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Evaluating Uptake of Risk Management Recommendations by Mutation-Positive Patients in the Cancer Genetics Clinic

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Genetic Counseling

by

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DEDICATION

To my family and friends for their love and support.

To my mentors, past and present, for their wisdom and encouragement.

To my classmates for their resilience and kindness.

And to the patients who make this work possible.

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ABSTRACT OF THE THESIS

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Rushna Raza

Master of Science in Genetic Counseling

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Professor Moyra Smith, MD, PhD, Chair

An important benefit of cancer genetic testing is the potential for detection of an actionable mutation in genes conferring an increased lifetime risk for hereditary cancer. Individuals with a suggestive personal or family history may seek genetic counseling to assess their risk and pursue genetic testing. Genetic counselors review detected pathogenic variants, in combination with personal and family history, to make recommendations for cancer risk management. Two major recommendations include clinical screening (such as imaging) and surgical methodologies designed to prevent or detect cancer at an early and more treatable stage. Uptake of recommendations can vary significantly across patient populations with diverse medical histories, family histories, socioeconomic factors, and institutional factors. Previous studies have identified trends in risk management behavior for high-risk patients after genetic counseling, including facilitators and barriers to uptake. Cancer genetics clinics can apply this knowledge to improve outcomes for low-uptake groups through enhanced service delivery models, provider education, and community engagement. This study aimed to characterize a population of mutation-positive patients (n=149) who have received genetic counseling at UCI from 2018-

2020 in order to evaluate uptake of risk management recommendations. In general, uptake of recommended screening and suggested surgery was high for this group of patients; 74% of those who were provided with screening recommendations were documented as having completed screening, and 36% of those who had discussed surgery with a genetic counselor were documented as having completed a subsequent surgery. Patient demographics, personal medical history, family history, and genetic counseling visit details were analyzed as possible predictors of uptake, and were ultimately not determined to be strong predictors. However, for a subset of the population (n=22, 14.8%), the charts which may have documented risk management behavior were not available, perhaps because these patients had on-going healthcare outside of the medical system. Whether patients initiated genetic testing outside of UCI, and whether they received only post-test counseling were predictors for availability of charts. The lack of complete information on all study participants limited the statistical power to identify significant predictors of risk management behavior. Overall, this study revealed high uptake for risk management recommended in the genetic counseling clinic, though significant predictors for uptake were not identified. The findings of this study underscore the importance of accessible, thorough documentation available between care sites to improve longitudinal research on genetic counseling outcomes and achieve comprehensive continuity of care.

CHAPTER 1: INTRODUCTION

1.1 Cancer Genetics

Cancer is a complex disease affecting over one million Americans each year (CDC 2018). In individuals without cancer, healthy cells are able to efficiently regulate their own growth and proliferation through multiple internal mechanisms driven by genetic factors. When healthy cells acquire DNA damage, there is a potential for this regulation to be disturbed. As a result, cells may uncontrollably grow into a mass, or tumor. When rapidly-growing abnormal cell masses infiltrate neighboring tissues, a benign tumor becomes a malignant cancer (Stratton et. al 2010). Cancers originating from one site in the body are primary cancers, which may metastasize to other sites. New cancers after the first cancer is identified are defined as secondary cancers, and new cancers appearing again at the primary site are recurrences.

For the majority of cancers, DNA damage is acquired over an individual's lifetime due to various exposures including environmental, dietary, and other lifestyle carcinogens. Typically, each cell has two copies of each tumor suppressor gene. When both copies of a tumor suppressor gene are defective due to biallelic mutations, the resulting molecular changes can disrupt that gene's ability to effectively regulate cell growth, survival, and DNA repair pathways. Tumor suppressor genes which typically prevent cells from excessive proliferation become defective with loss-of-function mutations, eventually giving rise to cancer. Oncogenes, on the other hand, promote excessive cell proliferation with gain-of-function mutations, which speeds up tumorigenesis. Tumor suppressor genes are more frequently involved in hereditary cancers. Cancer-causing (pathogenic) gene mutations range from small sequence changes to larger missing or extra portions of genes or other genomic elements (introns, regulatory regions, etc.) As such, all cancers are caused by genetic changes, but not all cancers are hereditary (Tomasetti et. al, 2017).

