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Variant Reclassification in Cancer Genetic Testing: Are Genetic Counselors Prepared? A Review of Current Practices

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Variant Reclassification in Cancer Genetic Testing: Are Genetic Counselors Prepared?
A Review of Current Practices

by

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Dedication

For my parents Peter and Gemma, without your never-ending love, support and encouragement I would not be where I am today.

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First and foremost I would like to say thank you to Peggy. Thank you for allowing me to pester you with endless questions throughout this whole process, thank you for not becoming frustrated with me and thank you for providing thoughtful insights and helpful suggestions.

Thank you is also due to all my committee members, Brook, Karen and Cristi, without whom I would have been lost. You have all provided both support and guidance that I have greatly appreciated. I am so thankful to have had each of you on my committee. I think it is fair to say that your support for my project has allowed it to flourish.

'Go raibh mile maith agat as gach rud'

Abstract

Purpose: Cancer genetics has emerged as a critical specialty within the field of genetic counseling. Advancements in research are constantly uncovering new insights into the genetics of cancer and inherited cancer syndromes. It is crucial that genetic counselors and the institutions in which they work are in sync with these advancements. Currently, multiplex or multi-gene cancer testing is rapidly being adapted into the cancer genetic counseling setting. The 'hot topic' of an increased likelihood of receiving variant results following such testing has been explored in depth in the literature. However, research surrounding genetic counseling practices and the reclassification of VUS results is lacking. No consensus guidelines addressing variant reclassification yet exist. This study aimed to identify current practices of genetic counselors with regard to variant reclassification, and to explore whether genetic counselors feel they need official guidelines relating to the reclassification of variant results.

Method: An online survey distributed through the National Society of Genetic Counselors and the Cancer Special Interest Group (SIG) was utilized in this research study. Statistical Analysis System (SAS) 9.4 was employed for quantitative data and statistical analysis while qualitative data was coded and analyzed for major themes using grounded theory methods.

Results: We determined that cancer genetic counselors are handling the reclassification of VUS results in a unified manner. Common themes across almost 200 respondents demonstrated that they approach benign or deleterious reclassification in a similar

fashion. 95% of respondents (n = 209) discuss variant reclassification with their patients upon receiving a VUS result. Similarly, 95% of respondents (n = 209) will sometimes or always make a plan to communicate VUS reclassification results should they arise in the future. The overwhelming majority (97%) of respondents (n = 183) indicated that the protocol for re-contacting patients with a VUS reclassification would not be different from what they had used in the past for single-gene analysis. Varying opinions existed on whether practice guidelines relating to VUS reclassification are necessary. The majority, 62% of respondents (n = 178), agreed or strongly agreed that there was a need for guidelines relating to variant reclassification. Those who disagreed expressed concerns surrounding liability issues and the feasibility of implementing recommendations across different institutions.

Conclusions: Findings from this study indicate that most genetic counselors are utilizing unified practices when handling the reclassification of variant results. Additionally, a proportion of genetic counselors felt that guidance or recommendations for certain areas relating to variant reclassification are necessary. While future research is needed to explore more in-depth the issues and opinions identified in this research project, another possible approach is for the NSGC Cancer SIG to address this topic at their earliest opportunity, given the coming wave of VUS reclassifications from multiple collaborative efforts to more urgently reclassify VUS results.

Keywords: Cancer genetics, genetic testing, multi-gene panels, multiplex genetic testing, variant(s), VUS, reclassification

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List of Abbreviations

GC.....Genetic counselor

HBOC ..... Hereditary Breast and Ovarian Cancer

NGS..... Next Generation Sequencing

TAT.....Turn-around-time

VUS..... Variant of uncertain significance

Chapter 1. Background

The basis of an inherited susceptibility to cancer is complex. Mutations in specific genes can increase an individual's risk for developing cancer (Domchek, Bradbury, Garber, Offit, & Robson, 2013). Identifying mutations in these cancer predisposition genes is a valuable clinical tool, as it identifies which individuals are at a particularly high risk of developing cancer. Traditionally, it has been common practice to analyze single genes for mutations. The genes being analyzed are those that are the most likely to carry mutations, dependent on one's personal and family history (Domchek et al., 2013; Mauer, Pirzadeh-Miller, Robinson, & Euhus, 2014). If no mutation is identified, further single gene tests may then be carried out (Domchek et al., 2013; Mauer et al., 2014). An example of this is the traditional manner in which testing has been conducted to uncover a genetic cause for Hereditary Breast and Ovarian Cancer (HBOC) Syndrome. Mutations in *BRCA1* and *BRCA2* increase the risk for breast and ovarian cancer and are the most common genes associated with HBOC Syndrome (Hall et al., 1990; Hilbers, Vreeswijk, van Asperen, & Devilee, 2013; Wooster et al., 1995). HBOC syndrome was originally linked to an autosomal dominant trait in the early 70's and it was in the years following that *BRCA1* and *BRCA2* were identified (Lynch, Snyder, & Casey, 2013). Since their discovery in the mid 1990's, these two genes have dominated much of research and thus have led to the recommendation of specific surgical and management interventions when a mutation is identified (Lee & Ang, 2014; Rainville & Rana, 2014). National recommendations

outlining surveillance options, prophylactic surgical measures and chemoprevention for *BRCA*1 or *BRCA2* mutation carriers exist (Pruthi, Gostout, & Lindor, 2010; Robson & Offit, 2007).

Since the identification of *BRCA1* and *BRCA2,* multiple other genes involved in the same DNA repair pathway have been uncovered (Lynch et al., 2013; Rainville & Rana, 2014). Although *BRCA1* and *BRCA2* remain the main players and account for the majority of HBOC syndrome cases, other genes are now known to modify an individual's risk. Some examples include genes such as *TP53, PTEN, NBN and STKII* (Hilbers et al., 2013; Kobayashi, Ohno, Sasaki, & Matsuura, 2013; Lynch et al., 2013; Rainville & Rana, 2014). In addition, a more recent discovery is the *PALB2* gene*,* partner and localizer of *BRCA2*. *PALB2* is considered a 'moderate risk' susceptibility gene; if a deleterious mutation is identified the susceptibility to breast and pancreatic cancer increases (Hofstatter et al., 2011; Rainville & Rana, 2014; Tischkowitz et al., 2009). Some of the cancer susceptibility genes that can, when mutated, increase an individual's risk for either breast and/or ovarian cancer may in fact be associated with other cancer syndromes and not HBOC syndrome. For example, deleterious changes in the mismatch repair genes associated with Lynch Syndrome are known to increase the risk for the development of ovarian cancer. Despite all these advances there is undoubtedly still more to uncover and learn about gene changes that can increase an individual's risk to certain types of cancer.

Previously, if no mutations were identified in *BRCA1* and *BRCA2*, it was deemed appropriate in specific high-risk patients to carry out serial testing to investigate other susceptibility genes. This manner of serial genetic testing can be both time consuming and expensive (Domchek et al., 2013). Some may argue that multiplex genetic testing is

even less economical. A study conducted by Yorczyk et al. (2014) averaged the dollar cost of multiplex genetic testing per person from nine different laboratories and found that offering multiplex genetic testing as a first tier approach was 21% more expensive than conducting serial genetic testing. The panel test offered to patients as a first tier option was the Myriad *MyRisk* panel that included 25 different genes. Despite this increase in cost, authors of the study argued that multiplex genetic testing is cost effective due to the higher detection rate and the elimination of multiple follow up clinic visits should serial genetic testing be conducted.

In contrast to how clinical genetic testing has occurred in the past, the improvement of sequencing techniques and the advent of next-generation sequencing (NGS) technology has allowed for the simultaneous analysis of multiple genes (Domchek et al., 2013; Fecteau, Vogel, Hanson, & Morrill-Cornelius, 2014; Mauer et al., 2014; Walsh et al., 2010; Wolfe Schneider et al., 2014). Genes included on panels are laboratory specific, but it appears there is a general concurrence about which genes should be included (Hiraki, Rinella, Schnabel, Oratz, & Ostrer, 2014; Mauer et al., 2014). NGS is currently the sequencing method of choice for analyzing multiple genes at the same time. It appears that this strategy of testing multiple genes at once is becoming the preference for many health professionals (Hiraki et al., 2014; LaDuca et al., 2014). Importantly, the cost of multiplex genetic testing is not vastly greater than single gene analysis (Domchek et al., 2013; Hilbers et al., 2013; Hiraki et al., 2014). Additionally, multiplex genetic testing allows for testing in a timely manner (LaDuca et al., 2014). High throughput NGS has allowed for much more time effective sequencing compared to single gene analysis using Sanger sequencing (LaDuca et al., 2014; Walsh et al., 2010).

