized into two levels – health related factors (Belief, Direct experience, Salience, and Demographics) and information carrier factors (Information carrier characteristics, and Utility of information channel) (Figure 4). Together, these are expected to predict information seeking behavior.

Figure 4: Comprehensive model of information seeking adapted for VUS.



According to the model, the antecedents prompt search behavior, helps determine a user's choice of information carriers and a user's set of search skills. The information carrier characteristics also determine consumer choices of information sources and shape the nature of the search process (Johnson, 1992; Hartoonian *et. al.,* 2014; Kim *et. al.,* 2017). Model variables were adapted for the context of this study. Selected demographic factors include: age, gender, education, and parenthood. We add parenthood as a factor that is important in genetically inherited diseases (Kaphingst *et. al.,* 2009). Additionally, direct experience with cancer and/or VUS through a social network or personal experience with is a determinant of information seeking is included. Similarly, salience, which is a combination of the personal significance of VUS and perceived relevance of VUS; beliefs about the efficacy of cancer genetic testing, and

effect on prevention and treatment can influence information seeking and are used as additional health related factors. Information carrier factors such as its characteristic (e.g., perceived message credibility of the source) and utility (e.g., satisfaction of information needs from the source) influence the ultimate scope of one's VUS information seeking.

In summary, the research questions explored in this study are:
Research question # 1: Describe patients' information seeking behavior after receiving a VUS result, *Research question # 2:* Describe patients' VUS management behavior, and *Research question # 3:* Is VUS specific information seeking behavior associated with patient VUS management behavior?

MATERIALS AND METHODS

Sampling

We reviewed medical records of patients seen at the Seattle Cancer Care Alliance (SCCA) genetic counseling clinic to identify patients who met the study inclusion criteria: (1) above 18 years of age, (2) seen at the clinic's Hereditary Breast and Ovarian Cancer (HBOC), Colorectal Cancer (CRC) and Pancreatic Cancer (PC) programs between October 2013 and March 2017; (3) received at least one clinically confirmed VUS result. 146 patients who met these criteria were contacted over telephone. The two remaining eligibility criteria of (4) speaking English, and (5) access to the internet were confirmed over the telephone as a part of the screening. 137 patients met all eligibility criteria were invited to participate in the study. This study was approved by the University of Washington institutional review board (STUDY00000175).

Data Collection

In total, 62 patients agreed to participate and provided oral informed consent over the telephone. Consenting participants were emailed a link to the study survey administered through Redcap (Harris *et. al.*, 2009). Two reminder emails were sent at 3 and 4 weeks. In total, 46 participants completed more than 95% of the survey between November 2016 and March 2017 and were included in the study. The remaining participants were not recruited due to one of the following reasons – they declined to participate (n=7), did not have valid contact information (n=9), lost to follow up (n=16) or did not return voice messages left on the phone. The response rate was 33.5% (46/137).

Survey instrument

The final survey instrument consisted of 3 sections: (1) demographics, (2) use and trust of VUS information sources, and (3) VUS related health behavior.

Measures

Patient demographics and covariates

Patient characteristic included in the survey were age, education, cancer diagnosis, and number of biological children. Demographic characteristics - sex and ethnicity were extracted from patient medical records.

Acquiring VUS specific information

Selected questions from the Health Information National Trends Survey (HINTS; HINTS 4 Cycle 4), based on relevance to our study, were adapted to measure VUS specific information seeking. VUS specific information seeking behavior was assessed using 3 items: “Have you ever looked for information about health or medical topics from any source?” (Emanuel *et. al.*, 2015), “Have you looked for information about cancer genetic testing from any source?”

(Emanuel *et. al.*, 2015) and "Have you looked for information about Variants of Uncertain/Unknown Significance (VUS) from any source?" (Emanuel *et. al.*, 2015) (Yes, No, I don't know). Individuals who responded "No" to the health and genetic testing information-seeking questions were re-coded as having not sought VUS information.

Source of information seeking was assessed indirectly with seven items that shared a question stem: "The most recent time you looked for information about health and medical topics (such as general health, cancer, genetic testing or VUS), which information source did you go to first [Family; Friend/Co-worker; Doctor, health care provider or genetic counselor; Cancer and/or Research Organizations (e.g., Fred Hutch, University of Washington); General medical information websites (e.g., WebMD, CDC); Genetic testing laboratory (e.g., Myriad, UW Lab Medicine); Other]?" (Roach *et. al.*, 2009).

Influences on information processing

Trust in the information source was assessed with two items: "In general, how much you would trust information about VUS from each of the following: [a genetic provider (genetic counselor, medical geneticist etc.), family or friends, newspapers or magazines, Internet, government health agencies]?" (Roach *et. al.*, 2009) Response options ranged from (1) not at all to (4) a lot.

CMIS model based factors: Antecedents

Belief: Survey questions used to asses beliefs were 'Do you believe a confirmed genetic test result (positive or negative) is important for cancer prevention (e.g., prevention by screening)?', 'Do you believe that a confirmed genetic test result (positive or negative) is important for cancer diagnosis?' and 'Do you believe that a confirmed genetic test result (positive or negative) is important for cancer treatment?' with two categories (yes and no).

Direct experience: Cancer diagnosis and the number of cancer patients in social network were included as predictors of direct experience.

Salience: Survey questions used to asses salience were (1) 'How often have you thought about your chances of getting cancer (again) based on your VUS result?', (2) Have these thoughts affected your mood?', (3) 'Have these thoughts interfered with your ability to do daily activities?', (4) 'How often do you worry about developing cancer as a result of VUS?' and (5) 'How often do you worry about the chance of family member also carrying a VUS and developing cancer?'. Answer choices to these questions were: Not at all, A little bit, Somewhat, Quite a bit, Very much. Lastly, they were asked, 'Based on your VUS result, how likely is it that you will develop cancer in the future?' with categories: Very high, High, Average, Low, Very low.

Demographic: Demographic characteristics included age, sex, race, education, and parenthood.

CMIS model based factors: Information carrier characteristics

Utility: Predictors of utility were 'The information I found was hard to understand' (Strongly agree to Strongly disagree) and 'Overall, how confident are you that you could get clarification about VUS if you needed it?' (Completely confident to Not confident at all).

Information carrier characteristics: As an information carrier factor we included 'It took a lot of effort to get the information I needed', 'I felt frustrated during my search for information', and 'I was concerned about the quality of (VUS) information' with categories (Strongly agree to Strongly disagree).

VUS management recommendation

We abstracted medical management recommendations from Electronic Health Records, specifically, from patient summary letters or telephone call notes written by genetic counselors. Only documented recommendations (entries described as a task/instruction for the patient) made in response to VUS test result were recorded. Conversations with genetic counselors and observed patient interactions revealed discordance between verbally reported recommendations and those documented in health records – verbal recommendations being more comprehensive than documentation. Based on observed patient visits we assumed that VUS patients uniformly received the three recommendations as the standard of care: (1) Do not use VUS for medical management such as surgery and screening, (2) Do not test family members for clinical purposes, (3) Check back for updates regarding VUS reclassification.

VUS related health behavior

Types of VUS management recommendations were gathered from published literature, patient summary letters, and genetic testing laboratory reports. This information was then converted into survey questions to assess patients' health behavior related VUS. In order to assess patients' VUS related health behavior, patients were asked to complete a series of survey questions. For patients who answered 'yes' to the question: "Have you EVER undergone cancer-related surgery (such as mastectomy, oophorectomy, colectomy etc.)?" a follow-up question was asked: "Did you consider VUS result in your surgical decision?" (No, VUS was not important in my surgical decision/ Yes, VUS result was why I underwent surgery/ Yes, a VUS result was part of my surgical decision). Patients who did not undergo cancer related surgery were asked: "Did you consider a VUS result in your decision not to undergo surgery?" (I did not undergo surgery because it was medically unnecessary/ VUS was not important in my surgical decision/ I did not undergo surgery because of my VUS result).

To assess patients' screening behavior in response to VUS, we asked: "Did you consider VUS result in your screening decision?" (Yes, I began screening because of my VUS result/ Yes, I increased the frequency of screening because of my VUS result / Yes, I decreased the frequency of screening because of my VUS result/ No, my screening frequency did not change).

To assess VUS related familial sharing behavior, we asked: "Did you encourage/ask any of your family members to get genetic testing as a result of your VUS result?" With Yes/No answer choices. Participants were then asked a follow-up question about reasons for their decision with the following answer choices: to help determine my family's cancer risk, to prevent cancer in my family in future, to obtain information that can clarify VUS test result, because my provider had asked me to.

To assess patient behavior related to checking back for VUS reclassification, patients were asked: "Did you ever check back for VUS reclassification with your provider?" As patients may also be given a VUS reclassification result by a provider, we also asked "Did your provider ever contact you with updates on VUS reclassification?" (Yes/No).

Analytic strategy

Bivariate logistic regression was used to examine the unadjusted associations between socio-demographic characteristics (predictor) and information seeking (outcome). Types of VUS management behaviors were qualitatively categorized into "Action", "Inaction" or other. For patients who underwent cancer surgery, "Action" included the responses "VUS result was the reason for undergoing surgery" and "VUS result was part of surgical decision"; "Inaction" included the response "VUS was not important in surgical decision". For patients who did not undergo surgery, "Action" included "Did not undergo surgery because of VUS result"; "Inaction" included "VUS was not important in surgical decision" and "Surgery was medically

unnecessary". For patients who underwent cancer screening, "Action" included the responses "Began screening because of VUS result", "Increased the frequency of screening" or "Decreased the frequency of screening"; "Inaction" included the response "No, my screening frequency did not change".

Internal consistency of survey items under each CMIS construct was measured using Cronbach's alpha (Cronbach, 1951). Mediation analysis (preacher and Hayes, 2008) was used to examine whether CMIS based constructs explain VUS information seeking. In model 1, we modeled the odds of information seeking using multiple logistic regression with all level one CMIS based predictors - belief, direct experience, salience, demographics, and information carrier characteristics as predictors (i.e., all constructs except Utility). In model 2, we ran a similar analysis with only utility as the predictor. In model 3, we modeled the odds of information seeking with all CMIS based constructs as predictors. To facilitate interpretation of the resulting odds ratios, all ordinal predictor variables representing measures of each CMIS construct (belief, direct experience, salience, information carrier characteristics and utility of information source) were combined to create continuous scores.

Descriptive statistics were used to compare VUS related health behavior between information seekers and non-seekers. Chi-squared test was used to measure association between management behavior and information seeking. Respondents were allowed to skip questions; therefore, we analyzed each question with N equal to the number of valid responses to that particular question. All data were analyzed using the R software package (version 3.3.2) and an alpha value of 0.05 was employed as the criterion for statistical significance.

RESULTS

Background Data

Detailed demographic information about the 46 study respondents is presented in Table 2. Respondents were primarily female, of European ancestry, highly educated, and on average 48.0 years of age. The majority of respondents had one or more biological children (69%), and had been diagnosed with cancer (69%). All respondents had health insurance. All but 2 participants had undergone a cancer panel test – 34 of the 46 participants had a VUS only result, whereas the remaining 12 had a deleterious mutation accompanying their VUS result. Genetic test results for 41 of 46 participants were disclosed by a genetic counselor. Approximately half of the respondents had completed the study survey within 7 months of genetic testing (48%), while over 7 months had elapsed between genetic testing and survey completion for the rest (52%).

Table 2: Demographics and genetic test characteristics of study participants (N=46).

Demographic factors		N	%
Gender			
	Male	6	13
	Female	40	87
Age (years)			
	Mean	48.0 ± 12.1	
	Median	47	
Ethnicity			
	European	38	84.4
	Asian	4	8.9
	Middle Eastern/African	2	4.4
Education			
	12 years or High school	3	6.7
	Post high school or vocational	4	8.9
	Some college	4	8.9
	College graduate	22	48.9
	Postgraduate	12	26.7
Parenthood			

	Yes	32	69.6
	No	14	30.4
Insurance			
	Medicare/Medicaid	4	8.9
	Others (VA, private, etc.)	42	93.3
Health status			
	Diagnosed with cancer	32	69.6
	Never diagnosed with cancer	14	30.4
Genetic testing factors			
No of genes tested (n=44)			
	1 gene	2	4.5
	≥ 2 genes	42	95.5
Type of variant detected (n=46)			
	VUS only	34	73.9
	VUS and pathogenic	12	26.1
Time between genetic testing and survey completion			
	≤ 12 months	30	65.2
	> 12 months	16	34.7
Test results disclosed by			
	Genetic counselor	41	89.1
	Non-genetic counselor	5	10.9

Recommendations given on result disclosure

Medical management recommendations abstracted form patient summary letters or telephone call notes written by genetic counselors and providers are shown in Table 3. The most commonly given recommendation recorded in medical records (recorded for 65% of patients) was to not change medical management based on the VUS result. 50% of patients' medical records stated they were also asked not to test family members based on the VUS test result. The least frequent recommendation recorded in the medical record (recorded for 24% of patients) was to check back for VUS reclassification. Non-Genetic Counselor (GC) providers never noted a VUS specific recommendation in patient medical records. There was no statistically significant association between provider recorded VUS recommendations in the EHR and patient action/inaction ($\chi2=0.027$, $p=0.86$; $\chi2=0.29$, $p=0.58$; $\chi2=0.09$, $p=0.75$ and $\chi2=0.02$, $p=0.87$ for surgery, screening, VUS check back and family testing respectively).

Table 3: VUS recommendations given by providers during genetic test result disclosure.

Recommendation	All patients N (%)	VUS only patients N (%)
1. Do not change medical management based on VUS	30 (65.2)	23 (67.6)
2. Do not test family members based on VUS	23 (50)	18 (52.9)
3. Check back for reclassification	11 (23.9)	9 (26.4)

Information seeking behavior

About half of all patients (52.4%) reported seeking information about VUS. Bivariate examination of the relationship between demographic variables and information seeking showed not statistically significant association. Gender, educational attainment, parenthood or cancer diagnosis were not significant predictors of information seeking in our sample however there was trend for women to engage in more information seeking than men (OR=2.24, *p*=0.33), but higher information seeking was associated with having a postgraduate degree (OR=0.28, *p*=0.09 for college graduates, and OR= 0.83, *p*=0.85 for vocational/technical or some college), being a parent (OR = 0.75, *p*=0.66) or being diagnosed with cancer (OR=0.49, *p*=0.28) (Table 4).

Table 4: Bivariate relationship between patient demographic characteristics and VUS information seeking (N=46).

Predictor	Information seeker		
	OR	**95% CI**	*p*
Female	2.24	[0.42 - 19.1]	0.33
Age (years)	0.98	[0.93 - 1.03]	0.58
Education			
12 years or completed high school	1.0	[0.07 - 25.4]	1
Vocational/technical or some college	0.83	[0.12 - 5.77]	0.85
College graduate	0.28	[0.05 - 1.20]	0.09
Postgraduate†	1.0		

Parenthood	0.75	[0.20 - 2.64]	0.66
Diagnosed with cancer	0.49	[0.12 - 1.74]	0.28

Note: OR = Odds ratio; CI = Confidence interval
†Referent

To seek information about VUS, patients commonly went to health care providers first (47.1%), and then to cancer research organizations (39.1%). Family and friends were the least reported source of VUS information (Figure 5). Genetic providers were the most trusted source of VUS information, followed by government health agencies (Figure 6).

Figure 5: Different information sources used by patients (N=46) to seek information about Variants of Uncertain Significance (VUS).