1.2 Hereditary Cancer Syndromes

Cancers can be categorized by etiology, and the majority (80%) are attributed to sporadic, randomly acquired DNA changes over an individual's lifetime. In the general population, sporadic cancers are typically diagnosed over age 50 years without a suggestive family history. Nearly 10% of cancers are clustered in families, which can be attributed to shared environment or to the effect of variation across multiple genes, but not to a single gene change causing hereditary predisposition. The rarest cancers (5-10%) are hereditary due to a single pathogenic gene change, or variant, inherited between generations which confer a higher lifetime risk of certain cancers (Garber and Offit 2005).

Individuals born with a hereditary cancer syndrome, whether diagnosed with cancer or not, have a germline mutation in at least one cancer gene most likely inherited from one parent, however new variants can arise in an individual (Garber and Offit, 2005). The exact genetic variant can be detected by genetic testing, which sequences selected cancer genes by “reading” for any erroneous changes, which are determined to be pathogenic mutations. The various sequence changes that can be detected include single base-pair substitutions, and deletions or duplications of varying lengths. Each of these mutation types can disrupt the gene’s specific amino acid sequence, thereby altering its function and potentially affecting downstream pathways for cell cycle regulation to induce cancer.

Certain patterns are apparent in families with a hereditary predisposition to cancer. Firstly, affected individuals are often diagnosed with similar cancers at earlier ages compared to the general population, and affected individuals are often observed in every generation. Multiple primary cancers in one individual or rare cancers in a family may suggest a hereditary cancer syndrome.

Additionally, family members who have more than one type of cancer related to the same syndrome may indicate a hereditary predisposition. Different tumor suppressor genes are associated with high risk for different cancers; some are associated with multiple primary cancers to varying degrees of risk. The group of cancers for which a gene confers high risk are part of a hereditary cancer syndrome. Hereditary Breast and Ovarian Cancer syndrome (HBOC), for example, includes additional increased risks for prostate, melanoma, and pancreatic cancers caused by pathogenic changes in *BRCA1* or *BRCA2*. Both an individual's personal history and family history of cancer are important considerations to determine how they may benefit from genetics evaluation and testing for a hereditary cancer syndrome.

1.3 Cancer Genetic Counseling

Patients' past medical history is one factor that can help to determine the likelihood of a hereditary cancer syndrome. When an individual has been diagnosed with a cancer in the past, or with an active cancer, their age, cancer site, tumor pathology are considerations for a possible germline etiology.

Regardless of whether an individual has ever been diagnosed with cancer themselves, assessment of family history is crucial to discovering potential clues for hereditary cancer. With a strong family history including the criteria described previously, individuals are encouraged to seek genetics consultation for their own risk assessment

Previous genetic testing in an individual or family can also warrant further testing. Individuals in a family share a proportion of their genes with each other. When one individual is identified to carry a pathogenic variant in a cancer gene, their close relatives are also encouraged to pursue their own testing. Thus, a previously detected familial variant warrants genetic testing for other relatives. Additionally, when an individual has had testing in the past, further testing may be

indicated, especially if this testing pre-dates the year 2014 (the advent of accessible multi-gene testing), or they may benefit from testing for additional cancer genes.

When a hereditary predisposition for cancer is suspected, referral to a cancer genetics specialist is indicated. Individuals may come to the genetics clinic through self-referral, or obtain a referral from a current provider. Their referring provider may be their primary care provider, or other medical specialist who can determine when a genetics consultation is appropriate.

Cancer genetic counselors are experts in risk assessment for hereditary cancer syndromes. These unique providers practice across diverse settings including academic medical centers, community hospitals, and genetic testing laboratories. The typical course of cancer genetic counseling includes pre-test counseling, coordination of genetic testing if indicated, and post-test counseling (Riley et. al, 2012). Pre-test counseling entails a detailed conversation between patient and genetic counselor. This meeting includes several key elements: collection of personal and family history, personalized risk assessment, and discussion of risks and benefits of genetic testing.

Once a pathogenic variant is detected, genetic counselors and patients engage in interpretation of results during a post-test visit. The result itself, testing limitations, associated cancer risks, and clinical recommendations are discussed. Additionally, genetic counselors are able to clarify patients' understanding of their result and personal cancer risk, including implications for family members. It has been demonstrated that patients' comprehension of their personal cancer risk is improved after receiving genetic counseling for their test results. Both affected and unaffected patients find value in knowing their genetic status so they may be proactive in preventing or reducing risk for cancer in themselves or family members (Smith-Uffen et al., 2021).