Testing laboratories are now advertising a 2-4 week turn-around-time (TAT) for many of their panels.

Furthermore, the use of multiplex genetic testing has allowed for individuals to be tested for genes they may not have previously been tested for due to cost, patient fatigue or they were considered not consistent with their personal and/or family history (LaDuca et al., 2014; Meldrum, Doyle, & Tothill, 2011). As a result, many individuals have received a genetic diagnosis that may not have been detected through single gene analysis. Yorczyk et al. (2014) found that when offering a single tiered approach (beginning with a multiplex cancer panel) the mutation detection rate increased from 3.8% to 6.7% compared to offering a panel reflexively. In their study group of 105 individuals, four mutations would not have been identified if single gene analysis were conducted. This advanced ability has aided the implementation of a more widespread analysis and personalized testing approach (Hiraki et al., 2014; Walsh et al., 2010). The clinical implication of being able to rapidly test many genes at once is permeating most subspecialties of genetic counseling, including pediatrics, cardiology, prenatal and other areas (LaDuca et al., 2014). A specific example of NGS panels outside the cancer realm that are becoming widely used includes panels for issues related to intellectual disability (Mauer et al., 2014; Walsh et al., 2010).

The integration of NGS panels does, however, bring with it novel challenges such as the increased likelihood of finding an ambiguous result, referred to as a variant of uncertain significance or VUS (Domchek et al., 2013; Hilbers et al., 2013; Hiraki et al., 2014; Walsh et al., 2010; Wolfe Schneider et al., 2014). A VUS is a change in sequence for which the implication on gene function is uncertain. Therefore, risk assessment and

management options cannot be based on the test result but rather must default to personal and family history (Hilbers et al., 2013). For genetic counselors, old practices and guidelines are not sufficient to deal with the complexities of multiplex genetic testing and the results that come with them (LaDuca et al., 2014). Advances in technology have highlighted the need for the establishment of guidelines in clinical practice.

Molecular laboratories developing cancer gene panels and carrying out testing are continuously detecting unique, novel sequence variants (Richards et al., 2008). These variants are typically classified within a spectrum with the American College of Medical Genetics and Genomics (ACMG) defining different categories of sequence variation (Richards et al., 2008; Richards et al., 2015). ACMG along with the Association for Molecular Pathology and College of American Pathologists recently recommended the use of a 5-tier standard terminology system (Richards et al., 2015) These categories include the following: (1) benign; (2) likely benign; (3) uncertain significance; (4) likely pathogenic; and (5) pathogenic (Richards et al., 2015). Additionally, ACMG recommends that 'likely' be used only for variants for which there is over 90% certainty that the variant is either benign or deleterious (Richards et al., 2015). Over time, the chance of identifying a VUS significantly decreases, as larger data sets are available and the ability to review and interpret variants improves (LaDuca et al., 2014; Mauer et al., 2014). For example, Myriad reported that they have reduced the VUS rate in *BRCA1* and *BRCA2* from 12.8% to 2.1% over ten years during the testing of hundreds of thousands of samples from 2002 to 2013 (Eggington et al., 2013).

A primary reason that individuals undergo genetic testing is to be able to direct their own medical management (Vos et al., 2008). Deleterious mutations specifically

define patient risk and may be accompanied by guidelines for management and treatment, while VUS results may warrant risk assessment and management based more heavily on family history (Murray, Cerrato, Bennett, & Jarvik, 2011). The National Society for Genetic Counseling (NSGC) recommended that personal and family history and not genetic testing results be used in order to determine medical management and prophylactic options when an uncertain test result is received (Berliner, Fay, Cummings, Burnett, & Tillmanns, 2013). As it is recommended that only individuals who are considered 'high-risk' and have a strong family history suggestive of a cancer syndrome undergo multiplex genetic testing, it makes sense to base any medical decisions on that family history when genetic testing results do not provide a clear answer. Misinterpretation or misunderstanding of a VUS result or VUS reclassification by the physician or patient may lead to sub-optimal management of that individual. Additionally, the National Comprehensive Cancer Network (NCCN) does not recommend testing of other family members when a VUS is identified. Reclassification of a VUS is therefore also critical information for other family members (Murray et al., 2011).

Richter et al. (2013) studied both the recall of VUS results and their interpretations. Recall is defined as bringing a fact back into one's mind while interpretation is related to explaining the meaning of information one has been told. In a study conducted by Richter et al. (2013), 20% of participants were unable to correctly recall a VUS result. Recall of results was incorrect more often in individuals with a VUS than in individuals who had a positive or negative result. The situation was similar when patients were asked to recall the risk associated with the VUS result. Patients categorized

as having a VUS had the highest rate of incorrect risk recall and/or incorrect interpretation of their VUS result. However, uptake of surgeries and surveillance was similar to the 'negative' group of patients and worry associated with the risk of cancer was similar to those who had a negative result. Vos et al. (2008) focused primarily on how the counselee recalls and interprets a test result of uncertain significance. The majority, 67%, was able to recall the VUS as not informative, 29% recalled it as a pathogenic result, and 4% recalled a non-pathogenic result. However, with regard to interpretation, 79% of participants interpreted a VUS as a predisposition to cancer while 21% interpreted it as non-informative. An additional study supported this outcome by showing that the largest difference between recollecting what counselees were told by their genetic counselor and how they interpreted the information was found in the group who had a VUS communicated to them (Vos et al., 2011). Therefore, patients are at risk of recalling a VUS result incorrectly in addition to misinterpreting the meaning of the VUS result.

In an ever-evolving genetics world, patients are expecting to hear and discuss genetic aspects of their disease with their primary care physicians (PCPs) (Houwink et al., 2011; Miller et al., 2010) have shown that patients not only show genetic test results to their PCP's, but they seek out their advice about what to do with such results. If the healthcare profession wants to maximize the benefit of the advances being made, important members of the healthcare team need to be educated properly. As part of their study Richter et al. surveyed a small cohort of family physicians (n = 21) regarding VUS test results (2013). All physicians participating in the study would send a sibling of an individual with a VUS for predictive genetic testing. In addition, half of the participating

family physicians who referred patients for genetic testing never mentioned the possibility of a VUS result. A multitude of studies have also looked at PCPs' understanding of genetic risk, genetic testing, and appropriate referrals. Research has suggested that in order for family physicians and PCPs to remain up to date with the quick advances occurring in the genetic field, there is a need for improved strategies to educate these important healthcare providers. Inevitably, this education will need to include education about VUS results as well as reclassification.

It is feasible to see how genetic counselors can play a role in aiding the understanding of the PCPs regarding VUS results and ensure that patients referred are receiving appropriate care and information. However, a bigger healthcare wide educational program or educational tools may be required. It is imperative that a referring physician can explain a VUS result correctly to his or her patient. In addition to educating PCPs about test results, education about the vital importance of reclassification and what it could mean for their patients is also critical.