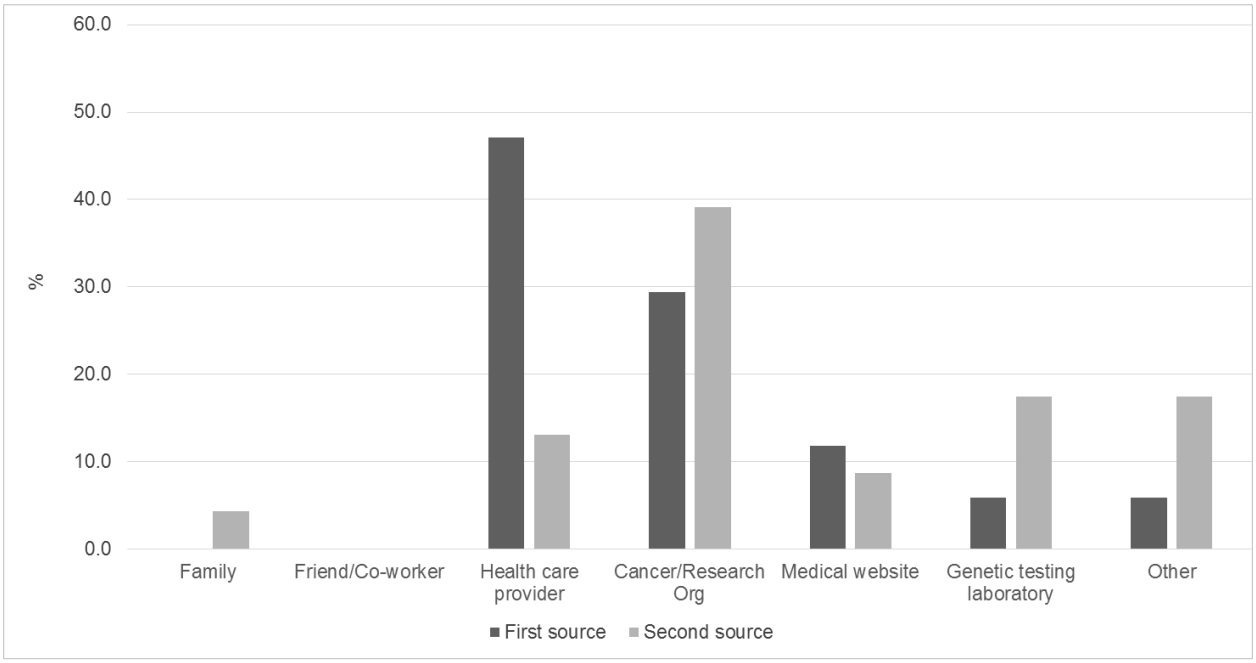
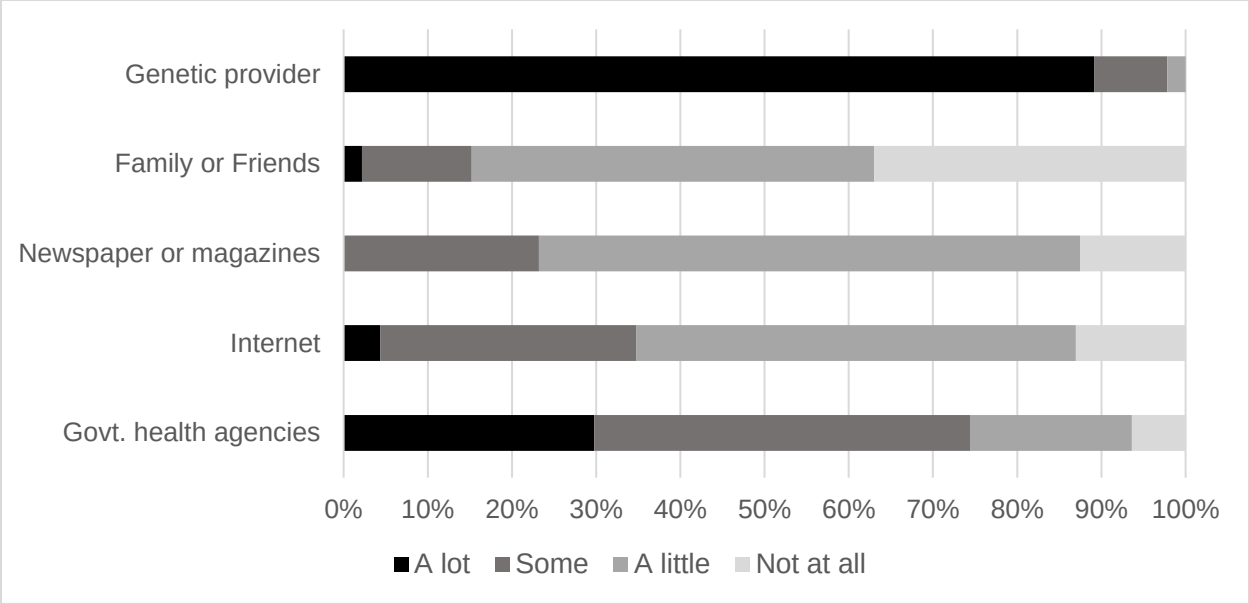


Figure 6: Levels of trust in various Variants of Uncertain Significance (VUS) information sources as reported by patients with a clinically confirmed VUS (N=46).



Survey items used to measure CMIS constructs showed moderate internal consistency, Cronbach's alpha ranged from 0.43 – 0.85 (Table 5). We dropped one item (the number of cancer patients in social network) from the item with the lowest alpha value, i.e., direct experience in subsequent analysis to improve internal consistency.

Table 5: Reliability coefficients of CMIS constructs

CMIS Constructs	Cronbach alpha values
1. Belief (3 items)	0.61
2. Direct experience (2 items)	0.43
3. Salience (6 items)	0.80
4. Utility (2 items)	0.55
5. Information carrier characteristic (3 items)	0.85

Results from mediation analysis of VUS information seeking behavior are shown in Table 6 below. In model 1, we did not observe statistically significant associations between the predictors – demographic variables (age, gender and education), belief, direct experience,

salience, information carrier characteristics and outcome – information seeking. We found suggestive evidence that: information seeking was less frequent among males (OR= 0.44, *p*=0.42), among patients with higher direct experience with cancer (OR=0.86, *p*=0.84), who felt that information was easy to navigate (OR=0.91, *p*=0.51), and believed VUS information to be salient for their disease risk (OR=0.96, p=0.67). On the other hand, more VUS information seeking was reported by patients who believed in the efficacy of genetic testing for their diagnosis, treatment, and management (OR=1.19, *p*=0.65).

Including utility as a predictor in model 2, generally decreased the effect sizes association between individual predictors and information seeking, although the associations were not statistically significant. In the full model 3, the effect sizes of the predictors from model 1 decreased overall, while the effect size of Utility of Information Channel increased. None of the effects were statistically significant. Utility was the outcome variable in model 4, where information carrier characteristics was a significant predictor of utility (OR=2.69, p=0.01). This provides inconclusive evidence that the effect of Demographics, Belief, Direct experience and Salience on information seeking is mediated through Utility as predicted by CMIS.

Table 6: Mediation analysis of CMIS constructs as predictors of VUS related information seeking behavior (N=46).

	Model 1*		**Model 2***		**Model 3***		**Model 4^**	
Predictor	OR	*p*	OR	*p*	OR	*p*	OR	*p*
Demographics								
Age	0.99	0.86	1.0	0.96			0.97	0.64
Male	0.44	0.42	0.29	0.26			0.33	0.45
Education	0.86	0.71	0.78	0.57			0.77	0.69
Belief	1.19	0.65	1.39	0.42			0.67	0.49
Direct experience	0.86	0.84	0.46	0.41			2.37	0.46
Salience	0.96	0.67	0.91	0.37			1.16	0.28
Information carrier characteristics	0.91	0.51	0.72	0.18			2.69	**0.01**
Utility of information channel			1.31	0.41	0.87	0.44		

*Information seeking is the outcome in Models 1-3
^Utility is the outcome in Model 4

VUS management behavior and information seeking:

In order to check that VUS management behavior was not influenced by an accompanying deleterious mutation, we separately analyzed people with only a VUS. Patterns of VUS related behavior among patients with only VUS results (and no accompanying deleterious results) were similar to patients with VUS as well as an accompanying deleterious mutation (Table S2).

Table 7: Use of VUS result in medical decision making and influence on health behavior among patients with clinically confirmed VUS (N=46).

Health decision/Health behavior	N	%	Information seeker N (%)	Information non-seeker N (%)	X^2	P-value
Surgical decision making						
Patients who underwent cancer surgery:	34					
Action[1]	6	17.6	4 (66.6)	2 (33.3)		
Inaction[2]	21	61.8	11 (52.3)	10 (47.6)	0.932	0.63
Other	4	11.7	3 (75)	1 (25)		
Patients who did not undergo surgery:	12					
Action[3]	2	16.6	0 (0)	2 (100)		
Inaction[4]	5	41.6	2 (40)	3 (60)	NA	NA
Other	2	16.6	2 (100)	0 (0)		
Screening decision making						
Patients who underwent cancer screening:	40					
Action[5]	8	20	6 (75)	2 (25)		
Inaction[6]	25	62.5	11 (44)	14 (56)	2.33	0.31
Other	4	10	2 (50)	2		
Family testing based on VUS						
Asked family to get tested because of VUS	21	46.7	12 (57.1)	9 (42.8)	0.22	0.63
Did not ask family to get tested	24	53.3	12 (50)	12 (50)		
Checking back for VUS reclassification						
Checked back for reclassification:	8	17.4	7 (87.5)	1 (12.5)	3.15	0.076
Did not check back for reclassification	32	69.5	17 (53.1)	15 (46.8)		
VUS was reclassified	6	13.0	NA	NA		

[1]Includes “VUS result was the reason for undergoing surgery”, “VUS result was part of surgical decision”

[2]Includes “No, VUS was not important in surgical decision”
[3]Includes “Did not undergo surgery because of VUS result”
[4]Includes “VUS was not important in surgical decision”, “Surgery was medically unnecessary”
[5]Includes “Began screening because of VUS result”, “Increased the frequency of screening”, “Decreased the frequency of screening”
[6]Includes “No, my screening frequency did not change”

Table 7 shows how patients used VUS result for medical decision making (surgical and screening), for health behavior (asking family members to get genetic test and checking back for VUS reclassification) as well as their VUS related information seeking behavior. Among patients who underwent cancer related surgery (n=34), 6 reported that the medical decision was at least in part based on the VUS result whereas 21 reported that VUS was not important in their decision. For patients who did not undergo surgery (5/12), the most commonly reported reason for inaction was that surgery was medically unnecessary (4/5). While 25 of 40 patients reported that VUS was not relevant in their screening decision, 8 of 40 informed the frequency (either decreased or increased frequency) of their cancer screening based on the VUS. Half of all study participants (21/46) asked their family to get a genetic test because of their VUS result, while the remaining (24/46) did not engage in this health behavior (1/46 did not respond). Most patients (32/46) did not check back for a VUS reclassification and the most common reason for doing so was not knowing that VUS can be reclassified (data not shown). 8/46 patients checked back for reclassification at least once, and the test result of 6/46 patients were reclassified at the time of the survey.

Overall, the proportion of respondents who reported seeking different kinds of information ranged from 44 to 87.5%: patients who checked back for VUS reclassification engaged in the highest rate of information seeking (87.5%). There was no statistically significant association between information seeking and VUS management behavior.

DISCUSSION

We find that 50% of patients in our study sought VUS information after their result was disclosed to them. Information seeking is a known response to uncertainty (Guillaume & Bath, 2004) and lack of information is a principle reason for VUS related uncertainty reported by patients (Makhnoon *et. al.*, 2017). Therefore, information seeking in response to VUS is expected and endorses the Uncertainty Management Theory. The rate of information seeking in response to a VUS observed in our study is higher than information seeking following confirmed genetic results observed by others- such as 25% for *BRCA1/2* (Shim, Kelly & Hornik, 2006), 32% in type 2 Diabetes (Mills *et. al.*, 2014). Reasons why the remaining patients in our study did not seek VUS information may be because they were satisfied with their genetic counseling experience and all their VUS related questions had been answered, as satisfaction with genetic consultation has been associated with lower information seeking about *BRCA* genetic testing previously (Cypowyi *et. al.*, 2003). It may also be because these patients had the dispositional characteristic of being more tolerant of uncertainty (Freeston *et. al*., 1994) - which refers to a trait of the individual rather than a perceived characteristic of the situation (Rosen, Ivanova & Knäuper, 2014). We did not investigate whether the type of uncertainty itself or the interpersonal differences in ability to cope with uncertainty prompted information seeking in our participants. Understanding this distinction may be necessary to provide support for managing uncertainty and patients' emotional response to uncertainty.

There was a trend for women, patients with higher educational attainment, and those without a cancer diagnosis to be more likely to seek information about VUS. These sociodemographic characteristics are consistent with research on the association between health information seeking and gender (Finney Rutten *et. al.*, 2016), and education (Kaphingst,

Lachance & Condit, 2009). Lower information seeking among cancer patients in this study is likely explained by the fact that medical management of patients with cancer will not change due to VUS. However, cancer patients motivated to understand the implication of their VUS result for their family members may still seek VUS information. In contrast, management of patients without cancer is dependent on their genetic test result, thus VUS related information seeking might yield answers to questions on screening or preventative surgery. Overall, sociodemographic characteristics associated with VUS information seeking seems to be similar to characteristics of cancer information seekers in general. We find suggestive evidence to extend the Comprehensive Model of Information Seeking to VUS information seeking. We find that VUS information seeking behavior generally follows the relationship between constructs as described by CMIS; however, not all pathways within the original model was confirmed in our study – no observed effect of age, education, direct experience, and salience on information seeking in the present study.

Health care providers and cancer research organizations were reported as the most common sources of VUS information by our patients, whereas family and friends were not major sources. Genetic testing is a relatively new phenomenon in medicine, thus patient reliance on health care providers who are generally considered more important (Pecchioni & Sparks, 2007), trustworthy (Hesse *et. al*., 2005), and credible (Johnson & Meischke, 1992) sources of information, and able to provide more useful medical information (Carmo-Fonseca, Mendes-Soares & Campos, 2002) than the Internet, friends and family, or mass media sources for VUS related information is reasonable. Health care providers also provide highly tailored information that enable patients to acquire advice unique to their situation and we know that preference for personalized material is important for cancer patients (Ling, Klein & Dang, 2006). Convenience is highly prioritized by individuals, and internet and friends/family tend to be most convenient

information sources (Case, 2007). This may explain why cancer research organizations (perhaps accessed through the internet) were reported as the second most common source of information. The 2003 HINTS data for cancer-related information seeking (Rutten, Squiers & Hesse, 2006) were similar to our findings in that internet and health care professionals were trusted sources, whereas interpersonal sources were not as common; but different in that printed materials were also a common source in HINTS (Andrykowski *et al*., 2001). Overall, sources of VUS information utilized by patients were similar to those used by general health information seekers, however we do not know if these information sources yielded actionable information related to VUS. The fact that family members are a disfavored information source may have implications for the current cascade testing methods, which rely on index patients to disseminate genetic information to their relatives (Jasperson, 2013).

We report wide heterogeneity in patient use of VUS result for decision making. While most patients did not use VUS for more important management decisions such as surgery (61%) or screening (62%), other patients did act on the VUS information. VUS was used by many index patients to ask their family members to get genetic tests which may reflect the infrequency at which providers give out the recommendation to not test family members based on VUS (not recorded as recommended to 50% of patients). The overwhelming majority of patients did not check back for a VUS reclassification, likely because their providers did not inform them of the possibility that a VUS could undergo reclassification (not recorded as recommended to 76.1% of patients). A combination of patient and provider related cognitive and situational factors may explain these observations. The lack of correlation between provider recommendation and patient action may have resulted from differences in VUS management between providers. The present study was not powered to detect these differences; but should be examined further in future studies that objectively measure adherence and control for

contextual factors of patient-provider interaction that may impact adherence (e.g., in-person or telephone consultation, presentation of recommendation).

Medical decisions such as surgery and screening require provider authorization to ensure that no unnecessary procedures are carried out. The high frequency of inaction based on VUS result in our patient sample may indicate the skill and experience of providers in the cancer center in managing VUS results. This hypothesis is supported by the fact that the recommendation to not act on VUS information was recorded in the medical records of the majority of patients. Although, generally, most patients prefer to leave their medical decisions to their physicians (Arora & McHorney, 2000), patient values are also important in medical decisions. Decision to undergo prophylactic surgery is highly dependent on situational factors that matter most to a patient, e.g., family planning (Lloyd *et. al.*, 2000). Screening decisions are also influenced by patient values, e.g., feelings of embarrassment and vulnerability (McLachlan, Clements & Austoker, 2012). Therefore, patients' decision to undergo surgery and screening may be influenced by factors beyond genetic test result such as, family history of cancer, to avoid suffering experienced by others etc.