1.4 Cancer Risk Management for Mutation Carriers

1.4.1 Risk Management Options

Recommendations discussed with a genetic counselor following testing vary depending on the specific gene in which a pathogenic variant detected. These recommendations are guided by professional organizations, such as the National Comprehensive Cancer Network (NCCN) and are developed by expert clinicians and researchers who use an evidence-based approach to make recommendations which are anticipated to be beneficial and effective. An individual's age, cancer type, co-morbidities, and other personal health factors are considered for the best course of management. The overarching goal of cancer risk management is to delay or prevent a primary cancer or recurrence in a specific organ, and personalized strategies contribute to improved outcomes for mutation carriers.

Screening recommendations aim to monitor organs which are at increased risk for developing cancer due to a pathogenic mutation. Early detection and prevention are prioritized in screening strategies, and methods vary by organ system involved. HBOC and Lynch syndrome, for example, are two conditions for which screening recommendations are well-studied. In the former, detailed mammograms every 6 months are standard, with adjustments to regimen as determined by a breast care specialist. For the latter, increased colonoscopies are recommended at a more frequent rate than for those without a Lynch syndrome pathogenic mutation. In addition to these procedures, other screening recommendations include self-monitoring (e.g. breast awareness), blood screening (e.g. for Prostate Specific Antigen, PSA), or ultrasonography. To accomplish these screenings, referral to a non-genetics specialist, such as a gastroenterologist, is necessary.

Although more intrusive than screening alone, surgical interventions are also a consideration for some mutation-positive patients. These procedures aim to remove all or a portion of the tissues of an organ that is susceptible to cancer. Risk-reducing surgeries are an effective option that can

drastically decrease one's likelihood of developing a hereditary form of cancer. For example, unaffected *BRCA1/2* mutation carriers have a lifetime cancer risk of greater than 60%, depending on the specific mutation. For HBOC, major surgery options include mastectomy, hysterectomy, and salpingo-oopherectomy. After a double mastectomy, the lifetime risk of breast cancer risk is reduced by nearly 90%. While not all hereditary cancers can be prevented in this way, eligible patients can work with multiple specialists to coordinate their optimal risk reduction plan. Importantly, additional psychosocial implications can be addressed by genetic counselors to explore patients' motivations, concerns, and other feelings towards irreversible surgery .

1.4.2 Trends in Risk Management

Individuals' approach to risk management varies across multiple personal and family histories, and socioeconomic factors. For example, well-established predictors for uptake of risk-reducing salpingoopherectomy (RRSO) by *BRCA1/2* carriers are a family history of ovarian cancer, personal history of breast cancer, and age above 40 years (Miller et. al, 2010). Unaffected *BRCA1/2* carriers of older age, White ancestry, with higher knowledge of breast cancer genetics are more likely to pursue follow-up recommendations (Buchanan et. al, 2017). Between sexes, females with a *BRCA1/2* mutation are more likely to uptake screening for breast cancer than mutation-positive males are for prostate cancer screening.

There are a number of barriers to uptake of risk management recommendations. For example, one's perception of their own risk can be lower than their actual risk based on genetic test results and personal/family. history. This may explain the lower uptake of *BRCA1/2* screening recommendations for men (as compared to women), due to the erroneous belief that HBOC confers high risk only to women (Rauscher 2017). Other psychosocial factors include anxiety,

lack of emotional support, or low medical literacy. Institutional barriers to compliance exist in inadequate access to recommended screenings or procedures, providers and clinics without experience in high-risk cancer prevention methods.