Reclassification of VUS results may have important implications for a patient's cancer risk assessment in addition to their management options (Murray et al., 2011). VUS reclassification is a convoluted and complicated process (Domchek & Weber, 2008; Eggington et al., 2013). Reclassification includes constant monitoring of data in the lab, literature review, multidisciplinary discussion, as well as searching of public databases to continually survey for potential new variants (Eggington et al., 2013). Today, numerous different databases and registries exist that are attempting to delineate the association between rare, uncommon sequence variants and phenotypes. The goal of these databases and registries is to enable clinicians and medical professionals to assess cancer risk and

significance of VUS's found through multiplex cancer testing. An exemplary example of one such database is the Evidence – based Network for the Interpretation of Germline Mutant Alleles (ENIGMA). ENIGMA is a large consortium consisting of a multidisciplinary, international team (Spurdle et al., 2012). In January 2012, over 100 research scientists and clinicians were involved in the ENIGMA effort. Beginning in 2009, ENIGMA aimed to start interpreting variants found in *BRCA1* and *BRCA2* with the hope of utilizing what has been learned to expand their efforts to other cancer susceptibility genes, most likely beginning with *PALB2* and *ATM*. Researchers clearly understood that the variants being uncovered via genetic testing were individually rare and uncommon. Thus, building ENIGMA as an international effort would help allow for statistically significant data collection. As stated by the consortium, they want to 'pool resources, exchange methods and data and coordinately develop and apply algorithms for the classification of BRCA1 and BRCA2' (Spurdle et al., 2012). In addition, results are communicated to the Breast Cancer Information Core (BIC).

A separate, more recent endeavor with regards to the classification of variants is the Prospective Registry of Multi-Plex Testing (PROMPT). PROMPT is a registry that aims to gather data required to comprehend the risks that are associated with VUS results following multiplex gene testing ("PROMPT to Detail Breast Cancer Risk," 2014). Four significant cancer institutes including the Dana-Farber Cancer Institute, Mayo Clinic, Memorial Sloan Kettering Cancer Centre, and Abramson Cancer Centre of The University of Pennsylvania have partnered with Ambry Genetics, GeneDx, Myriad Genetics, Pathway Genomics, and Quest Diagnostics launch this online registry. The patient is made aware of PROMPT via the genetic testing laboratories and it is the

patient's own decision whether she/he wishes to share information or not via an online website. It has been stated that the study findings will be made public. The efforts of PROMPT will begin with breast cancer but eventually will transcend to other cancer syndromes. Finally, new information obtained via PROMPT will be provided directly to patients.

Additional registries such as ClinVar also exist. ClinVar is a free and publically accessible database whose aim is to define the relationship between genotype and phenotype (Landrum et al., 2014). Family studies that are routinely offered to individuals presenting with a variant are a separate but also important manner in which variants can become reclassified. Together, the aim of all these endeavors is to enable variant cancer genetic testing results to have significance and meaning in the clinical setting.

In addition to the complex process of reclassification, there remains a significant question regarding who is ultimately responsible for notifying the patient if reclassification occurs. In previous years, ACMG has released statements that help to define the process of informing patients of reclassification. Specifically, they recommended that the laboratory re-contact primary care physicians when updated information regarding VUS reclassification occurs (Richards et al., 2008). This responsibility of the laboratory may be particularly important as sequence variations identified may be rare in the population, and it may only be single laboratories who have knowledge of them (Richards et al., 2008). Myriad Genetic Laboratories, who have reclassified *BRCA1* and *BRCA2* variants over the years, stated that 'Amended reports are sent weekly to healthcare providers who have patients for whom a VUS reclassification affects their report' (Eggington et al., 2013). However, this protocol may be challenged,

as the increasing number of tests being ordered will lead to more VUS results and an increasing workload. (Eggington et al., 2013).

The need to set forth clear guidelines and a working plan of who is responsible for re-contacting the patient and primary care physician is necessary. In addition to the laboratory, the clinic ordering testing may benefit from implementing a system whereby they can re-contact a patient if their VUS becomes reclassified (Murray et al., 2011). Thus, the role of the cancer genetic counselor in communicating the possibility of VUS results and their clinical implications becomes a critical responsibility. For genetic counselors, a primary role is to ensure that the patient is given full and thorough informed consent prior to genetic testing.

Several researchers argue that a patient must also bear some responsibility for future re-contact. Murray et al. (2011) cite several examples of practices that are currently in place to address this need. For example, the patient must inform the genetic counselor and clinic of a change of address. Others propose the patient re-contact the clinic every one to three years for an update on whether their particular VUS has been reclassified, while others may send a letter to the patient informing them that updated information is available and inviting them to contact the clinic for more information. Challenges can arise, as it can take many years for a VUS reclassification to occur. For example, questions around who should be informed of a VUS reclassification if the patient has passed away may be a difficulty that can be an issue. (Fecteau et al., 2014; Murray et al., 2011) Some researchers maintain that it may be advisable to discuss this in the session with the patient as the reclassification information could be of importance to family members in years to come (Murray et al., 2011).

Research regarding genetic counseling and VUS reclassification is lacking. Addressing some of the issues with multiplex genetic testing, such as reclassification, now before the gap widens even more with the growing use of these panels is crucial (Hiraki et al., 2014). A survey of 24 Canadian genetic counselors confirmed that all would like to see guidelines relating to reclassification and further work required of the genetic counselor (Richter et al., 2013). Also, as Mauer et al. (2011) stated, "Providers need to be prepared for an increase in case management time and the associated long-term follow-up of these VUSs in regards to reclassification" (p. 411).

As of yet, no practice guidelines have been published to which genetic counselors should adhere when dealing with multiplex genetic testing and VUS reclassification. This study is intended to uncover current 'best practices' and identify areas for which genetic counselors feel they need direction is of major benefit to this revolutionary field. It therefore brings value to not only genetic counselors but also to their patients. It is important to note that this study may have wider reaching implications, as the issue of VUS reclassification is not unique or limited to cancer genetics only (Plon et al., 2008).

Chapter 2: Manuscript

Variant Reclassification in Cancer Genetic Testing: Are Genetic Counselors Prepared?

A Review of Current Practices [1]

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2.1 Abstract

Purpose: Cancer genetics has emerged as a critical specialty within the field of genetic counseling. Advancements in research are constantly uncovering new insights into the genetics of cancer and inherited cancer syndromes. It is crucial that genetic counselors and the institutions in which they work are in sync with these advancements. Currently, multiplex or multi-gene cancer testing is rapidly being adapted into the cancer genetic counseling setting. The 'hot topic' of an increased likelihood of receiving variant results following such testing has been explored in depth in the literature. However, research surrounding genetic counseling practices and the reclassification of VUS results is lacking. No consensus guidelines addressing variant reclassification yet exist. This study aimed to identify current practices of genetic counselors with regard to variant reclassification, and to explore whether genetic counselors feel they need official guidelines relating to the reclassification of variant results.

Method: An online survey distributed through the National Society of Genetic Counselors and the Cancer Special Interest Group (SIG) was utilized in this research study. Statistical Analysis System (SAS) 9.4 was employed for quantitative data and statistical analysis while qualitative data was coded and analyzed for major themes using grounded theory methods.

Results: We determined that cancer genetic counselors are handling the reclassification of VUS results in a unified manner. Common themes across almost 200 respondents demonstrated that they approach benign or deleterious reclassification in a similar fashion. 95% of respondents (n = 209) discuss variant reclassification with their patients upon receiving a VUS result. Similarly, 95% of respondents (n = 209) will sometimes or always make a plan to communicate VUS reclassification results should they arise in the

future. The overwhelming majority (97%) of respondents (n = 183) indicated that the protocol for re-contacting patients with a VUS reclassification would not be different from what they had used in the past for single-gene analysis. Varying opinions existed on whether practice guidelines relating to VUS reclassification are necessary. The majority, 62% of respondents (n = 178), agreed or strongly agreed that there was a need for guidelines relating to variant reclassification. Those who disagreed expressed concerns surrounding liability issues and the feasibility of implementing recommendations across different institutions.

Conclusions: Findings from this study indicate that most genetic counselors are utilizing unified practices when handling the reclassification of variant results. Additionally, a proportion of genetic counselors felt that guidance or recommendations for certain areas relating to variant reclassification are necessary. While future research is needed to explore more in-depth the issues and opinions identified in this research project, another possible approach is for the NSGC Cancer SIG to address this topic at their earliest opportunity, given the coming wave of VUS reclassifications from multiple collaborative efforts to more urgently reclassify VUS results.