A number of factors may also influence the two important classes of VUS related health behaviors – communicating VUS test result with family members and checking back for VUS reclassification. Although, testing family members of an index patient with VUS is not recommended for clinical purposes, testing family members may be important if the patient is eligible for and decides to participate in a research study to attempt variant reclassification. Thus, it may be important to share a VUS result with family members under certain circumstances. This sharing behavior depends on patients' understanding of VUS and its lack of

clinical implication for themselves as well as their family members. As the first step to achieving these outcomes, providers must inform all patients about the lack of clinical implication of a VUS and about available VUS reclassification study opportunities. Discordance in provider practices related to VUS recommendation observed in our study, and lack of patient comprehension of VUS may explain these sharing practices of VUS information.

Checking back for VUS reclassification is also dependent on a number of clinical factors that are yet to be standardized through professional practice guidelines, e.g.,: Did the provider ask the patient to check back? How frequently were they asked to check back? 6 months? 1 year? 2 years? How convenient is it for the patient to check back – can they easily make a phone call to the provider? Call the testing laboratory? Send the provider an electronic message? Intolerance of medical uncertainty may also motivate patients to check back, whereas participants of reclassification research studies may be less likely to check back for reclassification with their providers. Some providers may also explain the unlikelihood that a reclassified VUS will alter medical management, thus discouraging patients from checking back for reclassification.

Lack of association between information seeking and VUS management may be explained by the unavailability of actionable VUS information. According to recent work by Timmermans, Tietbohl & Skaperdas (2017) VUS is a type of epistemic uncertainty, meaning findings for which the evidence falls short of known pathogenic or benign, unknown susceptibility and risk etc. In most cases, the bioclinical collective can negotiate epistemic uncertainties in order to address a patient's diagnostic uncertainty. However, this is not true for VUS – no matter how much one learns about the reason a variant is a VUS it still does not help

explain their diagnostic dilemma. Therefore, seeking information about VUS only explains its epistemic uncertainty but not the overall diagnostic uncertainty. Furthermore, we do not know if even prohibitive recommendations (such as, do not use VUS for medical decisions) exist in publicly available information sources. If patients did not obtain a concrete recommendation from their information seeking, it is understandable why VUS information seeking is not associated with VUS management behavior.

Several elements of study limit the generalizability of the findings. With a N=46, the study was underpowered to detect statistically significant associations, and the suggestive effect sizes need to be confirmed in larger cohorts. The cross-sectional study design cannot inform the temporality of association between information seeking and VUS management behavior. Furthermore, the experiences of a highly specialized cancer clinic cannot be extrapolated to patients in other clinical settings. Possible future research to be conducted based on these findings include observational prospective cohort studies using medical records to understand predictors of VUS management behavior. Experimental mixed method studies could also provide richer data about why patients were motivated to engage in certain management behaviors. Content analysis of publicly available VUS information sources could also help explain the relationship between information seeking and VUS management.

In conclusion, half of the VUS patients in our study engaged in information seeking behavior. Health care providers were the preferred and trusted sources whereas family members were least desirable sources of VUS information. We also found that, information seeking is one of many factors that determine how patients make decisions about VUS management, but receipt of VUS related recommendations from providers is likely a major

determinant of management behavior. Data from this study about patients' management behavior in response to all VUS recommendations emphasize the importance of VUS related guidelines for result disclosure, management and follow-up.

CHAPTER 4: Relationship between genomic knowledge, gender and familial communication of genomic information**.**

ABSTRACT

Genomic knowledge and gender are believed to be important determinants that facilitate the process of familial communication of genetic risk information. However, little evidence exists about how or if patients' genetics-related knowledge affects downstream outcomes in genomic medicine such as familial communication of genomic risk information. We examined whether health gender was related to knowledge, frequency of current familial communication about Colorectal Cancer and Polyposis (CRCP) risk, and future intention to share CRCP related genomic test results with family members in a clinical sample of patients who have not undergone genetic counseling. This study reports baseline survey data collected from the first 163 patients of a randomized controlled trial conducted as a part of eMERGE Phase III. There was no gender difference in overall genomic knowledge or familial communication behavior. Individuals with lower educational attainment and older individuals had lower knowledge about the limitations of genomic sequencing (β=-0.05, p=<0.01 and β=-2.5, p=<0.01). In multivariable models, frequent familial communication was associated with lower educational attainment (β=1.5, p=0.02) and with families that reported better communication of cancer information among relatives (β=0.12, p=0.01). The results presented here show that patients' factual knowledge about the benefits and limitations of genomic sequencing have little impact on their current frequency and future intention of communicating genomic results to family members. However, clinical practices that increase patients' knowledge about genomic sequencing may still be important for shared and informed decision-making in medical genomics and likely improves other patient-centered outcomes.

Keywords: Genomic knowledge, familial communication, cancer

INTRODUCTION

It is believed that successful translation of genomic information into patient-centered care and improved outcomes depend, at least in part, on patients' genomic knowledge. Borrowing and adapting the concept of genomic literacy (Hurle *et. al.*, 2013), genomic knowledge was defined as background knowledge required to understand genomic sequencing information. Differing levels of basic and applied genetic and genomic knowledge may have an impact on the decision-making process of individuals (Fitzgerald-Butt *et. al.,* 2016). This belief is reflected in the education centered goals of genetic counseling practice which aims to "to increase the counsellee's genetic knowledge" and enable them "to appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives" (Beisecker, 2001). The presumption also justifies the widespread practice of assessing participants' genetic and genomic knowledge in genomic research studies (Richman *et. al.,* 2011; Lipkus *et. al.,* 2011). Studies measure genetic or genomic knowledge for various purposes – to describe baseline knowledge, knowledge gains after intervention, and relationship between knowledge and use of genetic services (Kaphingst, SBM, 2018). However, little empirical work has been done on how or if patients' genetics-related knowledge affects downstream outcomes in genomic medicine.

Familial communication of genomic risk information is one important outcome of genomic medicine which is also partly dependent on patients' knowledge of genomics (Wiseman *et. al.,* 2010). Communication of genetic risk is influenced by family level factors (e.g., level of openness in family communication) as well as individual level factors such as genomic knowledge and gender (Gaff *et. al.,* 2007). The importance of genomic knowledge in achieving greater family communication is supported by literature – probands have reported fear of not being able to answer relatives' questions about genomics as a barrier to sharing genomic test results (Fullerton *et. al.,* 2018). Other known knowledge-related inhibiting influences to family

communication include probands' genomic proficiency – such as need for more information before telling relatives (Weiseman *et. al.,* 2010), misunderstanding about inheritance (Adelsward & Sachs, 2003; Finlay *et. al.,* 2008), and proband's belief that relative will not benefit from the information (Mellon *et. al.,* 2006; Weiseman *et. al.,* 2010). Knowledge of genetic information was also found to have a positive effect on family communication through a qualitative exploration of individuals carrying mutated genes for cardiac condition (Whyte *et. al.,* 2016). These pieces of evidence suggest that greater genomic knowledge may facilitate familial communication of genetic risk by enabling patients to overcome the knowledge barrier that impedes communication. To test these qualitative observations, quantitative studies are needed to directly examine the association between knowledge and familial communication.

Although knowledge is generally not sufficient to drive health behavior change (Baranowski *et. al.,* 2003), some amount of knowledge and appreciation of genomics is generally believed to be necessary in adopting genomic medicine services. The relative importance of knowledge compared to other factors that influence familial communication also remains unknown. On one hand, the studies mentioned above indicate that greater knowledge may increase familial communication, but evidence to the contrary also exists. Higher genomic literacy (which includes genomic knowledge) was not associated with individual's confidence in their ability to communicate about genomics topics (i.e., their self- efficacy) (Kaphingst *et. al.,* 2016). Furthermore, the process of familial communication is not always through direct verbal communication and may occur through summary letters provided by genetic counselors (VandenBoom *et. al.,* 2017). Such means of communication limit the necessity for patients' to relay facts of recommendations about genomics and thus diminishes the importance of self-efficacy. Only limited attempts have been made to associate patients' genomic proficiency with genomics-related outcomes. In one related study lower genomic literacy was not associated with greater familial communication of family health history but was associated with greater

frequency of communication with provider (Kaphingst *et. al.,* 2016). However, the exact influence of patients' genomic knowledge on familial communication of genetic risk information remains an open question.

A better understood predictor of family communication is female gender (Wiseman *et. al.,* 2010; Forrest *et. al.,* 2003; Gaff *et. al.,* 2007). Women are more likely to be "kinkeepers" in the family (i.e., individuals who keep in touch with other family members) (Wilson *et. al.,* 2004) and thus more likely to communicate genetic test results (d'Agincourt-Canning, 2001; Forrest *et. al.,* 2003; Hughes *et. al.,* 1999; Lerman *et. al.,* 1998) to their family members compared to men. It is believed that the reason for this gendered difference is the social role and expectations where women are expected to take responsibility for their families' health (Lerman *et. al.,* 1998; d'Agincourt-Canning, 2001). Although much of the initial evidence of gendered communication came from studies on gendered diseases such as hereditary breast and ovarian cancer (Foster *et. al.,* 2004; Hughes *et. al.,* 2001; Kenen *et. al.,* 2003), subsequent research in non-gendered diseases such as Colorectal Cancer (CRC) and Huntington's disease have mirrored these findings (Mesters *et. al.,* 2005). Still, it is possible that factors beyond social expectations of gender roles, such as genomic knowledge may also affect this gendered activity. For example, there is some evidence to suggest that men are less likely to think that learning genetic information is very important compared to women (Kaphingst *et. al.,* 2016) which indicates that lower genomic awareness among men may contribute to their lower familial communication. This lack of awareness may affect the frequency at which men communicate genetic risk information with family members. Such gendering of health knowledge have also been observed in other health related domains including diet (Guiné *et. al.,* 2016), stroke warning signs (Madsen *et. al.,* 2015; Jensen *et. al.,* 2008), sexual health (Kim, 2013), and cancer (Evans *et. al.,* 2005) where women consistently outperform men. If knowledge is important for familial communication, these evidence suggest that gender difference in genomic knowledge may be

partly responsible for gendered communication of genetic risk among families. Greater familial communication by women could be explained by their greater knowledge of genomic information.

Conversely, literature on educational psychology has found gender differences favoring men for many knowledge domains. Whereas intelligence tests are constrained by design to yield equal mean scores for men and women, domain-knowledge tests (which by design are content validated rather than norm referenced) do not usually yield equal mean scores for women and men (Ackerman *et. al.,* 2001). However, in one study, women performed better than men in two domains – Medicine and Cookery (Lynn and Irwing, 2002). Women's better performance in these stereotypical nurturing subjects supports the previous social explanation of women's role in family communication. Considering these evidence in aggregate, a genomic-domain specific test administered in a medical research context – a predominantly health setting suggests that women will score higher than men.

We therefore conducted a study to examine the association between individuals' knowledge about genomics and familial communication behaviors; gender differences in genomic knowledge; and association between gender and familial communication behavior. Based on the prior literature and our conceptualization of genomic knowledge and familial communication, we hypothesized that (a) Individuals with higher genomic knowledge will have increased familial communication about genomic risk information, (b) Females will score higher than males in genomic knowledge, and (c) there will be minor unique contribution of genomic knowledge in the association between gender and familial communication.

MATERIALS AND METHODS

Recruitment

The electronic MEdical Records and GEnomics (eMERGE) Network is a National Human Genome Research Institute funded consortium of research institutions across the United States which has been described in detail elsewhere (Fossey *et. al.,* 2018). Briefly, this consortium of research institutions across the United States recruit patients and leverage biorepositories linked to Electronic Health Records (EHRs) for genomic discovery and implementation studies (McCarty *et. al.,* 2011; Gottesman *et. al.,* 2013). The network was initiated in 2007, consists of 9 sites, 2 central sequencing facilities, a coordinating center and is currently in its third funding phase. In addition to its main goals, eMERGE Phase III aims to assess the health impact, cost effectiveness, and ethical, legal and social implications of reporting genetic variants on a broader population scale for patients, clinicians and healthcare institutions.

This study reports results from partial baseline data collected from patients recruited as a part of a randomized control trial by one of the eMERGE Phase III sites, namely, the Kaiser Permanente Washington and University of Washington. The broader aim of the RCT is to assess the effectiveness and social and economic impact of an innovative online tool to increase family communication about Colorectal Cancer and Polyposis (CRCP) risk and screening. The target study population of 2,500 patients (including 1,000 CRCP cases) were identified from a bioreporsitory consisting of patients who had provided broad consent for research participation. Prospective participants were mailed a consent form asking for permission to return whole genome sequencing results to the patient, their primary care provider and to the EHR. This study reports partial baseline data from the first 163 patients who

consented to participate. At the time of data collection, study participants had not undergone genetic counseling as a part of the study.

Measures

At baseline, each participant completed a survey, either over telephone or via a website, which included questions about intention to share genomic result with family members, knowledge and understanding of genomics, and background and demographic data.

Independent Variables

Participant demographics and clinical variables

Participants' sociodemographic characteristics including education, age, race, marital status, and income were measured for the study. We also collected clinical variables such as history of genetic testing, personal/family history of genetic disorder.

Knowledge about genome sequencing

Knowledge of genomic sequencing and impact on disease diagnosis and treatment was measured using an 11 item validated genetic knowledge measure (Kaphingst *et. al.,* 2012). Items included 'Genome sequencing may find variants in a person's genes that they can pass on to their children', and 'Genome sequencing is a routine test that most people can have through their physician's office' (see Appendix for complete list). This measure has two subscales, items 1- 5 indicate knowledge of sequencing limitations (e.g., "scientists know how all variants of genes will affect a person's chances of developing diseases") and items 6-11 indicate knowledge of sequencing benefits (e.g., "genome sequencing may find variants in a person's genes that will increase their chance of developing a disease in their lifetime"). Participants responded to these items on a 5 point Likert scale ranging from strongly agree to

strongly disagree. Four negatively worded items were reverse scored so that 'agree' reflected a correct response and 'strongly agree' reflected a more confident correct response in the correct direction for all items. To create knowledge scale scores, responses of 'strongly agree' were assigned a value of 2 and 'agree' a value of 1. The maximum possible points from these 11 items was therefore 22. Genomic knowledge score was treated as continuous in analysis.

Communication and flow of cancer information within families:

The perception of family communication measure used here is a combination of two subscales within the Cancer Family Impact Scale (CFIS) (Sinicorpe *et. al.,* 2008). To capture participants' perception communication and flow of cancer information within family, we used seven items from two subscales of CFIS – Communicate (reliability, α=0.72) and Flow (reliability, α=0.47) (See appendix). Communicate refers to how families communicate about cancer and flow refers to how information about cancer is conveyed in families (Sinicorpe *et. al.,* 2008). Collectively, the factors communicate and flow link well with the existing research on family communication about genetic testing and behavior, and family systems theory. Participants responded to these items on a 5 point Likert scale ranging from strongly agree to strongly disagree. Adapting the Kaphingst (2012) method above, four negatively worded items (3, 5, 6, and 7) were reverse scored so that 'agree' reflected a correct response and 'strongly agree' reflected a more confident correct response in the correct direction for all items. To create perception of family communication scores, responses of 'strongly agree' were assigned a value of 2 and 'agree' a value of 1. The maximum possible points from these 7 items was therefore 14. Higher summed scores indicated a greater communication and flow of about cancer information within family.

Outcome variables

We examined two different familial communication behaviors. Current frequency of communication about CRC- related risk and intention to share CRC-related genomic test results in future.

Frequency of current communication about CRC risk:

Frequency of communication about colon cancer risk was measured with a previously used scale (Bowen *et. al.,* 2017). We asked participants about how frequently in the past year they had communicated with each of the following family members about colon cancer risk (mother, father, sister, brother, children, grandchildren). Communication was rated on a 4-point Likert scale, from 1 (not at all) to 4 (a lot). An option for ‘‘I do not currently have this relative” was provided. As previously described by Bowen and colleagues (2017), for all living relatives, an overall frequency of communication score was computed by summing responses within person and calculating an average. Communication frequency was dichotomized into two categories: less frequently (average score: 1–2) versus more frequently (average score >2), which were compared in analysis.

Intention to share CRC-related genetic test result:

Participants’ intention to share genetic test result from the clinical trial was investigated using one question: “When I receive my genetic research results, I plan to share them with: My spouse or partner, My children, My mother, My father, My siblings, My friend, My primary care physician, My oncologist”. Responses were rated on as follows – 2 (Yes), 1 (Unsure or have not decided), 0 (No), 3 (Not Applicable). We adapted the method from Bowen and colleagues (2017) to sum responses across all applicable relatives within a person and calculating an average. Intention to share was dichotomized into two categories: lower intention (average score: < 2) versus higher intention (average score: 2).