1.4.3 Improving Risk Management

As awareness and utilization of genetic services increases, cancer genetics clinics must meet the rising volume of individuals seeking evaluation and testing. In 2016, 62% of genetic counselors reported their patient volumes had increased since 2014 (NSGC, 2016). The combination of increased clinic volumes and various barriers to screening adherence poses a need for solutions. To provide quality care to all patients, high-risk mutation-positive individuals can be prioritized for targeted interventions which may include increasing dedicated clinic time, community screening events, peer support groups, amongst other possibilities. Developing such a system requires identification of both individuals who are generally compliant with follow-up, and those who would benefit from additional interventions to improve low uptake. Some clinic workflows have piloted alternate delivery models for follow-up appointments for individuals with high compliance, including brief phone calls, surveys, and chatbots (Schmidlen et. Al, 2019) (Kaphingst et. Al, 2021). This strategy could potentially create more time in a clinic schedule for in-depth counseling for clinical management with high-risk patients.

1.5 Study Aims

This study aims to better understand the uptake of genetic counselor's risk management recommendations by a diverse group of high-risk patients with a pathogenic cancer gene mutation. A retrospective chart review was conducted for a cohort of patients at an academic medical center over a period of three years in order to:

1. Characterize a population of high-risk individuals with pathogenic mutations who have received genetic testing
2. Evaluate the uptake of genetic counselor's post-test recommendations using available records
3. Identify possible personal and family history factors that may predict uptake of risk management recommendations.

CHAPTER 2: METHODS

2.1 IRB approval

This study was approved by the University of California, Irvine (UCI) Institutional Review Board (IRB) under study HS# 2018-4417, Expedited Category 5. The records reviewed in this study were originally collected for non-research purposes. The study protocol was approved with a waiver of the requirement for patient consent, given the minimal risk of harm to patient privacy and well-being. The waiver of patient consent was justified due to the impracticality of obtaining informed consent for a retrospective chart review, given the large number of records across the study period and the likelihood that patients may not be reachable with the contact information that was available at the time of their appointment in the cancer genetics clinic.

2.2 Retrospective Chart Review

2.2.1 Patient Chart Selection

A retrospective chart review was conducted using the cancer genetics clinic database (CaGen) and electronic medical records in EPIC at UCI Health.

First, a list of patient charts from January 2014 through November 2021 was generated from the database. A total of 2880 patient records from this period were available to review. Patients with Pathogenic/Very Likely Pathogenic (P/VLP), or "positive", gene variants based on DNA analysis, and who were age 18 years or older at the time of the time the result was reported, were included for analysis. In total, 230 of the 2880 charts met criteria for inclusion.

Patients whose results were reported in 2018 through 2020 were included. Patients with results reported prior to 2018 were excluded due to the hospital's transition to the current EPIC Electronic Medical Record (EMR) in late 2017. Records from 2018 and later are easily accessible in the current EMR environment, and therefore could be reviewed more

systematically with less error than retrieving older records from archives. Patients with positive results after 2020 were not included in this study due to the possibility of insufficient time between post-testing counseling and the date of data collection for these patients to perform recommended risk management. For example, a *BRCA2* mutation carrier receiving annual mammogram recommendations in late 2020 would have had over one year to complete at least one mammogram between date of recommendation to current day.

All patient information was uploaded into a secure folder, where they were accessible only by secure password-protected log-in. Each patient was assigned a unique non-identifying code, with the code key stored in this secure folder.

In total, 149 records were reviewed for this study. Inclusion and Exclusion criteria are described below.

Patients under 18 years of age at the time of their reported result were excluded from this study. Because the study is designed to assess uptake of recommendations for high-risk patients with a detected P/VLP mutation in a hereditary cancer gene, patients were excluded from this study if they had only Benign/Likely Benign variants, or "negative" results from genetic testing. Similarly, patients with Variants of Uncertain Significance (VUS) found on genetic testing were excluded from this study.

During data collection, it became clear that not all 149 patients reviewed for this study continued care at UCI Health after their genetic counseling visit. For example, some patients established care at UCI only to have an appointment with a genetic counselor, but are (presumably) receiving further care at an outside institution for which records are not available to us. Therefore, we were unable to collect data on uptake of genetic counseling recommendations for patients whose records were unavailable to us after time of genetic counseling. This was the case

for 22 (14.8%) of the 149 charts reviewed. Patients with incomplete management uptake data were still included in personal/family history and visit analyses.

Additionally, 9 of the 149 patients did not receive post-test counseling, and therefore did not receive gene-specific management recommendations by a UCI genetic counselor. These 9 cases were included in descriptive analyses, but ultimately were not used in analyses evaluating uptake of recommendations.