Keywords: Cancer genetics, genetic testing, multi-gene panels, multiplex genetic testing, variant(s), VUS, reclassification

2.2 Introduction

Cancer genetics is an ever-evolving specialty within the field of genetic counseling. The advent of next-generation sequencing technologies has allowed for the expansion of genetic testing options for those individuals considered to be 'high-risk' due to personal or family history. As a profession, genetic counselors must develop and grow alongside

these improvements to ensure they are capable of providing the best possible care to their patients.

Conventionally, sequential single gene analysis has been the manner in which genetic testing has been conducted in the cancer setting (Domchek et al., 2013; Mauer et al., 2014). Genes that were most likely to carry a mutation based on the personal and family history were first analyzed. However, advances in sequencing technologies now enable the simultaneous analysis of many genes associated with cancer risk (Domchek et al., 2013; Fecteau et al., 2014; Mauer et al., 2014; Walsh et al., 2010; Wolfe Schneider et al., 2014). Multiplex genetic testing using next-generation sequencing (NGS) is becoming increasingly popular and it appears to be the preference for many healthcare professionals (Hiraki et al., 2014; LaDuca et al., 2014). However, analyzing multiple genes concurrently brings with it unique and novel challenges. The likelihood that a variant of uncertain significance (VUS) will be identified is increased (Domchek et al., 2013; Hilbers et al., 2013; Wolfe Schneider et al., 2014). A VUS is a change in sequence for which the implication on gene function is unknown.

The American College of Medical Genetics and Genomics (ACMG) recently defined five different categories of sequence variation (1) benign; (2) likely benign; (3) uncertain significance; (4) likely pathogenic; and (5) pathogenic (Richards et al., 2015). With the accumulation of larger data sets the VUS rate associated with multiplex genetic testing will decrease and in turn VUS reclassification will increase (LaDuca et al., 2014; Mauer et al., 2014). The reclassification of VUS results conceivably could have significant implications for a patient; the reclassification could alter the patient's own cancer risk assessment as well as their management options (Murray et al., 2011).

Reclassification may also provide family members with the ability to obtain meaningful genetic test results, as NCCN guidelines do not recommend testing of relatives when a VUS is identified (Murray et al., 2011).

As VUS reclassification becomes increasingly common, new practice guidelines will perhaps be needed, to specifically address who is responsible for notifying the patient (LaDuca et al., 2014).Previously, ACMG has recommended that laboratories re-contact primary care physicians when updated information regarding VUS reclassification occurs (Richards et al., 2008). Myriad Genetic Laboratories, state that 'Amended reports are sent weekly to healthcare providers who have patients for whom a variant reclassification affects their report' (Eggington et al., 2013). In fact, we note that these reclassification reports from this company are being sent directly to genetic counselors (and presumably other ordering providers) rather than to patients or physicians not listed as ordering providers (Personal communication, P. Walker, April, 2015). As reclassification efforts increase and the workload grows, current practices may be difficult to maintain (Eggington et al., 2013).

Research into genetic counseling and VUS reclassification is lacking. Addressing some of the issues associated with multiplex cancer genetic testing is crucial, as variant reclassification will continue to occur, presumably at an increasing rate (Hiraki et al., 2014). Studies indicate providers are interested in guidelines to help guide practice, but no such guidelines exist for genetic counselors (Richter et al., 2013). This particular study looks to identify specific areas within VUS reclassification in which genetic counselors need direction, as well as to uncover 'best practices' for the handling of VUS

reclassifications. Results may have wide reaching implications, as the issue of VUS reclassification is not unique or limited to cancer genetics only (Plon et al., 2008).

2.3 Materials and Methods

2.3.1 Participants.

Genetic counselors that are currently offering multiplex cancer genetic testing to their patients on an ongoing basis were eligible to participate in this study. We anticipated minimal risk for those counselors who participated, as they were responding to questions regarding ongoing practices in their working environment. The following inclusion criteria applied to the research conducted:

- Genetic counselors working in the cancer field and offering multiplex genetic testing
- Cancer genetic counselors practicing in the United States
- Cancer genetic counselors practicing in Canada who may be members of the NSGC

While the following exclusion criteria applied:

- Genetic counselors not currently practicing as a cancer genetic counselor
- Cancer genetic counselors not offering multiplex genetic testing

2.3.2 Invitation to Participate.

Participants were invited to complete the study through the distribution of an online questionnaire through the National Society of Genetic Counselors (NSGC) Cancer Special Interest Group, as well as via an email blast to all NSGC members. Included in the notification was an invitation letter to participate in an online questionnaire regarding VUS reclassification. Originally flyers were distributed at the 2014 NSGC conference but

no participants were obtained via this method of recruitment. The participants remained completely anonymous; no identifying information was gathered unless they consented to take part in a telephone interview. It is important to note that due to difficulty in re-contacting participants no phone interviews were conducted. In addition, as a result of time constraints a pilot study was not carried out prior to this research study going live.

2.3.3 Data Collection.

The primary method of data collection for this research project was via an online questionnaire. The questionnaire was posted on www.surveymonkey.com and could be accessed by going to www.surveymonkey.com/s/VUSreclassificaiton. The online questionnaire consisted of a series of statements and questions for the participant to consider and answer with the final section collecting demographic information. In addition to the online survey it was originally proposed that volunteers from the participants would be interviewed via telephone in order to allow them to share their thoughts and opinions regarding VUS reclassification. Unfortunately, this qualitative aspect of the research project was not completed due to a difficulty in re-contacting those participants who had indicated that would be willing to be interviewed. The limitations of not conducting thorough qualitative analysis in addition to analyzing the quantitative results has been recognized and acknowledged. This research study was reviewed and approved by the Institutional Review Board, Office of Research Compliance, of the University of South Carolina, Columbia, SC, on August, 2014.

2.3.4 Data Analysis & Statistical Analysis.

Descriptive statistical analysis using Microsoft Office Excel software was used to address the research goal. The majority of survey items resulted in categorical information and

therefore percentages and frequencies could be calculated. For quantitative analysis, Statistical Analysis System (SAS) 9.4 was used after data was transferred from Excel spreadsheets. Inferential statistical techniques were used to make comparisons and explore associations between variables from the survey. To assess associations between two categorical variables, the chi-square test for independence was implemented as well as Fisher's Exact Test. Grounded theory methods were employed to code free-response questions and identify emergent themes.

2.4 Results

2.4.1 Demographic Information.

An invitation to participate in the online survey was sent in an email blast to the entire NSGC membership list, resulting in 216 responses from cancer genetic counselors. Of those who responded a total of 176 participants provided demographic information as seen in Table 2.1.

In addition to the demographics represented in Table 2.1, information regarding multiplex genetic testing was obtained. Of 215 respondents, 66% order multiplex panels at least 50% of the time. Monte Carlo Estimation for Fisher's Exact Test found that there was neither a statistically significant association between ordering multiplex genetic tests and the participant's age, (99% lower conf limit = .7737, 99% upper conf limit = .949, p = .7843) nor a statistically significant association between ordering multiplex genetic tests and years of work experience, (99% lower conf limit = .0967, 99% upper conf limit = .1125, p = .1046). Respondents (n = 176) reported that TAT (48%) and limited clinical utility (46%) are the two main reasons as to why they do not order multiplex genetic tests in certain situations. Almost half (43%) of respondents selected 'other' which included

reasons such as patient preference, known familial mutation, and specific clinical diagnosis. A clear majority (69%) of respondents (n = 215) are not deterred by the variant rate when ordering multiplex genetic testing and 70% of respondents (n = 216) indicated that variant rate was not a factor that played into their decision making process. Figure 2.1 illustrates what factors are important and not important to genetic counselors when deciding whether single gene or multiplex genetic testing is the best course of action. Family history and patient preference are the two most important factors.