Data Analysis

We examined descriptive statistics for all variables. We examined gender differences in the current frequency of familial communication about CRCP risk and future intention to share CRCP-related genetic test results with family members using Chi square tests. We examined the bivariate association between genomic knowledge score and each familial communication behavior using Chi square test. We then created multivariable logistic regression models to examine the association between two outcome variables (frequency of current familial communication of CRCP risk and future intention to share CRCP-related genomic test results) and independent variables (genomic knowledge), controlling for potential confounders. All multivariable models included age and education. Age was modeled continuously, education was categorized into less than or equal to High school degree and Some College or higher. We examined the relative contribution of genomic knowledge in the relationship between gender and familial communication by performing regression model comparisons following the approach of Judd, McClelland, and Ryan (2008). The full models containing all covariates including genomic knowledge was compared to the reduced models which did not contain genomic knowledge. Residual sum of squares of the two models were used to calculate the proportional reduction in error (PRE) that estimates the unique contribution of genomic knowledge to the variance of communication behavior. Data were analyzed using R Version 3.4.4; statistical significance was set at $p < 0.05$.

We acknowledge the ongoing debate about the threshold for statistical significance (Ioannidis JPA, 2018) and await the field to come to a consensus decision. In this analysis, the *p* value is not being used inform policy decisions and the permissive threshold of 0.05 allows an acceptable measure of statistical significance for exploring associations between known predictors (e.g., gender and knowledge) and multifactorial behavioral outcomes (e.g., familial communication).

RESULTS

Study Sample

As shown in Table 8, the study sample was primarily Caucasian, married/partnered, with an average age of 68 years, and roughly evenly split between genders (47% male and 53% female). In terms of socioeconomic status, participants were mostly highly educated with 63% having a bachelor's degree or higher, and high income levels. 8% of participants reported having a personal or family history of a genetic disorder and 16% of participants reported having undergone genetic testing before joining the study. There was nearly no statistically significant difference between male and female participants, except males reported higher educational attainment than females (p-value=0.01).

Participants who answered the survey over phone (n=35) and via website (n=127) were matched on most demographic characteristics, except participants who used the web were younger (p-value=0.02) and more educated (p-value=<0.01). To account for response bias, we controlled for age and educational status in our analysis.

Table 8: Demographic characteristics of participants (N=162).

		Total		Male		Female		p-value
Variable	**Categories**	**N**	**%**	**N**	**%**	**N**	**%**	
N		162	100.0	76	46.91	86	53.09	
Age	Mean (years)	68.04		69.27		67.11		0.26[+]
	Range	[31.6-102.8]		[40.73 - 94.42]		[31.71 - 102.9]		
Race								
	White or Caucasian	126	77.8	57	75.0	69	80.2	0.57
	Black or African American	3	1.9	1	1.3	2	2.3	
	Asian	13	8.0	7	9.2	6	7.0	
	Other	1	0.6	0	0.0	1	1.2	
	Mixed	9	5.6	4	5.3	5	5.8	
Education								
	≤Some high school (grades 9 to 12)	2	1.2	2	2.6	0	0.0	**<0.01**

	High school graduate or GED	8	4.9	7	9.2	1	1.2	
	Post high school training other than college	8	4.9	5	6.6	3	3.5	
	Some college	34	21.0	25	32.9	9	10.5	
	Bachelor's degree or equivalent	46	28.4	20	26.3	26	30.2	
	Master's degree	38	23.5	19	25.0	19	22.1	
	Doctoral or other professional degree	18	11.1	5	6.6	13	15.1	
Marital Status								
	Now married	113	69.8	58	76.3	55	64.0	0.24
	Widowed	18	11.1	5	6.6	13	15.1	
	Divorced/Separated	17	10.5	6	7.9	11	12.8	
	Never married	6	3.7	2	2.6	4	4.7	
Income								
	< 45 K	23	14.2	6	7.9	17	19.8	0.10
	45-90 K	52	32.1	24	31.6	28	32.6	
	> 90 K	76	43.2	39	51.3	37	43.0	
Genetic testing								
	Had genetic testing before	26	16.05	6	7.89	20	23.26	0.03
	Never had genetic testing	123	75.93	62	81.58	61	70.93	
	Don't know/Decline to answer	5	3.09	3	3.95	2	2.33	
Personal/Family history of genetic disorder								
	Yes	13	8.02	6	7.89	7	8.14	0.77
	No	138	85.19	63	82.89	75	87.21	
	Don't know/Decline to answer	3	1.85	2	2.63	1	1.16	

Chi square test was used to calculate p-values for all variables, except age
[+]t-test

Genomic sequencing knowledge

On average, men and females scored similarly on the knowledge scale - mean scores for males and females were 11.2 and 10.5 out of 22 points respectively - this difference was not statistically significant (p-value = 0.37). There was considerable variation in the number of questions that were answered correctly (i.e., either “Strongly Agree” or “Agree”) (Table 9). Welch two sample t-test showed a statistically significant difference between the means of negatively worded (and thereby reverse coded) items and positively worded items (p-value= <0.001). It appears that participants scored lower on knowledge of sequencing limitations, which contained all of the negatively worded items compared to knowledge on sequencing benefits,

which were all positively worded. In order to account for these differences, we compared gender difference in knowledge score between the two subscales (Table 10).

Table 9: Frequency of correct responses to knowledge questions (N=153). Items about limitations of genomic sequencing are in blue, and items about benefits of sequencing are in black.

Question	N	% Correct
1. Once a variant in a gene that affects a person's risk of a disease is found, that disease can always be prevented or cured (Reverse coded).	153	56.9
2. A health care provider can tell a person their exact chance of developing a disease based on the results from genome sequencing (Reverse coded).	153	58.8
3. Scientists know how all variants of genes will affect a person's chances of developing diseases (Reverse coded).	153	58.8
4. Even if a person has a variant in a gene that affects their risk of a disease, they may not develop that disease	153	85.0
5. Genome sequencing is a routine test that most people can have through their physician's office (Reverse coded).	152	**51.6**
6. Genome sequencing may find variants in a person's genes that they can pass on to their children	152	85.0
7. Genome sequencing may give a person information about their chances of developing several different diseases	153	**90.8**
8. Genome sequencing may find variants in a person's genes that will increase their chance of developing a disease in their lifetime	153	86.9
9. Genome sequencing may find variants in a person's genes that will decrease their chance of developing a disease in their lifetime.	153	64.1
10. Genome sequencing may find variants in a person's genes that may determine how they respond to certain medicines.	153	71.9
11. A person's health habits, such as diet and exercise, can affect whether or not their genes cause diseases	153	64.7

Knowledge about sequencing benefits and knowledge about sequencing limitations were similar in males and females (Table 10).

Table 10: Bivariate analysis of gender and genome sequencing knowledge

	Total score	Male	Female	t statistic	p-value
Genome sequencing knowledge	10.83 [7 – 14]	11.2	10.5	-0.88	0.37
Knowledge of limitations subscale (Items 1 – 5)	4.21 [1 – 10]	4.35	4.08	-0.54	0.59
Knowledge of benefits subscale (Items 6 - 11)	5.68 [4 – 12]	5.81	5.57	-0.51	0.61

In multivariable analysis of genomic sequencing knowledge score, we found a few significant relationships between knowledge and demographic predictors (Table 11). Younger participants had significantly lower genomic sequencing knowledge overall (β = -0.09, p = <0.001) as well as lower knowledge of limitations about genomic sequencing (β = -0.05, p = <0.001). Participants with less than post high school education had significantly lower knowledge of genome sequencing limitations compared to those with college of higher education (β = -2.5, p = <0.001). However, a similar difference was not observed for overall genome sequencing knowledge or regarding knowledge of sequencing benefits.

Table 11: Multivariate analysis of genome sequencing knowledge score with the predictors gender, age and education.

Characteristic	Genome sequencing knowledge			Knowledge of limitations subscale			Knowledge of benefits subscale		
	B	SE	p-value	B	SE	p-value	B	SE	p-value
Gender									
Male[a]	0.6	0.77	0.44	0.25	0.48	0.6	0.36	0.46	0.43
Age	-0.09	0.03	**0.003**	-0.05	0.02	**0.008**	-0.03	0.02	0.08
Education[b]									
< Post high School	-1.99	1.32	0.13	-2.5	0.75	**0.001**	-1.32	0.72	0.06

[a] Reference group is female; [b] Reference group is some college or higher;

Familial communication

In the bivariate analysis, we found few significant associations between demographic variables and communication behaviors. Participants with lower than a post high school education reported a significant lower intention to share genomic results with family members (p=0.03) (Table 12). The remaining associations between gender, age and income were not statistically significant.

Table 12: Bivariate associations between demographic variables and current frequency of CRC-related family communication and future intention to share CRC-related genomic results.

Characteristic		Current frequency of communication			Future intention to share		
		β	SE	*p*	B	SE	*p*
Gender	Male	0.19	0.26	0.45	0.04	0.08	0.49
	Female*						
Age	Under 50 years	-0.64	0.47	0.17	0.11	0.12	0.34
	50 years and over*						
Education	< Post high School	-0.14	0.39	0.73	-0.21	0.1	**0.03**
	≥ Some College						
Income	≤ 59K	0.45	0.24	0.06	0.06	0.06	0.36
	≥ 60K*						

Bivariate association between familial communication outcomes and gender and genomic knowledge scores are shown in Table 11. Difference in familial communication behaviors between males and females was not statistically significant. Of the communication outcomes, there was no difference in genomic knowledge between frequent and infrequent communicators (p-value= 0.25), or between those who had high and low intention to share CRCP-related genomic test results with family members (p-value = 0.6) (Table 13).

Table 13: Associations between CRC-related familial communication outcomes and gender and genomic knowledge score.

Communication behavior		Male	Female	X^2 (p-value)	Genomic knowledge score	T-test (p-value)
		N	N		Mean	
Current frequency of communication						
	Frequent (average score >2)	14	25	0.19	10.07	0.25
	Infrequent (average score <=2)	58	59		11.03	
Future intention to share						
	High (average score = 2)	13	22	0.43	11.44	0.6
	Low (average score < 2)	54	62		10.61	

We ran separate adjusted multivariable models for each type of familial communication behavior (Table 14). The full model for frequency of familial communication (Model 1) showed that participants with lower education had significantly higher frequency of familial communication than those with higher education (β = 1.5, *p* = 0.02). In this model, those with higher CFIS score had significantly higher frequency of familial communication compared to those with lower CFIS score (β = 0.12, *p* = 0.01); the effect size in the reduced model (Model 2) was even higher in the same direction (β = 3.31, *p* = <0.01). Comparing the two models, the unique contribution of genomic knowledge to the total variation of frequency of familial communication was 4.6%. For intention to share CRCP-related genomic test result in future, there was no statistically significant association between familial communication and any predictor in the full or reduced model. Comparison of the RSS between the two models showed that genomic knowledge contributed to 7.2% of the total variation in the intention to share test results. Because it is desirable to explain the majority, if not all, of the variation of an outcome, a conceptual threshold distinguishing a weak and strong relationship is indicated by a PRE of 50%. Using this threshold, genomic knowledge is a weak predictor of familial communication outcomes.

Table 14: Associations between communication outcomes, knowledge and covariates in multivariable models.

Predictors	Current frequency of communication				Intention to share in future			
	Full model		Reduced model		Full model		Reduced model	
	β	*p*	β	*p*	β	*p*	β	*p*
Age	-1.47	0.19	0.29	0.26	0.19	0.86	1.4	0.77
Gender Male	-0.48	0.25	0.602	0.21	-0.52	0.33	0.81	0.68
Education Low	1.51	**0.02**	2051	0.09	-0.94	0.39	0.68	0.64
CFIS	0.12	**0.01**	3.31	**<0.001**	0.09	0.08	1.08	0.13
Genomic knowledge	-0.004	0.92			0.04	0.38		
RSS	24.91		26.06		14.87		15.94	
PRE	4.6 %				7.2 %			

*CFIS= Communication and Flow subscales of the Cancer Family Impact Scale; RSS = Residual Sum of Squares; PRE = Proportional Reduction of Error

DISCUSSION

This study examined relationships between genomic knowledge, gender and familial communication of CRCP-related risk. Among the first 162 participants of the eMERGE Phase III RCT, we observed no gender difference in genomic sequencing knowledge, frequency of current familial communication about CRCP risk, or intention to share CRCP related genomic test results with relatives in future. In addition, this study found that factual knowledge about genetics has little impact on current or future intention of familial communication about CRCP related risk information. The gendered activity of women taking responsibility to disseminate genetic results to family members was not explained by gender difference in genomic knowledge. The relative unimportance of factual knowledge about genomic sequencing as a determinant for increased familial communication of genomic test results indicates that genetic education may be less important than commonly believed for certain genomic health outcomes.

Our first hypothesis was not supported: we found no significant association between genomic sequencing knowledge and family communication. However, consistent with prior research, participants with good communication and flow of cancer information within families reported frequent familial communication in our multivariable models (Peterson *et. al.,* 2003). The lack of association between knowledge and communication can be explained by the fact that family communication is a complex multifactorial phenomena that is largely influenced by the nature of family relationships between proband and relatives (Foster *et. al.,* 2014; Seymour *et. al.,* 2010; Smith *et. al.,* 2002). Concern about negatively impacting family relationships is routinely reported as a barrier that limits familial communication of genetic risk (Sobel & Cowan, 2000; Foster *et. al.,* 2004). This concern is also shared by those who believe that knowledge is power and genetic information should be share and acted upon (Speice *et. al.,* 2002; McGivern *et. al.,* 2004). It appears that genomic knowledge is not a sufficient condition increased familial

communication: fear of potential for backlash, blame and distancing family members may frequently trump the rationality of shared genetic risk and prevention. Estranged relatives may not be told about the genetic risk irrespective of proband's knowledge about genomics (Nycum *et. al.,* 2009). In addition, genomic knowledge is also not a necessary condition for familial communication – for example, probands may be motivated to share genetic information with family members solely to comply with professional advice (Mesters *et. al.,* 2005; van den Nieuwenhoff *et. al.,* 2007), which requires no appreciation of the genetic risk their relatives share or potential for disease prevention. Genomic knowledge is seldom sought out by counselees during genetic counseling (Joseph *et. al.,* 2017). Although counselors focus on dissemination of factual genomic knowledge (e.g., what are genes, what is a genetic test, how it is performed, possible test results, limitations of test), patients generally want to know less factual and more personally applicable information (e.g., is my cancer hereditary? What caused my cancer?) (Joseph *et. al.,* 2017). This mismatch of information need and delivery indicates that factual genomic knowledge may take a back seat in patient decision making. However, genomic knowledge is likely still important for familial communication as counselees with higher genomic knowledge may have greater appreciation for the importance of familial communication and the urgency with which information should be dispersed to certain relatives who are at higher risk. Indeed it has been shown that participants who had higher interest in genomic information communicated genetic results to a greater proportion of their family members (Elrick *et. al.,* 2017).

Participants with lower educational attainment in our study had lower knowledge about the limitations of genomic sequencing, compared to those with higher educational attainment. This finding is consistent with results from numerous prior studies which have found that genomic knowledge is lower among those with limited educational attainment or limited health literacy (Lea *et. al.,* 2011; Kaphingst *et. al.,* 2016; Kaphingst *et. al.,* 2018). However, we found

no difference in knowledge of the benefits of genome sequencing between those with lower or higher educational attainment. More knowledge about the limitations of genome sequencing could reduce patients' intention to share genomic results with family members. For example, knowledge of the fact that "even if a person has a variant in a gene that affects their risk of a disease, they may not develop that disease", may convey a non-urgency of familial communication of genomic variants. Therefore, lower knowledge about such limitations of genome sequencing in patients with lower educational attainment may explain their lower future intention to share genomic risk information with family members observed in this study. Similar findings have been reported by Kaphingst *et. al.* (2018) where higher knowledge about genomics was related to lower preference for return of genomic results as they were believed to be less clinically actionable. This knowledge gap and consequent impact on genomics outcomes will be an issue of increasing importance as genomic medicine is being widely adopted and used in diverse clinical settings.