2.2.2 Information Collected From Database and Electronic Medical Records

Demographic information, personal cancer and genetic testing history, pertinent family history, and appointment details for each patient were collected from the cancer genetics database and EPIC electronic medical records. These variables are listed below.

Demographic information collected from each patient's chart includes:

- Binary sex assigned at birth as reported in database
- Age at time of results reported. Patient birth year and genetic report year were used to calculate patients' age at the time of the result. Patients' ages were also categorized as "Under 50 years old" to "50 years and older". The age of 50 years was used to set up this categorical variable because 1) diagnosis of cancer under 50 years of age is commonly used as an indicator for suspicion of hereditary causes and 2) general population cancer screening is generally recommended by this age.
- Patient ancestry as recorded in the database. Ancestry groups include White, Asian, Other, Hispanic/Latino, Ashkenazi Jewish, Black/African-American. "Other" ancestry includes those of mixed ancestry, Native American ancestry, or those who declined to state.

Details of personal cancer and genetic testing history collected from each patient's chart include:

- Cancer site and age of diagnosis as reported in the database. For patients who had been diagnosed with a second primary cancer in a different site, the cancer associated most closely with the patient's referral indication and/or the reported gene was included in the analysis. Major cancer associations with reported genes were determined using current NCCN guidelines. For example, *BRCA1* positive patients initially referred for personal history of breast cancer, who also had history of renal cancer, were categorized within the breast cancer group.
- When a second cancer was also relevant to the initial referral indication and/or was also associated with the reported gene, both cancers were paired for analysis. For example, patients referred for a personal colon cancer who also had a previous uterine cancer were analyzed as one group, due to both cancers' strong associations with Lynch syndrome. Identified cancers were grouped by major category: Benign Tumor, Breast, Breast+Ovarian, Colorectal (CRC), CRC+Ovarian, CRC+Uterine, Genitourinary (GU, including Prostate and Renal), None, Other, Ovarian, Pancreas, Pancreas + Skin (including Melanoma), Polyps (of colon, benign), Skin (includes Melanoma and other skin cancers), and Uterine. Cancers classified as "Other" included those for which there were 3 or fewer cases. Ages at diagnosis for all cancers were recorded, and sorted into "<50y" and "≥50y" age groups.
- Results of genetic testing, which were available to review for all 149 patients. Each patient had one P/VLP variant in one cancer gene. 29 unique genes were found to have a P/VLP mutation in this study population. For analysis, genes representing 3% or less of total cases were categorized as "Other", except *MSH6* due to its role in Lynch syndrome.

- Genes associated with a specific hereditary cancer syndrome were grouped for analysis. Those marked "*APC* None" and "MAP-carrier" are due to genetic variants not conferring high cancer risk as detected in the patient (*APC* p. I1307K and *MUTYH* monoallelic variant, respectively). The *ATM* and *CHEK2* genes were grouped as "Mod. Breast", due to their association with moderately increased lifetime risk for breast cancer. When a gene did not have a specific associated cancer syndrome, and fewer than 5 cases, the gene was grouped into "Other".
- The extent of genetic testing as noted in the database: Expanded Panel, Targeted Panel, or Single-Site. Expanded panels are those described as such by the performing laboratory, typically analyzing over 50 genes. Targeted Panel includes panels limited to analysis of genes associated with specific cancer types relevant to a patient's history. Patients with Single-Site testing pursued analysis of only one specific genetic variant in one gene, typically determined by a previously identified family mutation.
- Each patient's genetic testing result was evaluated for consistency with their personal and/or family history of cancer. Strong associations between gene and cancer risk were determined by review of NCCN guidelines. Consistency was determined as follows:

The result was considered "Consistent" with personal history when the gene found to have a P/VLP mutation is associated strongly with increased risk for a cancer that the patient has been diagnosed with. Non-cancerous findings such as benign tumors or polyps were also evaluated for consistency. Results were considered "Inconsistent" for patients with no personal history of cancer, or a diagnosis of cancer not strongly associated with the gene detected.

Results were considered "Consistent" with a patient's family history when 1) a patient's family history of cancer was suspicious of the same hereditary cancer syndrome associated with the

patient's detected gene, as recorded in genetic counselor's notes detailing NCCN criteria met, and/or 2) the patient was found to have the same familial variant previously detected in another relative. Results were considered "Inconsistent" if the family history did not include cancers associated with the detected gene, or was limited.