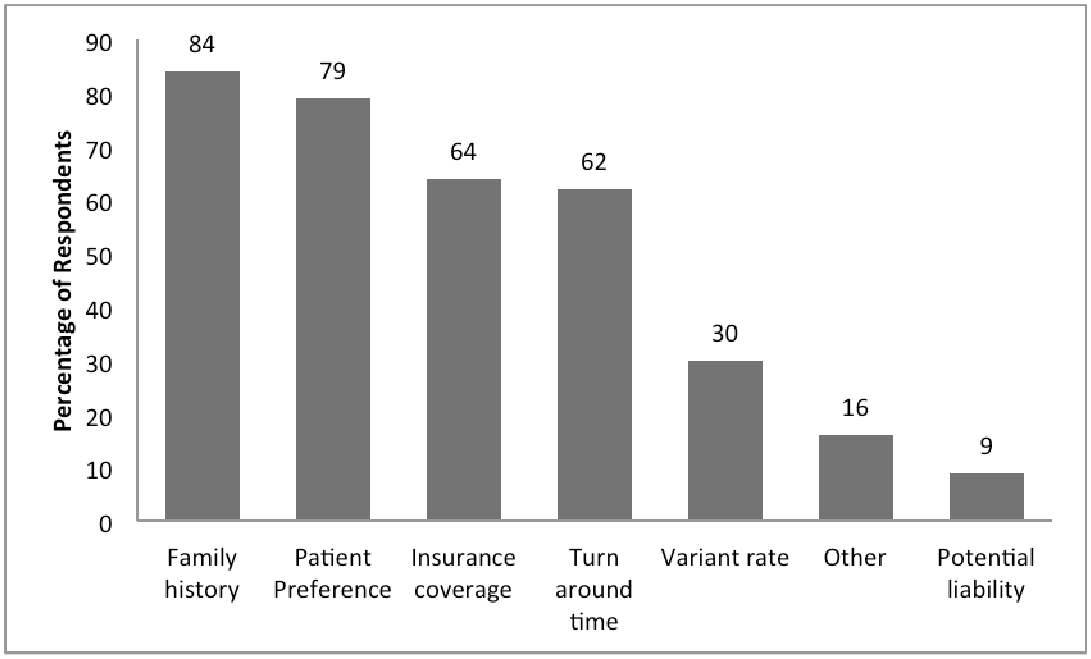

Figure 2.1 Contributing factors in respondents' decision to order single gene tests or multiplex genetic tests.

Table 2.1 Participant Demographics (*n* = 176)

	n	%
Age		
20-30	93	53%
31-40	38	22%
41-50	19	11%
51-60	19	11%
61-70	7	4%
Gender		
Female	172	98%
Male	4	2%
Years experience in the cancer field		
Less than 5 years	109	62%
5-10 years	30	17%
10 - 15 years	14	8%
15 – 20 years	11	6%
Greater than 20 years	12	7%
Setting in which they practice		
Academic Institution/University Hospital	61	35%
Public/Community Hospital	51	29%
Private Hospital	31	18%
Private Oncology Group	16	9%
Genetics Centre	3	2%
Laboratory	1	1%
Other (Unspecified hospital, HMO, federal group)	12	7%
Number of panel tests ordered per week		
Less than 5	83	47%
5-10	16	9%
10 - 15	74	42%
15 - 20	3	2%

2.4.2 'Best practices' or commonalities employed by genetic counselors when dealing with VUS reclassification.

Almost all (95%) of respondents (n = 183) reported that they felt genetic counselors should always be made aware of changes in reclassification. Additionally, of 207 respondents, 89% either agree or strongly agree that patients should be made aware of VUS reclassification regardless of what the reclassification is. Over half (59%) of respondents (n = 183) reported that there is not a set protocol in their workplace for re-contacting patients when a VUS reclassification report is received. A majority (67%) of respondents (n = 183) would contact the patient via telephone when a benign reclassification is received (Figure 2.2). Upon receiving a deleterious reclassification, 51% of respondents (n = 183) would notify the patient via telephone while 24% would have an in-person appointment, and 19% of respondents selected 'other' (Figure 2.3). Almost all of those who selected other reported that they would telephone the deleterious reclassification information and follow that with an in-person appointment. Of those who would not re-contact the patient for a benign reclassification (n = 7), two indicated that they would not re-contact the patient for a deleterious reclassification. At the alpha = 0.5 level of significance, there is a significant association between the reported action of genetic counselors for benign reclassification reports and deleterious reclassification reports (Monte Carlo Estimate for Fisher Exact Test, 99% Lower Conf Limit = <.0001, 99%; Upper Conf Limit = .0005; p = < .0001).

A free response question looked to determine under what circumstances respondents would consider non-disclosure of VUS reclassification results. The majority of respondents could not think of any situation in which they would feel comfortable not

disclosing VUS reclassification information. Many respondents stressed that such information was information the patient was entitled to know.

> *"I don't think there are any circumstances when a clinician should withhold information about a person's result. Even if a likely benign variant is reclassified to a polymorphism, I want to let the patient know, even if only for their peace of mind. Plus, it is their result and they have a right to know what we are calling it"*

> *"None. They deserve "results", whatever they are. I've never thought of "in case of death" but will now ask my patient every time."*

A number of respondents did express that if the reclassification resulted in a downgrade or did not change clinical utility nor medical management they would feel more comfortable with non-disclosure. Other themes identified were related to patient preference to not receive the information and barriers in re-contacting the patient.

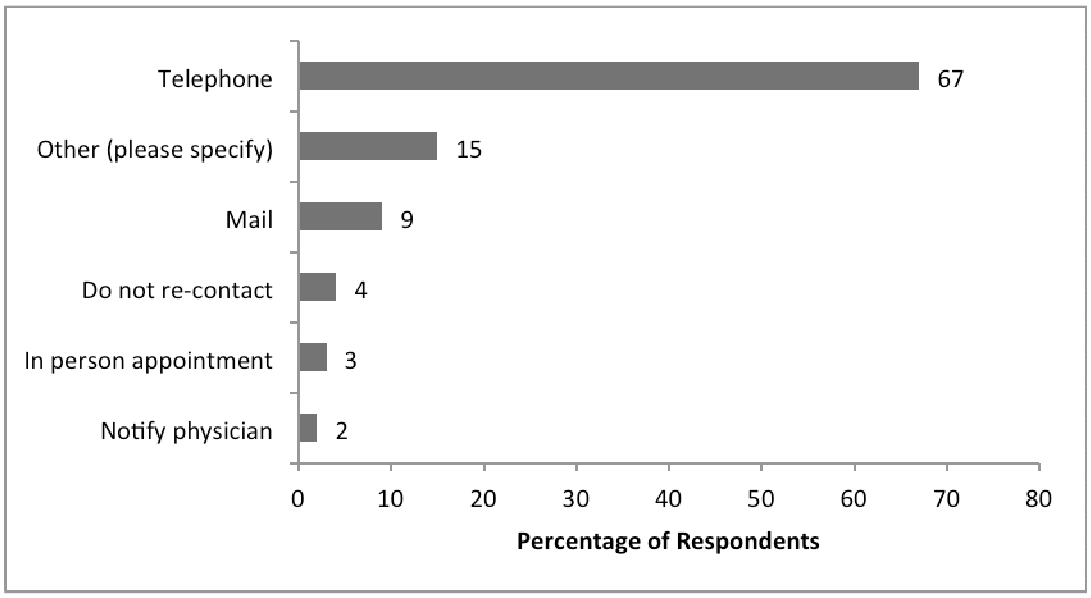

Figure 2.2 Primary means of discussing benign reclassification with the patient.