In agreement with prior research on public understanding of genetics and genomics (Lea *et. al.,* 2011), overall, participants in our study demonstrated good understanding of the role played by genomics in disease causation (85% or more correct on items 4, 6, 7 and 8). The concept of increased genetic risk was better understood than the disease protective effect provided by certain genomic variants (item 8 vs 9). This differential knowledge likely reflects the motivation of clinical genomic testing which focuses on identifying susceptibility variants for a disease and not, protective genetic variants. In addition, our results support prior research findings and show that higher educational attainment (Carlsbeek *et. al.,* 2007; Haga *et. al.*, 2013) and younger age (Ashida *et. al.*, 2011; Carlsbeek *et. al.*, 2007; Henneman *et. al.*, 2004) were associated with higher genomic knowledge which suggest that it is important to consider health literacy in educating individuals about genomics. Those with fewer years of education are likely to be less exposed to genetic information via school biology curricula, the primary source

of genetic information for many members of the general public (Bowling *et. al.,* 2008) and may have fewer opportunities for developing relevant skills in searching for sources of genetic information (Molster *et. al.,* 2009). Younger people may also have had more "incidental or opportunistic public exposure to basic genetic concepts and terms (e.g., DNA) through popular culture media" (Bates, 2005).

In partial support of our third hypothesis, genomic knowledge explained a small proportion (between 4 and 7%) of the total variation in familial communication in multivariable model, however our second hypothesis was not supported: we found no significant association between gender and genomic knowledge. This could be for a number of reasons. It is possible that there was gendered difference in prior genetic testing experience (clinical or direct to consumer) among our study participants which could have affected genomic knowledge. At the same time, unlike gendered diseases such as breast cancer and Human Papilloma Virus related sexual health awareness, there are no substantial gender differences in the incidence or inheritance of colorectal cancer. Thus the lack of gender difference in genomic knowledge in the context of colorectal cancer is not surprising. We may need to control for additional situational factors (e.g., having had a biology course in college, access to information source) that may be associated with genomic knowledge, as suggested by prior literature (Parrott *et. al.,* 2003). Although one cross-sectional telephone survey in Western Australia reported that women had higher genetic knowledge (Molster *et. al.,* 2009), other research has found that sex had no significant impact on genetic knowledge score (Harding *et. al.,* 2017).

The findings from this study should be considered in light of its limitations. This sample of eMERGE III patients were enriched for CRCP cases, some of whom had prior experience with genetic testing, thus the findings likely do not generalize to all patients undergoing clinical genome sequencing because of their greater likelihood of familiarity with genomic sequencing.

Knowledge about shared familial risk was not a validated subscale in the knowledge measure used in this study as it contained only one item on familial sharing of genomic variants. Knowledge about sharing variants with children (item 6) may not accurately capture patients' knowledge about sharing variants with other relative types (mother, father, sibling etc.). The cross sectional analysis of the baseline data cannot establish temporality between the dependent and independent variables explores in this study. In order to increase generalizability, future research should investigate gender differences in intention to communicate in a more demographically diverse population, where the distribution of education is more representative of the general population.

Possible future research to be conducted based on these findings include observational studies that consider the age of relatives and closeness of relationship between proband and relative in determining frequency of communication. A strength of our study is utilization of intention to communicate as one of the study outcomes measured at baseline (i.e., before return of study results) as it minimizes interaction with potential confounders such as affect, which is known to be important in decision making and information processing. It will be important to examine the concordance of expressed intention to communicate and actual familial communication once genomic results have been returned to participants.

In conclusion, we identified that men and women have equal genomic knowledge and express equal intent to share genomic results with family members. Patients with lower educational attainment had lower knowledge about the limitations of genomic sequencing and expressed higher intention to share genomic results with family members. The results presented here show that patients' factual knowledge about the benefits and limitations of genomic sequencing have little impact on their current frequency and future intention of communicating genomic results to family members. However, clinical practices that increase patients'

knowledge about genomic sequencing still very important for shared and informed decision-making in medical genomics and likely improves other patient-centered outcomes. Communication aids not heavily based on genomic education could therefore be more effective in facilitating the process of familial communication among clinical genomics patients.

CHAPTER 5: CONCLUSION

Overall Summary

The results from this dissertation add to our understanding of how is VUS-related uncertainty is perceived and managed by patients, how information seeking is used as an uncertainty management strategy and its relationship with VUS management behavior. One specific VUS management strategy is to participate in family studies of variant reclassification that require familial communication - we explore genomic knowledge and gender as determinants of familial communication of genetic risk.

Results from Chapter 2 suggest that, overall, the epistemological source (i.e., arising from limitations in the current state of knowledge) of VUS uncertainty was well recognized by patients with a clinically confirmed VUS result who were counseled in a regional cancer center. Patients who understood the epistemological source of uncertainty were also accepting of the prevalence of medical uncertainty in general. This acceptance gave them hope that VUS-related uncertainty is manageable would be resolved in future. However, when VUS was interpreted differently by clinicians, clinical ambiguity trumped information insufficiency as the source of uncertainty. This was more challenging for patients to accept and caused some confusion. Patients also identified several issues of VUS-related uncertainty such as implication for family members, and being informed about reclassification. We identified themes representing nearly all issue-related subdomains of Han's taxonomy of uncertainty. This demonstrates the wide range of diagnostic, prognostic, therapeutic and psychosocial difficulties that patients with VUS experience. More importantly however, patients also identified methods for managing VUS-related uncertainty. Uncovering various VUS-related uncertainty management strategies is a unique contribution of this dissertation work. We organize the various provider and patient level management strategies into a provisional framework of uncertainty management strategies that identify patient and provider level approaches for VUS management.

The organization of VUS-related uncertainty from the patients' perspective offers an opportunity for other stakeholders to better understand how patients experience VUS and what elicits uncertainty. Providers could use this information to guide patient counseling. For example, genetic counselors could be more proactive in their pre-test counseling to prepare patients for the possibility for upcoming uncertainty. In addition, they could discuss how patients plan to manage such uncertainty if they were to receive a VUS as a result. There was some indication that in-person counseling was preferable over telephone counseling as it offers patients more time to digest the complex information and ask follow up questions. Based on the finding that patients attempted to read the laboratory reports to learn more about the variant but found them too complex or uninformative, laboratories could design VUS-related laboratory reports to make them more patient friendly. Recognizing that management strategies can address much of the VUS related uncertainty offers hope for the thousands of VUS that will be returned to patients in genomic medicine clinics.

Chapter 3 offers a detailed examination of patients' VUS-related information seeking behavior and its relation to VUS management behavior. In agreement with the results from qualitative interviewees in Chapter 2 who reported proactively seeking VUS-related information on the internet, more than half of the survey respondents in Chapter 3 also reported seeking VUS-related information after they received their test result. Information from health care providers and cancer research organizations were preferred, but information was also sought from the internet. There was a trend for women, patients with higher educational attainment, and those without a cancer diagnosis to be more likely to seek information about VUS. Interviewees and survey respondents both expressed the ineffectiveness of information seeking. In accordance with VUS-related management guidelines, most patients did not undergo surgery (61.8%) or screening (62.5%) based on VUS results. The majority of patients

(69.5%) did not check back for a VUS reclassification, possibly because their providers did not inform them of the likelihood that a VUS could undergo reclassification (Skinner *et. al.,* 2018). A minority (46.7%) asked family members to get a genetic test because of their VUS result. They also reported that they did not use VUS information for making these clinical decisions. Lack of association between information seeking and VUS management may be explained by the unavailability of actionable VUS information, which was also a theme identified in our qualitative interviews in Chapter 2. Data from this study about patients' management behavior in response to all VUS recommendations emphasize the importance of VUS related guidelines for result disclosure, management and follow-up.

Results from Chapter 4 showed that men and women are equally knowledgeable about genomic sequencing, and report equal frequency of current familial communication of CRCP risk and express future intention to share CRCP related genomic test results with family members. Factual genomic knowledge explained only a small proportion of variation in familial communication of CRCP risk. Application of these findings to VUS family studies requires additional considerations. For example, VUS are a particularly challenging group of variants to communicate to family members and two major barriers to communicating VUS test results are – perception that VUS has no genetic or medical implication for family members, and that probands themselves are ambiguous about the result and thus do not feel confident about sharing (Li *et. al.,* 2017). Gaining knowledge about genomics, and specifically VUS, may help patients appreciate the importance for familial communication for VUS reclassification. However, despite the availability of family studies (Garrett *et. al.,* 2017), recommendation for family testing to resolve uncertainty is not always given, even by expert providers (Skinner *et. al.,* 2018). This may suggest that participation in research studies as a natural stage of clinical management may not be widely established. Curiously, female participants are the

overwhelming majority in VUS family studies (Makhnoon *et. al.,* 2017) – whether this represents the female-heavy demographic of typical research studies or if females are particularly uncertainty intolerant and thereby more likely to participate in VUS reclassification research is a question that warrants further investigation.

Looking forward

Using the term uncertain to describe VUS implies that non-VUS variants are classified with certainty, when nothing in the natural world is certain – biological systems are the least predictable of them all. Arguably, variants across the entire interpretive spectrum can be called "of uncertain significance". In the case of VUS we are more acceptably uncertain than usual, and since quantitation is valued in genomics:

"VUS, like democracy, is simply the worst choice except for all the other possible options." (Cooper, 2015).

Some uncertainty around VUS is unavoidable. As long as humans live, *de novo* mutations will continue to arise and be passed down when they reproduce – VUS are therefore impossible to eliminate altogether from medical genetics. On the bright side, however, uncertainty managed by skilled practitioners has always been a hallmark of medical practice (Han, 2011) and the National Cancer Institute identifies management of uncertainty is a core function of patient-centered communication (Epstein *et. al.,* 2007). Given the number of family specific unique variants, family studies will be always needed to understand rare variants which often get classified as VUS (Shirts *et. al.,* 2016). Medicine-based evidence as opposed to evidence-based medicine is likely the way forward for much of VUS (Tonelli & Shirts, 2017). It is likely impractical to wait for VUS evidence to be generated from functional studies or randomized control trials in order to guide reclassification (i.e., evidence based medicine) as many VUS are

rare. Medicine-based evidence, i.e., evidence generated from the medical clinic from studying families with VUS are likely to be more successful. Genetic discovery from individual families will offer cognitive closure for family members, may lead to clinical interventions, and advance the field of medical genetics. The VUS-related uncertainty management strategies uncovered in this dissertation can serve as a useful framework for successful management of patients' VUS-related uncertainty. Uncertain sequencing results, when explained and relayed by experts can produce congruence between clinician's communication and patient's understanding without causing undue harm (Skinner *et. al.,* 2018).

We also find that information-seeking was attempted by many patients but was often ineffective for VUS-management. In the absence of data on precisely what type of VUS-related information is publicly and freely available, it is challenging to interpret this lack of association, but greater availability of actionable VUS-related information is likely to help manage VUS uncertainty. Availability of VUS related information is a fluid as is the consequent utility of information seeking. Recently a number of VUS related patient education materials have become available online (for example: file:///C:/Users/sukhm/Downloads/PE2118.pdf). As patients are able to access reliable, quality information related to VUS, it can improve medical management decisions and their confidence in these decisions. Information avoidance, is another key tool for uncertainty management that patients opt for under threating conditions. Many cancer today is preventable and a principle goal of genetic testing is disease prevention; thus willful information avoidance is only likely to disserve disease prevention in oncology. VUS related issues originating from inconsistency in provider interpretation of VUS may be compounded by information avoidance if patients choose not to make use of actionable VUS information to guide medical management. Future research should also replicate this study in a population of patients devoid of possible confounders – i.e., one with only a VUS result (with no accompanying P/LP variant) and who do not have a cancer diagnosis.

Assessing patients' genomic knowledge is no simple task. In spite of the several measures that have been developed to date, scales to measure patients' clinically relevant genomic knowledge remains sparse. Clinically significant genomic knowledge likely has several different dimensions – factual knowledge about genetics (DNA, genes, inheritance), factual knowledge of diagnostic genomic sequencing (disease risk estimates, association between risk prediction and disease occurrence), clinical benefits of genomic sequencing for self, and for relatives, and limitations of clinical genomic sequencing. Different aspects of genomic knowledge is likely to be relevant for different patient-centered outcomes. In future work, genomic knowledge measures should be carefully chosen so that they are most relevant to the outcome of interest. For example, knowledge of shared genomic risk among biological relatives probably serves as a better predictor of the outcome of familial sharing of genomic information than knowledge of the fact that genomic sequencing can provide risk information about various diseases. While both items are likely relevant for informed decision making related to clinical sequencing, the former is likely to be a better predictor of familial communication compared to the latter. Physician's knowledge of genomic sequencing is likely to be even more impactful for improving outcomes in clinical genomics than patients' knowledge. In particular, how VUS related genomic risk (or lack thereof) is communicated to patients may impact patient perceptions of risk. The wealth of information of risk communication in medicine should be leveraged to guide future work on best methods for communication of genomic uncertainty.

Since variant reclassification research is one method of uncertainty management, it will also be important to know which patients – i.e., of which dispositional characteristic and under which clinical conditions – are motivated to participate variant reclassification research. Does inability to manage or cope with uncertainty drive research participation? Or does curiosity and altruism? We also do not know how genomic knowledge motivates participation in these studies. It will

also be important to know how VUS uncertainty manifests in diseases where genetic testing is common but clinical next steps are less clear compared to oncology – for example autism, developmental delays etc. In the absence of room to acknowledge gene-gene and gene-environment interactions in current models of clinical genomic testing, patients and providers try to conform to the single gene causality of diseases. As a result, there is a frantic effort to make clinical sense of any and all genomic variation, however inconsequential they may be - as is the case with VUS. Future research should also explore how VUS resulting from *genomic* (exome/genome) sequencing are perceived compared to targeted panel testing which are offered as tests specific to the phenotype of interest and thus consequently perhaps of greater clinical utility.

Omitting or including VUS in clinical genomic test reports is an ongoing topic of debate. While including VUS saves laboratories from liability, it also confuses readers. Perhaps a middle ground would be to deemphasize VUS on test reports so that readers are aware of its limited clinical utility. Recently, efforts are underway to sub-classify VUS into three different categories for reporting (personal communication with Steven Harrison) – VUS favor pathogenic, VUS and VUS favor benign. Whether this sub-classification helps or hurts clinical decision making should be explored in future research.

This dissertation research was designed as an inquiry into how patients understand and clinically manage VUS, and how genomic knowledge influences familial communication of genomic risk. The project, albeit small and exploratory, offers some useful and potentially actionable findings. Additional investigation of other VUS management strategies and contributors to familial communication of genetic results in general, and VUS in specific is warranted.

REFERENCES

Ackerman PL, Bowen KR, Beier ME, & Kanfer R. (2001). Determinants of individual differences and gender differences in knowledge. *Journal of Educational Psychology, 93*(4), 797-825.

Adelsward V, Sachs L (2003) The messenger's dilemmas—giving and getting information in genealogical mapping for hereditary cancer. *Health Risk Soc* 5(2):125–138.

Amendola LM, Jarvik GP, Leo MC McLaughlin HM, Akkari Y, Amaral MD, Berg JS, Biswas S, Bowling KM, Conlin LK, Cooper GM, Dorschner MO, Dulik MC, Ghazani AA, Ghosh R, Green RC, Hart R, Horton C, Johnston JJ, Lebo MS, Milosavljevic A, Ou J, Pak CM, Patel RY, Punj S, Richards CS, Salama J, Strande NT, Yang Y, Plon SE, Biesecker LG, Rehm HL. (2016) Performance of ACMG-AMP variant-interpretation guidelines among nine laboratories in the clinical sequencing exploratory research consortium. *Am J Hum Genet.* 2016 Jul 7;99(1):247.

Andrykowski MA, Carpenter JS, Studts JL, Cordova MJ, Cunningham LLC, Mager W, Sloan D, Kenady D, McGrath P. (2001). Adherence to recommendations for clinical follow-up after benign breast biopsy. *Breast Cancer Research and Treatment, 69*(2), 165-178.

Arora NK, & McHorney CA. (2000). Patient preferences for medical decision making: Who really wants to participate? *Medical Care, 38*(3), 335-341.

Ashida S, Goodman M, Pandaya C, Koehly LM, Lachance C, Stafford JD, & Kaphingst KA. (2011). Age differences in genetic knowledge, health literacy, and causal beliefs for health conditions. *Public Health Genomics*, 14(4–5), 307–316.

Atkin CK. (1973). Instrumental utilities and information seeking. In P. Clarke (Ed.), New models for communication research (pp. 205–242). Beverly Hills, CA: Sage.