Details regarding each patient's family history were collected from each chart by review of genetic counseling notes and pedigree.

- Number of relatives with cancer. Familial cancer cases were counted as present on pedigree and/or described in genetic counseling notes. Degree of relationship was not assessed for this study. Patients themselves were not included in this count. Number of relatives were then sorted into groups of "0-1", "2-5", "6+".
- Patients were recorded as either having or not having any living children, based on pedigree and genetic counseling note.
- Whether a familial mutation was known prior to genetic testing. This was documented in the genetic counseling note. The majority of patients with a known familial mutation pursued site-specific genetic testing, for which analysis of additional whole genes was not performed by the laboratory.
- Patients were recorded to have a limited family history as described in genetic counseling notes or noted in pedigree. Limited family history was applicable to patients with little to no information or contact with relatives, who had small family structures, or who were adopted out of biological families with little to no information or contact with blood relatives.

Details collected from each chart regarding the patient's genetic counseling appointments include:

- Patient's primary referral indication was recorded based on history of cancer or history of genetic testing. Many patients came to the genetics clinic with more than one referral indication (eg. both personal and family history of cancer). Therefore, the referral indications were characterized as follows.

"Personal History of Cancer" was assigned to patients with a cancer diagnosis warranting genetic counseling with no previously identified mutation, regardless of family history.

"Personal History of Genetic Testing" was assigned to every patient with a previously identified genetic mutation, regardless of personal or family history of cancer.

"Family History of Cancer" was assigned to patients with neither a personal history of cancer nor a known personal/familial variant, but a family history of cancer concerning a hereditary cancer syndrome.

"Family History of Genetic Testing" was assigned when patients came to their own genetic counseling with a known family variant, regardless of their personal or family history of cancer.

- Referral source. Patients were recorded to have either been referred by a provider or self-referred. Referring providers include those both practicing within and outside of UCI Health, across various specialties.
- Each patient's number of genetics appointment Cancellations and non-attendance were recorded. Cancellations due to scheduling errors and reschedules in advance were not counted toward the total.
- Patients were assessed to be either continuing or newly registered patients at UCI Health. New patients included those who had never seen any UCI provider prior to their first genetics consult. If patients had previously seen another UCI provider or received other services, they were counted as a continuing patient.

- A group of patients had genetic test results reported prior to meeting a genetic counselor at UCI. This group includes those who had testing ordered by an outside provider and are receiving post-test counseling at UC Irvine to review results in detail, and/or establish care for high-risk management. Additionally, this group includes those who completed testing a number of years prior to their meeting and pursued updated testing after UCI genetic counseling, regardless of previous results. In some cases, previously identified variants classified as Benign were found to be Pathogenic/Very Likely Pathogenic upon re-test, granting eligibility for patient's inclusion in this study.
- Patients who were tested prior to their most recent UCI genetics appointment (whether within or outside of UCI) and completed updated testing were recorded. Updated testing includes testing ordered a number of years after initial testing, and/or testing that offers a more targeted/broader analysis of genes than prior testing.
- After dates of each were collected, elapsed time between referral, pre-test counseling visits, and post-test counseling visits were calculated to determine whether time between appointments could predict a patient's uptake of genetic counseling recommendations.
- The format for each genetic counseling encounter was determined by reviewing visit notes. The three formats included "In-Person", "Voice Only", or "Videoconference".
- The proportions of patients who completed a follow-up genetics visit around 6 months or 1 year were collected.
- The proportion of patients receiving only post-test counseling was determined to evaluate whether completion of pre-test counseling influenced uptake of recommendations. This group includes patients who had pursued testing outside of UCI, and those who had testing ordered by a different provider within UCI prior to genetics visit for results

review. Some patients were noted to have had pre-test counseling at UCI, but had not received post-test counseling. These patients ultimately did not receive formal management recommendations by a genetic counselor, and thus were excluded from final analyses for uptake.

Details from post-test discussion with genetic counselor regarding recommended next steps are included below. The major categories of recommendations analyzed in this study include referral to other specialists and risk management via screening or surgery.