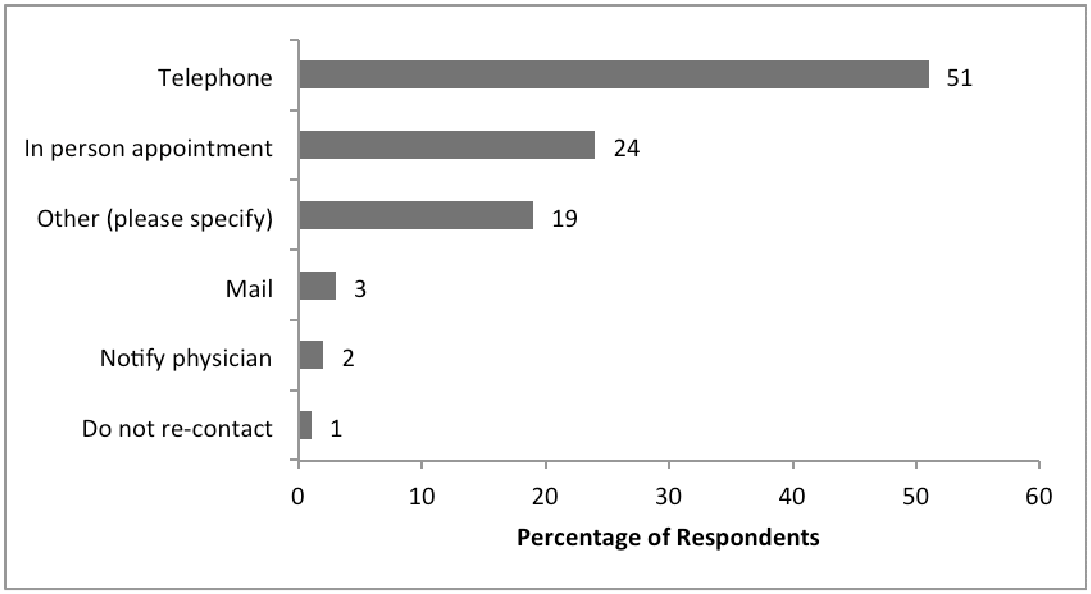

Figure 2.3 Primary means of discussing deleterious reclassification with the patient.

2.4.3 Dealing with issues surrounding VUS reclassification in a session.

Participants were asked a number of questions surrounding how they deal with VUS results and VUS reclassification in the genetic counseling session. These questions have been shown to be reliable with similar responses for similar groups (Cronbach's $\alpha = .70$). Nearly all, (99%) of respondents ($n = 210$) said that they sometimes or always discuss the possibility of VUS results prior to consenting the patient for single gene analysis. All respondents ($n = 210$) sometimes or always discussed the possibility of VUS results prior to consenting their patients for multiplex genetic testing.

Eleven respondents indicated that they do not discuss VUS reclassification before consenting patients for multiplex genetic testing. Of the subset of people who do not discuss VUS reclassification prior to ordering multiplex genetic testing seven respondents indicated that they would always discuss the reclassification of variants should a VUS result be received. Three respondents indicated they would sometimes discuss variant reclassification when a VUS result is received while one respondent indicated that she/he would never discuss reclassification. Of the 209 respondents who reported they would sometimes or always discuss variant reclassification when a VUS result is received 95% will sometimes or always make a plan to communicate the reclassification information. Within this plan 53% sometimes or always discuss who is to receive the reclassification information in the event of the patient's death.

The large majority (97%) of respondents ($n = 183$) indicated that the protocol for re-contacting patients would not be different from what they had used in the past for single-gene analysis. Participants were asked whether they felt that methods at their

institution were working sufficiently for the handling of VUS reclassifications. For those who answered 'yes', certain themes emerged. Firstly, a high proportion of respondents felt that there are not any issues at this time as the number of VUS reclassification reports is manageable. However, multiple participants also stated that with a bigger workload and more VUS reclassifications the protocol in place might not stand.

> *"They are working sufficiently now, but we do not have a large patient population so it has not been as thoroughly tested to find any weaknesses."*

> *"We have not had a large number of VUS reclassified so this has not become a volume issue"*

Additionally, a set of respondents explained how the methods employed at their institution are currently satisfactory, whether the methods are secure emails, letters, in person appointments or yearly scheduled follow-ups for patients with a VUS result. Genetic counselors who were setting their own protocol with regard to the handling of VUS reclassifications expressed their satisfaction at being able to alter it as needed. Of the respondents who indicated that methods at their institution were not working sufficiently the majority stated that they did not have a set protocol in place or had a limited number of VUS reclassification experiences. Commonly, the participants declared that they are learning as they go, figuring out how to deal with VUS reclassification reports as they gain more exposure to them. Barrier in re-contacting patients was another theme identified as having a role in why participants felt that current methods at their institution were not working.

"This year we started a variant follow up program which we enter all VUS results into we follow up with the patients every 6 months and update the lab with changed and vice versa"

"Many variants are reclassified 10 + years after the patient had testing and it can be difficult to get in contact with the patient if they have not provided updated contact information through the years"

When asked to describe the ideal situation with regard to genetic counseling and the management of VUS reclassification reports different key themes were identified as follows:

- Some respondents felt their current protocols worked adequately.
- Other respondents expressed that the availability of a central database to notify genetic counselors of reclassifications would be beneficial in reducing the burden on them.

"Database that constantly searches for reclassifications based on input from labs across the country and then will alert when a variant is reclassified."

- A number wanted all laboratories to always send VUS reclassification reports regardless of whether the VUS was upgraded or downgraded.

"Genetic counselors shouldn't have to waste their time looking into a VUS every year, etc. They should be able to trust that the lab will notify them if there is an update in the VUS status."

- A proportion of respondents felt the responsibility for re-contact should ideally fall on the patient.

"Patients MUST bear the responsibility to re-contact us--we try to find them if something needs to be conveyed, but people move/change phone numbers/change names so often that it is simply not possible to track everyone down. Sometimes I have trouble getting ahold of a patient we tested a few weeks ago to give the initial results; finding them months or years or decades after the fact is infinitely more challenging."

2.4.4 The needs and wants of genetic counselors with regard to practice guidelines.

Over half (62%) of respondents (n = 178) agreed or strongly agreed that there was a need for practice guidelines regarding VUS reclassifications. A proportion (30%) neither agreed nor disagreed while 8% disagreed and do not think that practice guidelines are necessary. Monte Carlo estimate for Fisher's Exact Test showed no significant association between whether the respondents felt that practice guidelines are necessary and their workplace (99% Lower Conf Limit = .1103; 99% Upper Conf Limit = .1269; $p < .1186$). There was a significant difference in belief about whether practice guidelines should be developed between people who order multiplex genetic tests less than 50% of the time and those who order multiplex genetic testing greater than 50% of the time (row mean scores differ $p < .0111$). The Cochran-Mantel-Haenszel Statistic used to calculate the row mean scores differ value is able to ignore the fact that twice as many people chose 'order more than 50% multiplex genetic testing'. Thus, those respondents who order multiplex genetic testing less than 50% of the time agree more strongly that practice guidelines are necessary. Respondents indicated that the most important issues to

be addressed in practice guidelines were "who is responsible for re-contact of the patient following a variant reclassification" and "the laboratories involvement and responsibilities". When asked who should be responsible for monitoring the status of a VUS and who should be responsible for re-contacting the patient should a VUS become reclassified, 77% of respondents (n = 183) indicated that laboratory personnel should be responsible for the monitoring of VUS's while 77% of respondents (n = 183) also indicated that genetic counselors should be responsible for re-contact of the patient if a VUS becomes reclassified. Chi-square analysis determined that there was a significant association between these two questions ($p < .0001$).

A number of free response questions aimed to gain a more in depth understanding of respondent's thoughts and opinions regarding VUS reclassification and practice guidelines. Many respondents felt that the issue regarding re-contacting of the patient and the barriers associated should be addressed within guidelines. The importance of clarifying to what extent genetic counselors must attempt to re-contact patients and what steps to take when they cannot re-contact the patient was evident in respondents answers.

> *"What the GC's responsibility is in the event the patient cannot be re-contacted - what is our due diligence?"*

> *"The most important item is who is responsible. We had a situation where a physician ordered a test and the patient had a VUS (GC was not involved). Then the GC saw a new ovarian patient, and it was found that she was the sister of the patient with a VUS. The GC discovered that the VUS had been reclassified as deleterious, but the original patient with the VUS had*

switched physicians and this info fell through the cracks. When this was discussed with both physicians, they blamed each other and neither would take responsibility."

An additional theme identified was a need for clarification of the role of laboratories in VUS reclassification. Many respondents expressed that although laboratories should be responsible for monitoring the status of a VUS, not all laboratories report out all reclassification results.

"Needs to be a guideline for all laboratories, since different labs have different protocols and this can be confusing for counselor and patients."

"The front end of the process is most important and needs to be standardized. Each lab must have a reliable process for reclassification and communication to the clinician who originally ordered the test (physician or GC). Once this information is sent to the clinician, how it's handled from there should be fairly straightforward and can vary by clinic."