Baranowski T, Cullen KW, Nicklas T, Thompson D, Baranowski J (20013). Are current health behavioral change models helpful in guiding prevention of weight gain efforts? *Obes Res,* 11 (Suppl): 23S–43S.

Baron RM, & Kenny DA. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic and statistical considerations. *J Pers Soc Psychol,* Dec;51(6):1173-82.

Bates BR, Templeton A, Achter PJ, HarrisTM, Condit CM (2003). What does ‘a gene for heart disease’ mean? A focus group study of public understanding of genetic risk factors. *Am J Med Genet A*, 119A:156–161.

Biesecker BB (2001) Goals of genetic counseling. *Clin Genet*, 60(5):323-30. Review.

Biesecker BB, Klein W, Lewis KL, Fisher TC, Wright MF, Biesecker LG, Han PK (2014). How do research participants perceive "uncertainty" in genome sequencing? *Genet Med*, 16(12):977-80.

Blandy C, Chabal F, Stoppa-Lyonnet D, Julian-Reynier C (2003) Testing participation in BRCA1/2-positive families: initiator role of index cases. *Genetic Testing* 7(3):225–233.

Bowen DJ, Hay JL, Harris-Wai JN, Meischke H, Burke W (2017). All in the family? Communication of cancer survivors with their families. *Fam Cancer*, 16(4):597-603.

Bowling BV, Acra EE, Wang L, Myers MF, Dean GE, Markle GC, Moskalik CL, Huether CA (2008). Development and evaluation of a genetics literacy assessment instrument for undergraduates. *Genetics*, 178(1):15-22.

Brashers DE, Goldsmith DJ, & Hsieh E. (2002). Information seeking and avoiding in health contexts. *Hum Comm Res*, 28, 258–271.

Brashers DE. (2001). Communication and uncertainty management. *Journal of Communication, 51*(3), 477-497.

Carlsbeek H, Morren M, Bensing J, & Rijken M. (2007). Knowledge and attitudes towards genetic testing: A two year follow-up study in patients with asthma, diabetes mellitus and cardiovascular disease. *J of Genet Couns*, 16(4), 493–504.

Carmo-Fonseca M, Mendes-Soares L, & Campos I. (2002). Patients' use of the internet for medical information. *Journal of General Internal Medicine, 17*(3), 180-185.

Caryn Lerman, Beth N. Peshkin, Chanita Hughes, & Claudine Isaacs, Family Disclosure in Genetic Testing for Cancer Susceptibility: Determinants and Consequences, 1 *J. Health Car*e L. & Pol'y 353 (1998).

Case DO. (2007). Looking for information: A survey of research on information seeking, needs, and behavior. London: Elsevier.

Cheon JY, Mozersky J, and Cook-Deegan R (2014). Variants of uncertain significance in BRCA: a harbinger of ethical and policy issues to come? *Genome Med*. 2014; 6(12): 121.

Cooper GM (2015). Parlez-vous VUS? *Genome Res*; 25(10): 1423–1426.

Cypowyj C, Eisinger F, Morin M, Mogoutov A, Sobol H, & Julian-Reynier C. (2003). Information-seeking behaviour and psycho-social interactions during the genetic testing process. *Community Genetics, 6*(4), 224-234.

Czaja R, Manfredi C, & Price J. (2003). The determinant and consequences of information-seeking among cancer patients. *Journal of Health Communication*, 8, 529-562.

d'Agincourt-Canning L (2001) Experiences of genetic risk: disclosure and the gendering of responsiblity. *Bioethics* 15(3): 231–247.

Davison BJ & Breckon EN. (2012). Impact of health information-seeking behavior and personal factors on preferred role in treatment decision making in men with newly diagnosed prostate cancer. *Cancer Nursing, 35*(6), 411-418.

Easton DF, Deffenbaugh AM, Pruss D, Frye C, Wenstrup RJ, Allen-Brady K, Tavtigian SV, Monteiro AN, Iversen ES, Couch FJ, Goldgar DE (2007). A systematic genetic assessment of 1,433 sequence variants of unknown clinical significance in the BRCA1 and BRCA2 breast cancer-predisposition genes. *Am J Hum Genet,* 81(5):873-83.

Eccles BK, Copson E, Maishman T, Abraham JE, Eccles DM (2015). Understanding of BRCA VUS genetic results by breast cancer specialists. *BMC Cancer,* 15:936.

Eccles DM, Mitchell G, Monteiro AN, Schmutzler R, Couch FJ, Spurdle AB, Gómez-García EB; ENIGMA Clinical Working Group (2015). BRCA1 and BRCA2 genetic testing-pitfalls and recommendations for managing variants of uncertain clinical significance. *Ann Oncol*, 26(10):2057-65.

Edwards JA, Snyder FJ, Allen PM, Makinson, KA, & Hamby DM. (2012). Decision making for risk management: A comparison of graphical methods for presenting quantitative uncertainty. *Risk Analysis, 32*(12), 2055-2070.

Elrick A, Ashida S, Ivanovich J, Lyons S, Biesecker BB, Goodman MS, & Kaphingst KA. (2017). Psychosocial and clinical factors associated with family communication of cancer genetic test results among women diagnosed with breast cancer at a young age. *Journal of Genetic Counseling, 26*(1), 173-181.

Emanuel AS, Kiviniemi MT, Howell JL, Hay JL, Waters EA, Orom H, & Shepperd JA. (2015). Avoiding cancer risk information. *Social Science and Medicine, 147*, 113-120.

Epstein, RM. Street, RLJ. Patient-Centered Communication in Cancer Care: Promoting Healing and Reducing Suffering. Bethesda, MD: 2007. NIH Publication No. 07-6225

Feero W (2014). Clinical application of whole-genome sequencing: proceed with care. *JAMA*, 311:1017–1019.

Finlay E, Stopfer JE, Burlingame E, Evans KG, Nathanson KL, Weber BL, Armstrong K, Rebbeck TR, Domchek SM (2008) Factors determining dissemination of results and uptake of genetic testing in families with known BRCA1/2 mutations. *Genetic Testing* 12(1):81–91.

Finney Rutten LJ, Agunwamba AA., Wilson P, Chawla N, Vieux S, Blanch-Hartigan D, Arora NK, Blake K, Hesse BW. (2016). Cancer-related information seeking among cancer survivors: Trends over a decade (2003–2013). *Journal of Cancer Education, 31*(2), 348-357.

Fisher CL, Roccotagliata, T, Rising CJ, Kissane DW, Glogowski EA & Bylund CL. (2017). "I Don't want to be an ostrich": Managing mothers' uncertainty during BRCA1/2 genetic counseling. *Journal of Genetic Counseling, 26*(3), 455-468.

Fitzgerald-Butt SM, Bodine A, Fry KM, Ash J, Zaidi AN, Garg V, Gerhardt CA, McBride KL (2016). Measuring genetic knowledge: a brief survey instrument for adolescents and adults. *Clin Genet*, 89(2):235-43.

Forrest K, Simpson SA, Wilson BJ, van Teijlingen ER, McKee L, Haites N, Matthews E (2003). To tell or not to tell: barriers and facilitators in family communication about genetic risk. *Clin Genet*, 64(4):317-26.

Fossey R, Kochan D, Winkler E, Pacyna JE, Olson J, Thibodeau S, Connolly JJ, Harr M, Behr MA, Prows CA, Cobb B, Myers MF, Leslie ND, Namjou-Khales B, Milo Rasouly H, Wynn J, Fedotov A, Chung WK, Gharavi A, Williams JL, Pais L, Holm I, Aufox S, Smith ME, Scrol A, Leppig K, Jarvik GP, Wiesner GL, Li R, Stroud M, Smoller JW, Sharp RR, Kullo IJ. Ethical Considerations Related to Return of Results from Genomic Medicine Projects: The eMERGE Network (Phase III) Experience (2018). *J Pers Med*, 3;8(1). pii: E2.

Foster C, Eeles R, Ardern-Jones A, Moynihan C, Watson M (2004) Juggling roles and expectations: dilemmas faced by women talking to relatives about cancer and genetic testing. *Psychol Health* 19(4):439–455.

Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gumpper KL, Scholl T, Tavtigian SV, Pruss DR, Critchfield GC (2002). Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol*, 20:1480–1490.

Freeston MH, Rhéaume J, Letarte H, Dugas MJ, & Ladouceur R. (1994). Why do people worry? *Personality and Individual Differences, 17*(6), 791-802.

Fullerton SM, Makhnoon S, Hart R, Amendola L, Niu X, Veenstra DL, Jarvik, GP (2018). American College of Medical Genetics Conference 2018. Charlotte NC. Sharing Clinical Genomic Test Results with Family Members: Experiences of Participants in an Exome Sequencing Study of CRC Risk.

Gaff CL, Clarke AJ, Atkinson P, Sivell S, Elwyn G, Iredale R, Thornton H, Dundon J, Shaw C, Edwards A (2007). Process and outcome in communication of genetic information within families: a systematic review. *Eur J Hum Genet*, 15(10):999-1011.

Garrett LT, Hickman N, Jacobson A, Bennett RL, Amendola LM, Rosenthal EA, Shirts BH. (2016) Family Studies for Classification of Variants of Uncertain Classification: Current Laboratory Clinical Practice and a New Web-Based Educational Tool. *J Genet Couns*., 25(6):1146-1156.

Glesne, C. (2016). Becoming qualitative researchers: An introduction (5th ed.). Boston, MA: Pearson Education, Inc.

Gottesman O, Kuivaniemi H, Tromp G, Faucett WA, Li R, Manolio TA, Sanderson SC, Kannry J, Zinberg R, Basford MA, Brilliant M, Carey DJ, Chisholm RL, Chute CG, Connolly JJ, Crosslin D, Denny JC, Gallego CJ, Haines JL, Hakonarson H, Harley J, Jarvik GP, Kohane I, Kullo IJ, Larson EB, McCarty C, Ritchie MD, Roden DM, Smith ME, Böttinger EP, Williams MS, eMERGE Network. The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future (2013). *Genet Med*, 15(10):761-71.

Griffin RJ, Dunwoody S, & Neuwirth K. (1999). Proposed model of the relationship of risk information seeking and processing to the development of preventive behaviors. Environmental Research, 80, S230–S245.

Guillaume, LR, & Bath PA. (2004). The impact of health scares on parents' information needs and preferred information sources: A case study of the MMR vaccine scare. *Health Informatics Journal, 10*(1), 5-22.

Guiné RP, Ferreira M, Correia P, Duarte J, Leal M, Rumbak I, Barić IC, Komes D, Satalić Z, Sarić MM, Tarcea M, Fazakas Z, Jovanoska D, Vanevski D, Vittadini E, Haga SB, Mills R, Pollak KI, *et. al.* (2014). Developing patient-friendly genetic and genomic test reports: formats to promote patient engagement and understanding. *Genome Med,* 6(7):58.

Haga SB, Barry WT, Mills R, Ginsberg GS, Svetkey LP, Sullivan J, & Willard HF. (2013). Public knowledge of and attitudes toward genetics and genetic testing. *Genetic Testing and Molecular Biomarkers*, 17(4), 327–335.

Hall MJ, Reid JE, Burbidge LA, Pruss D, Deffenbaugh AM, Frye C, Wenstrup RJ, Ward BE, Scholl TA, Noll WW. (2009) BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. *Cancer*, 115, pp. 2222-2233

Han PK.J, Umstead KL, Bernhardt BA, Green RC, Joffe S, Koenig B., . . . Biesecker BB. (2017). A taxonomy of medical uncertainties in clinical genome sequencing. *Genetics in Medicine, 19*(8), 918-925.

Han PKJ. (2013). Conceptual, methodological, and ethical problems in communicating uncertainty in clinical evidence. *Medical Care Research and Review, 70*(1_suppl), 14S-36S.

Harding B, Egan R, Kannu P, MacKenzie JJ. Parents' Understanding of Genetics and Heritability. J Genet Couns. 2017 Jun;26(3):541-547.

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. (2009). Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support, *Journal of Biomedical Informatics*, 42(2):377-81.

Hartoonian N, Ormseth SR, Hanson ER, Bantum EO, Owen JE. (2014) Information-seeking in cancer survivors: application of the Comprehensive Model of Information Seeking to HINTS 2007 data (2014). J Health Commun. 2014;19(11):1308-25.

Hay J, Kaphingst KA, Baser R, Li Y, Hensley-Alford S, & McBride CM. (2012). Skin cancer concerns and genetic risk information-seeking in primary care. *Public Health Genomics, 15*(2), 57-72.

Henneman L, Timmermans DRM, & van der Wal G. (2004). Public experiences, knowledge and expectations about medical genetics and the use of genetic information. *Community Genetics*, 7, 33–43.

Hesse BW, Nelson DE, Kreps GL, Croyle RT, Arora NK, Rimer BK, & Viswanath K. (2005). Trust and sources of health information. the impact of the internet and its implications for health care providers: Findings from the first health information national trends survey. *Archives of Internal Medicine, 165*(22), 2618-2624.

Hughes C, Lerman C, Schwartz M, Peshkin BN, Wenzel L, Narod S, Corio C, Tercyak KP, Hanna D, Isaacs C, Main D (2002) All in the family: evaluation of the process and content of sisters' communication about BRCA1 and BRCA2 genetic test results. Am J Med Genet 107(2):143–150.

Hurle B, Citrin T, Jenkins JF, Kaphingst KA, Lamb N, Roseman JE, Bonham VL. What does it mean to be genomically literate?: National Human Genome Research Institute Meeting Report (2013). *Genet Med*,15(8):658-63.

Ioannidis JPA. (2018) The Proposal to Lower P Value Thresholds to .005. JAMA. 2018 Apr 10;319(14):1429-1430.

Jasperson K (2013). Colorectal cancer: Cascade genetic testing in lynch syndrome: Room for improvement. *Nature Reviews. Gastroenterology & Hepatology, 10*(9), 506-508.

Jensen LA, Moser DK (2008). Gender differences in knowledge, attitudes, and beliefs about heart disease. *Nurs Clin North Am*, 43(1):77-104; vi-vii.

Johnson JD & Meischke H. (1992). Cancer-related channel selection: A focus on women who have had a mammography. *Journal of Applied Social Psychology*, 22, 1879-1893.

Johnson JD & Meischke H. (1992). Cancer-related channel selection: A focus on women who have had a mammography. *Journal of Applied Social Psychology*, 22, 1879_1893.

Johnson JD and Meischke H (1993).A comprehensive model of cancer-related information seeking applied to magazines. Human Communication Research. 19(3):343–367, 1993.

Joseph G, Pasick RJ, Schillinger D, Luce J, Guerra C, Cheng JKY (2017). Information Mismatch: Cancer Risk Counseling with Diverse Underserved Patients *Journal of Genetic Counseling*, *26*(5), 1105-1105.

Judd CM, McClelland GH, Ryan CR. Data analysis: a model comparison approach 2009 New York ; Hove : Routledge.

Julian-Reynier C, Eisinger F, Chabal F, Lasset C, Nogues C, Stoppa-Lyonnet D, Vennin P, Sobol H (2000) Disclosure to the family of breast/ovarian cancer genetic test results: patient's willingness and associated factors. *Am J Med Genet*, 94(1):13–18.

Kaphingst KA (2018). Conceptual and measurement issues in defining genomic literacy, Society of Behavioral Medicine, New Orleans, LA. April 11-14, 2018.

Kaphingst KA, Blanchard M, Milam L, Pokharel M, Elrick A, Goodman MS. (2016) Relationships Between Health Literacy and Genomics-Related Knowledge, Self-Efficacy, Perceived Importance, and Communication in a Medically Underserved Population. *J Health Commun*, 21 Suppl 1:58-68.

Kaphingst KA, Lachance CR, & Condit CM. (2009). Beliefs about heritability of cancer and health information seeking and preventive behaviors. *Journal of Cancer Education, 24*(4), 351-356.

Kaphingst KA, Lachance CR, Condit CM (2009). Beliefs about heritability of cancer and health information seeking and preventive behaviors. *J Cancer Educ*, 24(4):351-6.

Kenen R, Arden-Jones A, Eeles R (2004) We are talking, but are they listening? Communication patterns in families with a history of breast/ovarian cancer (HBOC). *Psycho Oncol,* 13(5):335–345.