- Referral to non-genetics specialists. Referrals were counted when documented in genetic counseling notes and/or formally entered in the patient's medical record, and all referrals were made to providers within UCI. Patients were referred to various specialists based on the cancer gene found to have a mutation. For example, Gastroenterology referrals were common for patients with Lynch Syndrome gene mutations, while a number of *BRCA1/2* positive patients received referrals to a Breast specialist. Patients received either one, two, or no referrals to different specialists. Uptake of referral recommendations was determined by review of available post-test records. Specialists were considered seen when encounters were clearly documented in office visit notes, procedure notes, or other available records. Specialists seen outside of UCI were available to review through EPIC's CareEverywhere feature, and these visits were counted towards compliance with recommendations. Specialists were considered not seen when the patient had clear documentation of continuing care at UCI beyond their genetic counseling appointments, and evidence of visit to a referred specialist was not found. "Not Available" charts encompass those who do not have any further services documented at UC Irvine beyond their genetic counseling appointments.

- Additionally, familial testing was recommended for over 90% of patients who received post-test counseling. Family testing was recommended due to the patient's P/VLP result in combination with any personal or health history factors. Uptake of family testing recommendation was difficult to determine following a proband's genetics visits. Achieved uptake of family testing was documented in the cancer genetics database for relatives also seen at UCI, or in 6- or 12-month follow up visits.
- Fewer than 5 patients were referred to another non-cancer genetics specialist at UCI due to their personal or family history of a potentially hereditary condition; this was not included in analysis.
- Recommendations for risk management include procedures intended to prevent and/or early detect new cancers. This group does not include therapeutic options for active cancers.
    - Patients were referred to initiate cancer screening for organ groups relevant to cancers associated with the gene found to have a P/VLP mutation. For example, annual colonoscopies were recommended for most Lynch Syndrome carriers. Compliance with surveillance recommendations was determined by UCI EPIC chart review, including CareEverywhere. Patients were considered compliant with screening when they had clear documentation of completing the appropriate screening within the recommended time interval. Any number of screening encounters was considered compliant, regardless of the date of results reviewed with a genetic counselor.
    - Many patients participated in discussions of surgeries for which they were eligible based on their genetic test result. Evaluation of uptake of surgery was determined

through relevant documentation in patient charts. Of note, some patients who were eligible for surgery due to their mutation had already undergone surgery prior to this discussion by a genetic counselor; these cases were not included in analyses. People who had surgical options available often opted to pursue high-risk screening instead, for reasons not explored in this study.

2.3 Data Analysis

IBM SPSS software version 28 (IBM 2021) was used to perform descriptive and univariate analyses. Descriptive analyses include patient demographics, and cancer and genetic testing history. Univariate analyses were performed to compare the independent variable of patient descriptives with their rate of uptake of genetic counselor's recommendations. Statistical analyses include chi-square analysis and Fisher's exact test. Statistical significance is reported for univariate analyses as a nominal p-value, and a p-value <0.05 was considered significant. For this exploratory analysis, no correction was made for multiple comparisons.

CHAPTER 3: RESULTS

3.1.1 Patient Demographics

Patient characteristics for this study cohort (n=149) are described in Table 1. Female patients were the majority of the study population at 67.8% (n=101). In total, 64.4% (n=96) of the study population was age 50 years or older at the time their result was reported, by calendar year. Ages ranged from 22 to 88 years old with a mean age of 53 years and standard deviation 16.02, (Figure 1). Individuals of White ancestry represented just over half the study population at 52.3% (n=78). Less than 10% of patients identified as Ashkenazi or Black/African American. In the cancer genetics database, some Ashkenazi Jewish patients were categorized as “White”, which may slightly alter the reported proportions

Table 1. Demographic characteristics and visit details of the study sample

Patient Demographics and Visit Details (n=149)		
	N	%
Sex		
Female	101	68
Male	48	32
Ancestry		
White	78	52
Asian	22	15
Other	18	12
Hispanic or Latino	15	10
Ashkenazi Jewish	13	9
Black or African American	3	2
Age at Report (Years)		
<50	53	36
≥50	96	64
Provider	121	81
Self-Referred	24	16
NA	4	3
New Patient at UCI		
Yes	63	42
No	86	58
Tested Prior to UCI		
Yes	22	15
No	127	85
Counseling Received		
Pre-Test Only (No Post-Test, No Recommendations)	9	6
Post-Test Only (No Pre-Test)	45	30
Both	95	64