Finally, some respondents indicated in their free responses that no practice guidelines are necessary. These genetic counselors either reasoned that such guidelines would set genetic counselors up for liability issues or could not be implemented due to many institutions and workplaces functioning uniquely.

"*There should not be a practice guideline for this. It would be a law suit waiting to happen*."

"I think this type of guideline has the potential to set GCs up for great liability ..... I strongly encourage people to think about legal liabilities this could create before setting a precedent and creating a guideline"

2.5 Discussion

The goal of this research study was to gain an understanding of the practices and methods currently being employed by cancer genetic counselors in their handling of the reclassification of VUS results. Additionally, we wanted to explore and assess both the needs and wants of genetic counselors with regard to the management of VUS reclassifications in the genetic counseling setting. As over half of respondents order multiplex genetic testing at least 50% of the time in their clinical practice it was felt that this was an appropriate population to survey regarding panel testing and issues that may arise in the cancer setting. Additionally, the genetic counselors surveyed are clearly not frightened by or scared of possible VUS results and variants do not seem to play an important factor in the decision to order multiplex testing over single gene testing.

Our first aim was to understand whether genetic counselors are employing similar practices across the board for the management of VUS reclassifications, despite a lack of guidelines. Unexpectedly, we determined that genetic counselors do appear to be applying standard procedures when it comes to VUS reclassifications. Common practices are being utilized. The majority of genetic counselors surveyed would telephone a patient with a benign reclassification while more genetic counselors felt an in-person appointment was appropriate for a deleterious reclassification. Similar observations were made in a recent study that looked at genetic counseling practices for VUS and VUS

reclassifications that arise due to *BRCA* testing. In their study population of 410 genetic counselors, the majority call the patient and mail benign VUS reclassifications while for deleterious reclassifications the majority also met the person face to face (Scherr, Lindor, Malo, Couch, & Vadaparampil, 2015).

Overall, it does appear that common practice is to inform patients of any reclassification, regardless of its status, as the large majority of respondents expressed how a reclassification result was information the patient was entitled to and had a right to know. Cancer genetic counselors appear to have a strong feeling that they are not gatekeepers of information and that test results, regardless of their meaning, are the patient's property.

Despite genetic counselors employing common practices, the majority of respondents indicated that their workplace did not have a set protocol for the handling of VUS reclassifications. A number of respondents expressed how they were formulating procedures to handle reclassifications as they go. Although this currently seems to be sufficient, with a larger workload likely over the course of time it must be considered that not having a set protocol could be detrimental. At present the workload is manageable but for many the methods they are employing have not yet been rigorously tested as to their limits and therefore may prove troublesome in the future. Several respondents expressed this same sentiment in open-ended responses. Therefore, genetic counselors must begin to think ahead to ensure that in the future their methods will continue to work sufficiently, otherwise, it could likely impact patient care.

Next, it was important for us to understand the manner in which genetic counselors handle VUS reclassifications during the genetic counseling session itself. Again, global similarities in practices were observed. In our population, it is standard of practice to discuss the possibility of VUS results prior to conducting genetic testing; all respondents stated they sometimes or always do this before both single gene and multiplex genetic testing. For the purpose of this study we were interested in whether the reclassification of VUS results was also included in this discussion as a standard of practice. VUS reclassification is something that genetic counselors appear to think about and see as an important factor to discuss prior to conducting testing. Only 11 of 210 respondents do not talk about reclassification of variants before conducting multiplex genetic testing. Three of these 11 respondents will only sometimes talk about reclassification when a VUS result is received, while one respondent will never talk about reclassification upon receiving a VUS result. This study did not specifically assess what genetic counselors include in their discussion about VUS reclassification but it was determined that 95% of those who talk about reclassification in the genetic counseling session make a plan to communicate reclassification information should it become available in the future. It has previously been discussed in the literature that due to the average time (typically in years) it takes for a VUS to become reclassified, a discussion surrounding who should receive reclassification information in the event of the patient's death should be broached by the genetic counselor (Murray et al., 2011). We did not expect the majority of genetic counselors to be doing this; however, approximately half indicated they were including this in their discussions with the patient.

Finally, we explored in-depth what areas genetic counselors feel they need guidance with or clarification of in terms of VUS reclassification. Furthermore, we wanted to investigate whether genetic counselors feel a need for specific practice guidelines relating to this topic. Interestingly, it appears that a majority of the genetic counselors surveyed feel that they are prepared for VUS reclassification if and when it arises, for many it may simply mean an extension of practice that they are already familiar with through single gene analysis. Most agreed or strongly agreed that practice guidelines regarding VUS reclassification are needed, while a proportion did not have an opinion either way. We further analysed the data to determine whether those ordering a larger proportion of multiplex genetic tests were either more for or against practice guidelines. The proportion of people who disagreed with the statement 'There is a need for practice guidelines regarding VUS reclassification and how the reclassification of VUS results should be handled by genetic counselors' was higher in those who ordered multiplex genetic tests more than 50% of the time in their clinical practice and vice versa, a higher proportion of those who order multiplex genetic tests less than 50% of the time more strongly agreed with the statement. Perhaps, genetic counselors with more experience and knowledge regarding multiplex genetic testing and the handling of related issues do not see VUS reclassifications as an area within cancer genetics that requires specific guidelines. Those with less experience who feel they need clear guidance may benefit from further education or management tips on how to handle VUS reclassifications rather than guidelines themselves. Some respondents disagreed and felt practice guidelines are unnecessary. Liability and the possibility of lawsuits was a

concern for some while others felt that guidelines could not be implemented across all institutions. Both of these topics are valid concerns that we had not previously identified.

An issue that has been discussed in other literature is the barrier that can arise in re-contacting a patient when a VUS is reclassified (Murray et al., 2011). In this study, this too was identified as an area of concern for genetic counselors. Precisely, respondents recognized that barriers in re-contacting patients may exist and questioned to what lengths must the genetic counselor go in order to contact the patient. A critical question we identified was when barriers in re-contacting arise, at what point is it no longer the responsibility of the genetic counselor to inform the patient of the reclassification information? An additional area identified as being of concern to respondents was the laboratories involvement and responsibilities. For respondents, this was identified as the second most important topic to be included in any guidelines relating to VUS reclassification. Genetic counselors felt strongly that the laboratories are responsible for the monitoring of variant states; however, many expressed unease due to laboratories each having different protocols. The unease and confusion seemed to lie with the fact that there are no standards for variant communication across the many laboratories performing clinical genetic analysis of cancer genes. It remains to be seen whether guidelines for the genetic counseling practice could influence or dictate laboratory standardization.

Study Limitations

There are several important study limitations to consider. First, a recognized limitation of this study is that many of the participants have not yet had to deal with a large number of

VUS reclassifications in their clinical practice. Importantly, a proportion of respondents have never received a VUS reclassification. Thus, it is possible that their responses to questions surrounding whether systems in place are working sufficiently or not will change in the future upon receiving more VUS reclassifications. Secondly, a potential limitation may be that the majority of participants had less than five years experience working in the cancer field. Finally, despite having a total of 216 participants, a number of questions, for reasons unknown were skipped by a significant number of respondents and henceforth were not as amenable to statistical analysis. This is particularly true for the demographics portion of the survey.

Directions for Future Research

Future research is needed to delve deeper into the observations made by this preliminary study and ensure genetic counselors are well prepared for the reclassification of VUS results. As this area is moving at such a breakneck pace, it is plausible to reason that should this survey be re-administered in six months time the answers and opinions of respondents may have changed. A reasonable 'next-step' would be to conduct in-depth qualitative analysis through interviewing cancer genetic counselors. Such research would allow for the thorough exploration of opinions and thoughts surrounding this topic that may not have been expressed nor explored through the online survey employed in this study. Specifically, we now know that genetic counselors discuss VUS reclassification with their patients so it would therefore be highly beneficial to determine the particular details about reclassification that are explained. Furthermore, it would be of interest to determine the details of the plan to communicate reclassification that is set up between the genetic counselor and their patient. Finally, we feel that it may be useful to gain an

understanding of how genetic counselors and the institutions in which they work keep track of their patients who have received VUS results in the past; this study did not assess this question. Advancing our knowledge in all these areas would help the genetic counseling profession reach a consensus in relation to the genetic counselors' role and responsibilities with regard to VUS reclassification results.