Kim H, Paige Powell M, Bhuyan SS. (2017) Seeking Medical Information Using Mobile Apps and the Internet: Are Family Caregivers Different from the General Public? J Med Syst. 2017 Mar;41(3):38.

Kim HW (2013). Gender differences in knowledge and health beliefs related to behavioral intentions to prevent human papillomavirus infection. *Asia Pac J Public Health,* 25(3):248-59.

Kurian AW, Li Y, Hamilton AS, Ward KC, Hawley ST, Morrow M, McLeod MC, Jagsi R, Katz SJ. (2017). Gaps in incorporating germline genetic testing into treatment decision-making for early-stage breast cancer. *Journal of Clinical Oncology, 35*(20), 2232-2239.

LaDuca H, Stuenkel AJ, Dolinsky JS, Keiles S, Tandy S, Pesaran T, Chen E, Gau CL, Palmaer E, Shoaepour K, Shah D, Speare V, Gandomi S, Chao E. (2014) Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. *Genet Med*,16:830–837.

Lambert SD & Loiselle CG. (2007). Health information-seeking behavior. *Qualitative Health Research, 17*(8), 1006-1019.

Lee MD, & Dry MJ. (2006). Decision making and confidence given uncertain advice. *Cognitive Science, 30*(6), 1081-1095.

Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell, T, O'Donnell-Luria AH, Ware JS, Hill AJ, Cummings BB, Tukiainen T, Birnbaum DP, Kosmicki JA, Duncan LE, Estrada K, Zhao F, Zou J, Pierce-Hoffman E, Berghout J, Cooper DN, Deflaux N, DePristo M, Do R, Flannick J, Fromer M, Gauthier L, Goldstein J, Gupta N, Howrigan D, Kiezun A, Kurki MI, Moonshine AL, Natarajan P, Orozco L, Peloso GM, Poplin R, Rivas MA, Ruano-Rubio V, Rose SA, Ruderfer DM, Shakir K, Stenson PD, Stevens C, Thomas BP, Tiao G, Tusie-Luna MT, Weisburd B, Won HH, Yu D, Altshuler DM, Ardissino D, Boehnke M, Danesh J, Donnelly S, Elosua R, Florez JC, Gabriel SB, Getz G, Glatt SJ, Hultman CM, Kathiresan S, Laakso M, McCarroll S, McCarthy MI, McGovern D, McPherson R, Neale BM, Palotie A, Purcell SM, Saleheen D, Scharf JM, Sklar P, Sullivan PF, Tuomilehto J, Tsuang MT, Watkins HC, Wilson JG, Daly MJ, MacArthur DG, Exome Aggregation Consortium. (2016). Analysis of protein-coding genetic variation in 60,706 humans. *Nature*, 536(7616), 285-291.

Li N, Orrange S, Kravitz RL, & Bell RA. (2014). Reasons for and predictors of patients' online health information seeking following a medical appointment. *Family Practice, 31*(5), 550-556.

Li ST, Sun S, Lie D, Met-Domestici M, Courtney E, Menon S, Lim GH, Ngeow J. Factors influencing the decision to share cancer genetic results among family members: An in-depth interview study of women in an Asian setting. *Psychooncology*. 2018 Mar;27(3):998-1004.

Lincoln SE, Yang S, Cline MS, Kobayashi Y, Zhang C, Topper S, Haussler D, Paten B, Nussbaum RL (2017). Consistency of BRCA1 and BRCA2 Variant Classifications Among Clinical Diagnostic Laboratories. *JCO Precis Oncol*. 2017 Jul; 1.

Ling BS, Klein WM, & Dang Q. (2006). Relationship of communication and information measures to colorectal cancer screening utilization: Results from HINTS. *Journal of Health Communication, 11*(SUPPL. 1), 181-190.

Lipkus IM, Vadaparampil ST, Jacobsen PB, & Miree CA. (2011). Knowledge about genomic recurrence risk testing among breast cancer survivors. *Journal of Cancer Education, 26*(4), 664-669.

Lloyd SM, Watson M, Oaker G, Sacks N, Querci Della Rovere U, & Gui G. (2000). Understanding the experience of prophylactic bilateral mastectomy: A qualitative study of ten women. *Psycho-Oncology, 9*(6), 473-485.

Lynn R, Irwing P, & Cammock T. (2002). Sex differences in general knowledge. *Intelligence*, 30(1), 27-39.

Madsen TE, Baird KA, Silver B, Gjelsvik A (2015. Analysis of Gender Differences in Knowledge of Stroke Warning Signs. *J Stroke Cerebrovasc Dis,* 24(7):1540-7.

Makhnoon S, Meischke HW, Shirts BH, Bowen DJ. (2018) *Dealing with Uncertainty: Information seeking to guide VUS management*. Manuscript submitted for publication.

Makhnoon S, Shirts BH, Bowen DJ, Fullerton SM (2018). Hereditary cancer gene panel test reports: wide heterogeneity suggests need for standardization. *Genet Med. 2018 Mar 1. doi: 10.1038/gim.2018.23. [Epub ahead of print]*

Makhnoon S, Thomas L, Wylie B, Bowen D, Shirts B. (2017). *Beyond uncertainty: Experiences of patients who participate in variant of uncertain significance reclassification research*. Manuscript submitted for publication.

Maxwell KN, Hart SN, Vijai J, Schrader KA, Slavin TP, Thomas T, Wubbenhorst B, Ravichandran V, Moore RM, Hu C, Guidugli L, Wenz B, Domchek SM, Robson ME, Szabo C, Neuhausen SL, Weitzel JN, Offit K, Couch FJ, Nathanson KL. (2016). Evaluation of ACMG-Guideline-Based Variant Classification of Cancer Susceptibility and Non-Cancer-Associated Genes in Families Affected by Breast Cancer. *Am J Hum Genet,* 98(5):801-817

McCarty CA, Chisholm RL, Chute CG, Kullo IJ, Jarvik GP, Larson EB, Li R, Masys DR, Ritchie MD, Roden DM, Struewing JP, Wolf WA, eMERGE Team (2011). The eMERGE Network: a consortium of biorepositories linked to electronic medical records data for conducting genomic studies. *BMC Med Genomics*, 4():13.

McGivern B, Everett J, Yager GG, Baumiller RC, Hafertepen A, Saal HM. (2004) Family communication about positive BRCA1 and BRCA2 genetic test results. *Genet Med*; 6: 503–509.

McLachlan S, Clements A, & Austoker J. (2012). Patients' experiences and reported barriers to colonoscopy in the screening context-A systematic review of the literature. *Patient Education and Counseling, 86*(2), 137-146.

Meischke H, Eisenberg M, Rowe S, & Cagle A. (2005). Do older adults use the internet for information on heart attacks? results from a survey of seniors in king county, washington. *Heart and Lung: Journal of Acute and Critical Care, 34*(1), 3-12.

Mellon S, Berry-Bobovski L, Gold R, Levin N, Tainsky MA (2006) Communication and decision-making about seeking inherited cancer risk information: findings from female survivor relative focus groups. *Psycho Oncol* 15(3):193–208.

Mesters I, Ausems A, De Vries H (2005) General public's knowledge, interest and information needs related to genetic cancer: an exploratory study. *Eur J Cancer Prev* 14(1):69–75.

Mills R, Powell J, Barry W, & Haga SB. (2014). Information-seeking and sharing behavior following genomic testing for diabetes risk. *Journal of Genetic Counseling, 24*(1), 58-66.

Mishel MH. (1999). Uncertainty in chronic illness. *Annual Review of Nursing Research, 17*, 269-294. Retrieved from www.scopus.com

Molster C, Charles T, Samanek A, O'Leary P: Australian study on public knowledge of genetics and health. *Public Health Genomics* 2009; 12:84–91.

Muha C, Smith KS, Baum S, Maat JT, & Ward JA. (1998). The use and selection of sources in information seeking: The cancer information service experience Part 8. *Journal of Health Communication*, 3(Suppl.), 109-120.

Murray ML, Cerrato F, Bennett RL, Jarvik GP. Follow-up of carriers of BRCA1 and BRCA2 variants of unknown significance: Variant reclassification and surgical decisions. Genetics in Medicine.2011;13(12):998–1005.

Nanda R, Schumm LP, Cummings S, Fackenthal JD, Sveen L, Ademuyiwa F, Cobleigh M, Esserman L, Lindor NM, Neuhausen SL, Olopade OI (2005). Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. *JAMA*, 294:1925–1933.

Niederdeppe J, Hornik RC, Kelly, BJ, Frosch DL, Romantan A, Stevens RS, Schwartz JS. (2007). Examining the dimensions of cancer-related information seeking and scanning behavior. *Health Communication*, 22(2), 153–167.

Nycum G, Avard D, Knoppers BM. (2009) Factors influencing intrafamilial communication of hereditary breast and ovarian cancer genetic information. *Eur J Hum Genet*, 17(7):872-80.

O'Neill SC, DeMarco T, Peshkin BN, Rogers S, Rispoli J, Brown K, Valdimarsdottir H, Schwartz MD. (2006) Tolerance for uncertainty and perceived risk among women receiving uninformative BRCA1/2 test results. *Am J Med Genet C Semin Med Genet*, 142C(4):251-259.

O'Neill SC, Rini C, Goldsmith RE, Valdimarsdottir H, Cohen LH, Schwartz MD. (2009) Distress among women receiving uninformative BRCA1/2 results: 12-month outcomes. *Psychooncology,* 18(10):1088-1096.

Opatt DM. Morrow M. Daly M (2006). The incidence of BRCA1 and BRCA2 variants of unknown significance varies in different ethnic populations. *J Clin Oncol*, 24(June 20 Supplement):10002.

Ormondroyd E, Moynihan C, Ardem-Jones A, Eeles R, Foster C, Davolls S, Watson M (2008) Communicating genetics research results to families: problems arising when the patient participant is deceased. *Psycho Oncol* 17(8):804–811.

Orom H, Biddle C, Waters EA, Kiviniemi MT, Sosnowski AN, Hay JL. (2017) Causes and consequences of uncertainty about illness risk perceptions. *J Health Psychol*, 1:1359105317745966.

Parrott RL1, Silk KJ, Condit C. (2003) Diversity in lay perceptions of the sources of human traits: genes, environments, and personal behaviors. *Soc Sci Med*, 56(5):1099-109.

Pecchioni LL, & Sparks L. (2007). Health information sources of individuals with cancer and their family members. *Health Communication, 21*(2), 143-151.

Pellegrini N, Szűcs V, Harangozó J, El-Kenawy A, El-Shenawy O, Yalçın E, Kösemeci C, Klava D, Straumite E. (2016). Knowledge about dietary fibre: a fibre study framework. Int *J Food Sci Nutr*, 67(6):707-14.

Peterson SK, Watts BG, Koehly LM, Vernon SW, Baile WF, Kohlmann WK, Gritz ER (2003) How families communicate about HNPCC genetic testing: findings from a qualitative study. *Am J Med Genetics* 119C(1):78–86.

Peterson SK, Watts BG, Koehly LM, Vernon SW, Baile WF, Kohlmann WK, Gritz ER (2003) How families communicate about HNPCC genetic testing: findings from a qualitative study. *Am J Med Genetics* 119C(1):78–86.

Petrucelli N, Lazebnik N, Huelsman KM, Lazebnik RS. (2002) Clinical interpretation and recommendations for patients with a variant of uncertain significance in BRCA1 or BRCA2: a survey of genetic counseling practice. *Genetic testing,* 6(2):107–113.

Placeholder for NCCN

Politi MC, Han PK, Col NF. (2007) Communicating the uncertainty of harms and benefits of medical interventions. *Med Decis Making,* 27(5):681–695.

Prince AER. (2015). Prevention for those who can pay: Insurance reimbursement of genetic-based preventive interventions in the liminal state between health and disease. *Journal of Law and the Biosciences*, 2, 365–395.

Rains SA, & Tukachinsky R. (2015). Information seeking in uncertainty management theory: Exposure to information about medical uncertainty and information-processing orientation as predictors of uncertainty management success. *Journal of Health Communication, 20*(11), 1275-1286.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, . . . Rehm HL. (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, 17*(5), 405-424.

Richman AR, Tzeng JP, Carey LA, Retèl VP, & Brewer NT. (2011). Knowledge of genomic testing among early-stage breast cancer patients. *Psycho-Oncology, 20*(1), 28-35.

Richter S, Haroun I, Graham TC, Eisen A, Kiss A, Warner E. (2013) Variants of unknown significance in BRCA testing: impact on risk perception, worry, prevention and counseling. *Ann Oncol*, 24 Suppl 8:viii69-viii74.

Ricker C, Culver JO, Lowstuter K, Sturgeon D, Sturgeon JD, Chanock CR, Gauderman WJ, McDonnell KJ, Idos GE, Gruber SB. (2016) Increased yield of actionable mutations using

multi-gene panels to assess hereditary cancer susceptibility in an ethnically diverse clinical cohort. *Cancer Genet*, 209(4):130-7.

Roach AR, Lykins ELB, Gochett CG, Brechting EH, Graue LO, & Andrykowski MA. (2009). Differences in cancer information-seeking behavior, preferences, and awareness between cancer survivors and healthy controls: A national, population-based survey. *Journal of Cancer Education, 24*(1), 73-79.

Rosen NO, Ivanova E, & Knäuper B. (2014). Differentiating intolerance of uncertainty from three related but distinct constructs. *Anxiety, Stress and Coping, 27*(1), 55-73.

Rothman AJ, & Salovey P. (1997). Shaping perceptions to motivate healthy behavior: The role of message framing. Psychological Bulletin, 121(1), 3-19.

Rutten LJF, Squiers L, & Hesse B. (2006). Cancer-related information seeking: Hints from the 2003 health information national trends survey (HINTS). *Journal of Health Communication, 11*(SUPPL. 1), 147-156.

Scherr CL, Lindor NM, Malo TL, Couch FJ, Vadaparampil ST (2015). A preliminary investigation of genetic counselors' information needs when receiving a variant of uncertain significance result: A mixed methods study. *Genetics in Medicine*; 17(9):739-46.

Scherr CL, Lindor NM, Malo TL, Couch FJ, Vadaparampil ST (2015). A preliminary investigation of genetic counselors' information needs when receiving a variant of uncertain significance result: a mixed methods study. *Genet Med*;17(9):739-746.

Scherr CL, Lindor NM, Malo TL, Couch FJ, Vadaparampil ST (2015). Genetic counselors' practices and confidence regarding variant of uncertain significance results and reclassification from BRCA testing. *Clin Genet*, 88(6):523-529.

Secretary's Advisory Committee on Genetics, Health and Society (2006). Coverage and Reimbursement of Genetic Tests and Services. http://osp.od.nih.gov/sites/default/files/CR_report.pdf. Accessed 12 March 2017.

Selkirk CG, Vogel KJ, Newlin AC, Weissman SM, Weiss SM, Wang CH, Hulick PJ (2014). Cancer genetic testing panels for inherited cancer susceptibility: the clinical experience of a large adult genetics practice. *Fam Cancer*;13(4):527-36.

Seymour K, Addington-Hall J, Lucassen A, Foster C (2010) What facilitates or impedes family communication following genetic testing for cancer risk? A systematic review and meta-synthesis of primary qualitative research. *J Genetic Couns*,19(4):330–342.

Shi H, Nakamura K, & Takano T. (2004). Health values and health-information-seeking in relation to positive change of health practice among middle-aged urban men. *Preventive Medicine, 39*(6), 1164-1171.

Shim M, Kelly B, & Hornik R. (2006). Cancer information scanning and seeking behavior is associated with knowledge, lifestyle choices, and screening. *Journal of Health Communication, 11*(SUPPL. 1), 157-172.

Shirts BH, Casadei S, Jacobson AL, Lee MK, Gulsuner S, Bennett RL, Miller M, Hall SA, Hampel H, Hisama FM, Naylor LV, Goetsch C, Leppig K, Tait JF, Scroggins SM, Turner EH, Livingston R, Salipante SJ, King MC, Walsh T, Pritchard CC. (2016) Improving performance of multigene panels for genomic analysis of cancer predisposition. *Genet Med*, 18(10):974-81.

Skinner D, Roche MI, Weck KE, Raspberry KA, Foreman AKM, Strande NT, Berg JS, Evans JP, Henderson GE. (2018) "Possibly positive or certainly uncertain?": participants' responses to uncertain diagnostic results from exome sequencing. *Genet Med*;20(3):313-319.

Smith KR, Zick CD, Mayer RN, Botkin JR (2002) Voluntary disclosure of BRCA1 mutation test results. *Genetic Testing* 6(2):89–92.

Sobel SK, Cowan DB (2000) Impact of genetic testing for Huntington disease on the family system. *Am J Med Genet* 90(1): 49–59.

Solomon I, Harrington E, Hooker G, Erby L, Axilbund J, Hampel H, Semotiuk K, Blanco A, Klein WMP, Giardiello F, Leonard L. (2017) Lynch Syndrome Limbo: Patient Understanding of Variants of Uncertain Significance. *J Genet Couns*, 26(4):866-877.

Speice J, McDaniel SH, Rowley PT, Loader S. (2002) Family issues in a psychoeducation group for women with a BRCA mutation. *Clin Genet*, 62: 121– 127.

Spoonamore KG, & Johnson NM. (2016). Who pays? Coverage challenges for cardiovascular genetic testing in U.S. patients. *Frontiers in Cardiovascular Medicine*, 3, 1–6.

Thompson BA, Goldgar DE, Paterson C, Clendenning M, Walters R, Arnold S, Parsons MT, Michael DW, Gallinger S, Haile RW, Hopper JL, Jenkins MA, Lemarchand L, Lindor NM, Newcomb PA, Thibodeau SN; Colon Cancer Family Registry, Young JP, Buchanan DD, Tavtigian SV, Spurdle AB. (2013) A multifactorial likelihood model for MMR gene variant classification incorporating probabilities based on sequence bioinformatics and tumor characteristics: a report from the Colon Cancer Family Registry. *Hum Mutat*, 34(1):200-9.

Timmermans S, Tietbohl C, & Skaperdas E. (2017). Narrating uncertainty: Variants of uncertain significance (VUS) in clinical exome sequencing. *BioSocieties, 12*(3), 439-458.

Tonelli MR, Shirts BH. (2017) Knowledge for Precision Medicine: Mechanistic Reasoning and Methodological Pluralism. *JAMA*;318(17):1649-1650.

Tung N, Battelli C, Allen B, Kaldate R, Bhatnagar S, Bowles K, Timms K, Garber JE, Herold C, Ellisen L, Krejdovsky J, DeLeonardis K, Sedgwick K, Soltis K, Roa B, Wenstrup RJ, Hartman AR. (2015) Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer*, 121:25–33.

Turna Ray, Mother's Negligence Suit Against Quest's Athena Could Broadly Impact Genetic Testing Labs, GENOMEWEB (2016) https://www.genomeweb.com/molecular-diagnostics/mothers-negligence-suit-against-quests-athena-could-broadly-impact-genetic (accessed April 25, 2018).

van den Nieuwenhoff HWP, Gielen C, De Vries NK (2007) Family communication regarding inherited high cholesterol: why and how do patients disclose genetic risk? *Soc Sci Med* 65(5):1025–1037.

van Dijk S, Timmermans DRM, Meijers-Heijboer H, Tibben A, van Asperen CJ, & Otten W. (2006). Clinical characteristics affect the impact of an uninformative DNA test result: The course of worry and distress experienced by women who apply for genetic testing for breast cancer. *Journal of Clinical Oncology, 24*(22), 3672-3677.

VandenBoom E, Trepanier AM, Carmany EP. (2017) Assessment of Current Genetic Counselor Practices in Post-Visit Written Communications to Patients. *J Genet Couns.* Oct 12.

Vos J, Gómez-García E, Oosterwijk JC, *et. al.*. Opening the psychological black box in genetic counseling. The psychological impact of DNA testing is predicted by the counselees'

perception, the medical impact by the pathogenic or uninformative BRCA1/2-result. *Psycho-Oncology*. 2012;21(1):29–42.

Vos J, Otten W, van Asperen C, Jansen A, Menko F, Tibben A. (2008) The counsellees' view of an unclassified variant in BRCA1/2: recall, interpretation, and impact on life. *Psycho-Oncology*;17(8):822–830.

Wagner CJ, Itzen M, Malick J, Babb JS, Bove B, Godwin AK, Daly MB (2003) Communication of BRCA1 and BRCA2 results to at-risk relatives: a cancer risk assessment program's experience. *Am J Med Genetics* 119C(1):11–18.

Waters EA, Wheeler C, & Hamilton JG. (2016). How are information seeking, scanning, and processing related to beliefs about the roles of genetics and behavior in cancer causation? *Journal of Health Communication, 21*, 6-15.

Weitzel JN, Lagos V, Blazer KR, Nelson R, Ricker C, Herzog J, McGuire C, Neuhausen S. (2015) Prevalence of BRCA mutations and founder effect in high-risk Hispanic families. *Cancer Epidemiol Biomarkers Prev,*14:1666–1671.

Whyte S, Green A, McAllister M, Shipman H. (2016) Family Communication in Inherited Cardiovascular Conditions in Ireland. *J Genet Couns*;25(6):1317-1326.

Wilson BJ, Forrest K, Van Teijlingen ER, Mckee L, Haites N, Matthews E, Simpson SA (2004) Family communication about genetic risk: the little that is known. *Commun Genetics* 7(1):15–24.

Wiseman M, Dancyger C, & Michie S. (2010). Communicating genetic risk information within families: A review. *Familial Cancer*, 9(4), 691-703.

Wong NC. (2012). Interaction of comparative cancer risk and cancer efficacy perceptions on cancer-related information seeking and scanning behaviors. *Communication Research Reports*, 29(3), 193–203.

SUPPLEMENTARY TABLES AND FIGURES

Table S1: Patient responses to survey questions.

Survey question	N
What is the highest grade or level of schooling you completed?	
Less than 8 years	0
8 through 11 years	0
12 years or completed high school	3
Post high school training other than college (vocational or technical)	4
Some college	4
College graduate	22
Postgraduate	12
Have you been diagnosed with a cancer?	
Yes	32
No	14
What type of cancer have you been diagnosed with?	
Do you have children?	
Yes	32
No	14
How many biological children do you have?	
Have you ever looked for information about health or medical topics from any source?	
Yes	44
No	2
I don't know	0
Have you looked for information about cancer genetic testing from any source?	
Yes	35
No	11
Have you looked for information about Variants of Uncertain/Unknown Significance (VUS) from any source?	
Yes	24
No	22
I don't know	0

The most recent time you looked for information about health and medical topics (such as general health, cancer, genetic testing or VUS), which information source did you go to first?				
	General health	Cancer	Genetic testing	VUS
Family	4	7	1	0
Friend/Co-worker	0	0	0	0
Doctor, health care provider or genetic counselor	14	22	16	16
Cancer and/or Research Organizations (e.g., Fred Hutch, University of Washington)	0	17	16	10
General medical information websites (e.g., WebMD, CDC)	20	9	8	4
Genetic testing laboratory (e.g., Myriad, UW Lab Medicine)	2	2	7	2
Other	2	3	1	2
In general, how much you would trust information about VUS from each of the following (Not at all to A lot)				
	A lot	A little	Some	Not at all
A genetic provider (genetic counselor, medical geneticist etc.)	41	4	1	0
Family or friends	1	6	22	17
Newspapers or magazines	0	13	36	7
Internet	2	14	24	6
Government health agencies	14	21	9	3
Have you EVER undergone cancer-related surgery (such as mastectomy, oophorectomy, colectomy etc.)?				
Yes	34			
No	12			
Did you consider VUS result in your surgical decision?				
No, VUS was not important in my surgical decision	21			
Yes, VUS result was why I underwent surgery	4			
Yes, a VUS result was part of my surgical decision	2			
Other	4			
Did you consider a VUS result in your decision not to undergo surgery?				
I did not undergo surgery because it was medically unnecessary	4			
VUS was not important in my surgical decision	1			
I did not undergo surgery because of my VUS result	2			

Other	2
Did you consider VUS result in your screening decision?	
Yes, I began screening because of my VUS result	3
Yes, I increased the frequency of screening because of my VUS result	5
Yes, I decreased the frequency of screening because of my VUS result	0
No, my screening frequency did not change	25
Other	4
Did you encourage/ask any of your family members to get genetic testing as a result of your VUS result?	
Yes	21
No	24
Did you ever check back for VUS reclassification with your provider?	
Yes	8
No	38
Did your provider ever contact you with updates on VUS reclassification?	
Yes	5
No	40

Table S2: Comparison of VUS related behavior between patients with only a VUS result (n =34) and with a VUS as well as a deleterious mutation (n = 12).

Health decision/Health behavior	N	%	VUS only (n = 34)		VUS + P/LP (n = 12)		X^2 (p-value)
Surgical decision making							
Patients who underwent cancer surgery:	34		27		7		
Action[1]	6	17.6	4	14.8	2	28.5	
Inaction[2]	21	61.8	17	62.9	4	57.1	0.48
Other	4	11.7	3	11.1	1	14.3	
Patients who did not undergo surgery:	12		7		5		
Action[3]	2	16.6	1	14.2	1	20	
Inaction[4]	5	41.6	2	28.5	3	60	0.40
Other	2	16.6	2	28.5	0	0	
Screening decision making							
Patients who underwent cancer screening:	40		28		12		
Action[5]	8	20	2	7.1	6	50	
Inaction[6]	25	32.5	21	75	4	33.3	0.008
Other	4	10	3	10.7	1	8.3	
Family testing based on VUS							
Asked family to get tested because of VUS	21	46.7	13	39.3	8	66.6	0.19
Did not ask family to get tested	24	53.3	20	60.6	4	33.3	
Checking back for VUS reclassification							
Checked back for reclassification:	8	17.4	5	13.1	3	21.4	
Did not check back for reclassification	32	69.5	29	76.3	9	64.2	0.71
VUS was reclassified	6	13.0	4	10.5	2	14.2	

[1]Includes “VUS result was the reason for undergoing surgery”, “VUS result was part of surgical decision”
[2]Includes “No, VUS was not important in surgical decision”
[3]Includes “Did not undergo surgery because of VUS result”
[4]Includes “VUS was not important in surgical decision”, “Surgery was medically unnecessary”
[5]Includes “Began screening because of VUS result”, “Increased the frequency of screening”, “Decreased the frequency of screening”
[6]Includes “No, my screening frequency did not change”

Table S3: Frequencies for genomics-related knowledge, frequency of current Colorectal Cancer and Polyposis-related familial communication and intention to share CRCP-related genomic test results in future.

Characteristic	*n*	%
Genomics-related knowledge (n = 147)		
High score (>10)	71	48.3
Low score (≤ 10)	76	51.7
Frequency of current familial communication with mother (*n* = 157)		
Don't currently have this relative	115	73.2
Not at all	22	14.0
A little	11	7.0
Some	7	4.5
A lot	2	1.3
Frequency of current familial communication with father (n = 158)		
Don't currently have this relative	126	79.7
Not at all	25	15.8
A little	3	1.9
Some	4	2.5
A lot	0	0.0
Frequency of current familial communication with sisters (n = 159)		
Don't currently have this relative	69	43.4
Not at all	55	34.6
A little	18	11.3
Some	12	7.5
A lot	5	3.1
Frequency of current familial communication with brothers (n = 159)		
Don't currently have this relative	62	39.0
Not at all	58	36.5
A little	20	12.6
Some	16	10.1
A lot	3	1.9
Frequency of current familial communication with children (n = 157)		
Don't currently have this relative	22	14.0
Not at all	59	37.6
A little	36	22.9
Some	26	16.6
A lot	14	8.9
Frequency of current familial communication with grandchildren (n = 153)		
Don't currently have this relative	69	45.1
Not at all	74	48.4

A little	3	2.0
Some	4	2.6
A lot	3	2.0
Intention to share genomic test results with Children (n = 156)		
Yes	116	74.4
No	4	2.6
Unsure or have not decided	14	9.0
Not applicable (N/A)	22	14.1
Intention to share genomic test results with Mother (n = 151)		
Yes	25	16.6
No	7	4.6
Unsure or have not decided	6	4.0
Not applicable (N/A)	113	74.8
Intention to share genomic test results with Father (n = 151)		
Yes	13	8.6
No	8	5.3
Unsure or have not decided	7	4.6
Not applicable (N/A)	123	81.5
Intention to share genomic test results with Siblings (n = 154)		
Yes	96	62.3
No	6	3.9
Unsure or have not decided	18	11.7
Not applicable (N/A)	34	22.1

APPENDIX

VUS Comprehension and Health Behavior

Oral consent script

Survey and Interview:

A. LIVE PERSON

Hello, may I please speak with (ppt's name)?

NO SUCH PERSON AT THIS NUMBER: [verify that number was dialed correctly.] Thank you for your time. Goodbye.

PPT MOVED OR IS NOT REACHABLE AT SPECIFIED NUMBER: Do you know the phone number and address where I can reach <INSERT PPT'S NAME>? [RECORD NEW NUMBER & ADDRESS ON CALL RECORD] Thank you for your time. Goodbye.

PPT IS NOT IN: Do you know when would be a better time to reach <INSERT PPT'S NAME>? [WRITE DOWN THAT INFORMATION ON CALL RECORD] Thank you for your time. Goodbye.

PPT IS IN:

Hi, my name is _____. I'm working on a study being conducted by the University of Washington. We would like to know how people with VUS test result understand their result. To do this, we want you to be in this study because you have a VUS test result. We learned of you VUS test result from your patient record at the Seattle Cancer Care Alliance (or other organization, if appropriate). Do you have a few minutes to discuss the study?

If yes, continue below.

- If no, but the potential subject is interested in participating, determine a better time to call back to discuss the study.
- If no, thank them for their time.

We are inviting you to take part in this study because you have been previously returned a certain type of cancer test result (VUS). The purpose of this study is to find out how patients understand their VUS test result. To do this, we need some information from medical records of patients who have a clinically confirmed VUS. The information that you provide will be utilized in order to help patients just like you by ensuring that we know how to adequately meet the needs of future patients with this type of test result. You will not benefit directly from taking part in this research.

If you decide to take part in this study, we will start by asking you to fill out a survey (20 mins) about some VUS related information. Here we may ask questions such as, "How many people in your social network has cancer?" You will then participate in a brief (30-60 minute) interview in which we will discuss topics such as how test results were explained to you after your genetic test. We may ask questions such as "How did you feel when you were first told about your VUS result?" The interview will be audio recorded but we will delete the recording as soon as we complete this research. We will also ask questions about how you think your providers could have better helped you with understanding this

test result. These interviews will be audio recorded and stored in a secure location.

If you agree to be in this study, we would like to obtain the following information from your medical records at the Seattle Cancer Care Alliance: your cancer diagnosis, genetic test results, and genetic consultation records. Some people do not want their medical records used for research. If you feel this way, you should not be in this study. If you have questions/concerns about how your data will be used, I am happy to answer your questions.

Information about you is confidential. We will code information you provide. We will keep the link between your name and the code in a separate, secured location until the study is completed. Then we will destroy the link. If we publish the results of this study, we will not use your name. Breach of confidentiality is a potential risk, and the necessary protections are in place to mitigate this risk.

You will receive a $30 payment for your time and help in conducting this study. In addition, we will enter you into a $50 prize drawing if you participate in the survey. There will be no cost to you to participate in this study. If you are interested you might be contacted again after completing the interview to check that we correctly interpreted your responses. There is no expected potential for injury related to this research project. We would also like you to know that your participation in this study is completely voluntary. You are free not to participate or to withdraw at any time, for whatever reason. Whether you choose to be in this study, or choose not be in this study, will not affect your health care here at SCCA (or other organization, if appropriate). If you have questions about your rights as a research subject, you can call the Human Subjects Division at (206) 543-0098.

Do you have any questions? Would you like to participate in this study?

☐ Yes: Document oral consent below and continue with interview.

☐ No: Thank them for their time.

Is it okay to re-contact you to check whether or not we have correctly interpreted your responses?

☐ Yes: Document oral consent for re-contact.

☐ No: Thank them for their time.

Initials of participant:

_____

Person Obtaining Consent

I have read this form to the subject. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information. The subject has provided oral consent to participate in this study.

_____

Name and Title (Print)

_____ _____

Signature of Person Obtaining Consent Date

When is a good time for you to complete the interview?

[WRITE DOWN THAT INFORMATION ON CALL RECORD]

Great! I look forward to talking with you then. Bye!

IF THIS IS A GOOD TIME, BEGIN INTERVIEW:

Let participant know that you are starting the recorder and beginning the interview.