2.6 Conclusions

To our knowledge the genetic counseling community has not yet explored in depth the genetic counselors role and responsibilities with regard to VUS reclassification. Therefore, we believe this study to be of great value to our profession.

Unexpectedly, this research study revealed that cancer genetic counselors across the board are currently employing similar methods in their handling of VUS reclassification results. As a whole they feel that reclassification results are important information for the patient to be aware of and a topic that is essential in the discussion surrounding multiplex cancer genetic testing. Despite this, we feel that cancer genetic counselors may not be completely prepared for an increase in the number of reclassification results and workload expected in the future. Mauer et al. (2011) have previously highlighted a need for providers to be prepared for such an increase in workload. Many participants are learning as they go without any set protocol in place for when a reclassification result is received.

Additionally, we propose that this study highlights the need for guidelines or recommendations surrounding the role and responsibilities of the genetic counselor with regard to VUS reclassification. Similar to findings that Richter et al. (2013) identified, the

majority of our study participants feel that guidelines would be both beneficial and useful. However, we are now aware of some important concerns regarding the possible implications of guidelines that require further in depth analysis.

Additional research into VUS reclassification and the role and responsibilities of the genetic counselor is warranted. We propose that thorough qualitative analysis which fully explores cancer genetic counselors' opinions, reservations and suggestions relating to VUS reclassification be conducted. Given additional studies, perhaps a Working Committee of the NSGC Cancer Special Interest Group (Cancer SIG) could be convened to consider the totality of information and propose a draft guideline (if needs for a guideline are confirmed), requesting input and comments from practicing cancer genetic counselors prior to finalization. Subsequent studies that expand on the knowledge gained through this research would be hugely beneficial to the genetic counseling community, and in turn, beneficial to their patients.

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Appendix A: Invitation Letter to Potential Participants

Dear Potential Participant:

You are invited to take part in a graduate research study focusing on variant reclassification in cancer genetic counseling. I am a graduate student in the genetic counseling program at the University of South Carolina School of Medicine. My research looks at whether cancer genetic counselors are preparing themselves for the work that will come with an increase in the number of variants that become reclassified**.** The research involves taking a survey that can be found at **www.surveymonkey.com/s/VUSreclassification**.

The survey proposes a number of questions and asks your opinion on different matters relating to multi-gene panel testing and variant reclassification. If you do not wish to answer a certain question, please skip that question and continue with the rest of the survey.

All responses from the surveys will be kept anonymous and confidential. We only ask for your name and phone number in the event that you are interested in providing more information at a later date over the phone. It is not necessary that you provide this information. The results of this study might be published or presented at scientific meetings; however, your answers will not be identified in any way. The survey should take about 15-20 minutes to complete.

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

Thank you for your time and consideration for taking part in this study. Your answers may help genetic counselors gain much needed guidance and provide the best care for their patients with regard to cancer panel testing and variant reclassification. If you have any questions about this research, you may contact either me or my advisor, Brook White, MS, CGC, at the information below. If you have any questions about your rights as a research member, you may contact the Office of Research Compliance at the University of South Carolina at (803)777-7095.

Sincerely,

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Appendix B: Online Survey

1. What percent of genetic tests that you order are multi-gene tests?

   □ 0% □ 1-25% □ 25-50% □ 50-75% □ 75-100%

2. When you do not order multi-gene tests, why not (check all that apply)

   □ Institutional protocol

   □ High rate of variants

   □ Guidelines do not recommend

   □ Expense or Insurance

   □ Limited Clinical Utility

   □ Turn around time

   □ Other (Please explain)

3. Does the variant rate deter you from ordering next generation sequencing and/or panel tests?

   □ Yes □ No

   Please elaborate

4. What do you consider to be a high variant rate?

5. If you order both single gene and multi gene, panel testing, what factors contribute to the decision to order one over the other (check all that apply)

   □ Family history

   □ Potential Liability

   □ Insurance coverage

   □ Variant rate

   □ Turn around time

   □ Patient preference

   □ Other (Please explain)

6. You discuss the possibility of variants and uncertain tests results in a session prior to conducting single gene/single site sequence analysis

   □ Never □ Sometimes □ Always

7. You discuss the possibility of variants and uncertain test results in a session prior to conducting next generation sequencing and/or panel testing

   □ Never □ Sometimes □ Always

8. Variant reclassification is discussed in a session prior to conducting next generation sequencing and/or panel testing

   □ Never □ Sometimes □ Always

9. If a VUS is received, variant reclassification is discussed during result disclosure

   □ Never □ Sometimes □ Always

10. In this discussion a plan to communicate reclassification information is determined

    □ Never □ Sometimes □ Always

11. You discuss who is to receive the reclassification information in the event of the patients death

□ Never □ Sometimes □ Always

12. Variant reclassification is information that the patient should be made aware of **only if the variant has been reclassified as deleterious**

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

13. Variant reclassification is information that the patient should be made aware of **regardless of what the reclassification status is**

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

14. Under what other circumstances would you consider non-disclosure of variant reclassification as appropriate?

15. In your workplace is there a set protocol to re-contact a patient with a variant reclassification for a VUS

□ Yes □ No

16. If you order multi-gene panels will the protocol for contacting the patient with a VUS be different than what you have used in the past? **Please explain.**

□ Yes □ No

17. If you have a protocol for NGS multi-gene panels, is your primary means of discussing benign reclassification with the patient

□ Telephone

□ Mail

□ In person appointment

□ Notify physician

□ Do not re-contact

□ Other

18. What is your primary means of discussing a deleterious reclassification with the patient

    □ Telephone

    □ Mail

    □ In person appointment

    □ Notify physician

    □ Do not re-contact

    □ Other (Please explain)

19. Are the methods employed at your institution working and sufficient? Please explain **why/why not**.

    □ Yes □ No

20. Given time and resources what would be the **ideal** situation with regards to genetic counseling and the management of variant reclassification

21. There is a need for official practice guidelines regarding variant reclassification and how the reclassification of variants should be handled by genetic counselors.

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

22. **Part A.** With regard to practice guidelines what should be included? Please list in order of importance (**1 being most important and 6 being least important**)

    □ what to discuss regarding variant reclassification in the counseling session

    □ who is responsible for re-contact of the patient following a variant reclassification

□ steps to ensure a reliable tracking system

□ procedure to be followed dependent on each specific situation (i.e. variant reclassified as benign compared to a variant reclassified as deleterious)

□ the laboratories involvement and responsibilities

□ what to do if a patient cannot be re-contacted

Part B. In your opinion what is important for you to be included in practice guidelines?

23. Who should be responsible for actively monitoring the status of a variant and its reclassification?

□ Patient

□ Primary Care Physician

□ Referring Physician

□ Genetic Counselor

□ Laboratory Personnel

□ Other (Please explain)

24. Whose duty should it be to re-contact the patient should a variant become reclassified? (Please mark with an X).

□ Primary Care Physician

□ Referring Physician

□ Genetic Counselor

□ Laboratory Personnel

□ Other (Please explain)

25. Genetic counselors should be made aware of changes in reclassification

□ Always □ Only when the reclassification is deleterious □ Never

26. What is the greatest barrier that you see arising in terms of re-contact of a patient after a variant has been reclassified?

□ Genetic counseling time and resources

□ Cannot find the patient

□ Genetic counselor not being notified of the reclassification

□ Other (Please explain)

Please answer the following questions about yourself.

27. What is your age?

□ 20-30 □ 31-40 □ 41-50 □ 51-60 □ 61-70

28. What is your gender?

□ Male □ Female

29. For how many years have you worked in the cancer field?

□ less than 5 years □ 5-10 years □ 10-15 years □ 15-20 years
□ greater than 20 years

30. Where do you practice (university hospital, private oncology group etc.)

31. Approximately how many gene panel tests do you order in a typical week?

□ less than 5 □ 5-10 □ 10-15 □ 15-20