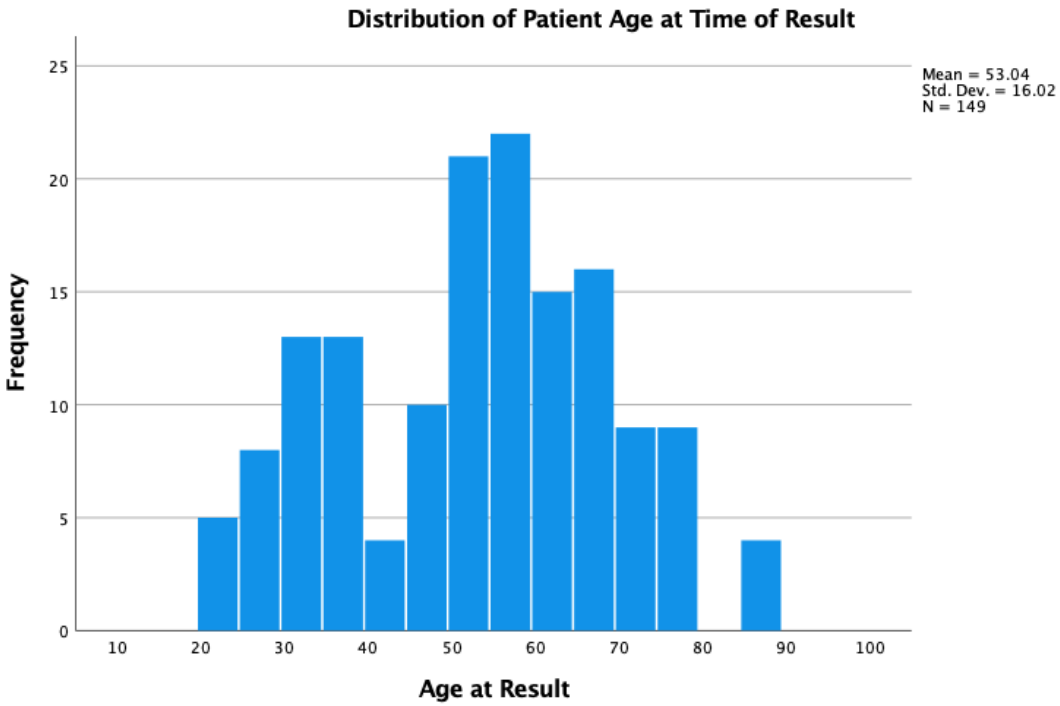

Figure 1. Distribution of Patient Age at Time of Genetic Test Result. N=149 patients whose age at the time their test result was reported was calculated using their birth year and the year stated on their genetic test report.

3.1.2 Patient Clinical History

Patients' cancer diagnoses are described in Figure 2 and Table 2. In total, 31% (n=46) patients in this study cohort did not have a personal history of cancer at the time they received genetic test results. The most prevalent personal cancers included Breast (15%, n=22), GU (10%, n=15), and Colorectal (9%, n=14). Ovarian and skin cancers were represented equally at 8% (n=12). Non-cancerous indications for referral due to personal history include benign colon polyps (3%, n=5) and benign tumors (2%, n=3) warranting genetics evaluation. About 10% (n=15) of patients had been diagnosed with a second cancer at a different site. Of these, one patient each (0.7%) was diagnosed with two cancers associated with the same hereditary cancer syndrome or cancer gene: Breast+Ovarian (HBOC), CRC+Ovarian (Lynch), CRC+Uterine (Lynch), Pancreas + Skin (*CDKN2A*). "Other" cancers represented 6.0% (n=9) of the study population, and included Peutz-Jeghers Syndrome, sarcoma, lung, and CNS cancers. When primary cancer referral without second cancer was considered, the majority of these cancers were diagnosed at age 50 or later (40.3%, n=60).

The range of genes identified to have pathogenic mutations in this cohort are described in Figure 3 and Table 3. As expected, the most common hereditary cancer syndromes in this group were HBOC (25%, n=37) and Lynch syndrome (24%, n=36) (Figure 4) (Table 4). A total of 13% (n=20) of individuals had a genetic result not associated with a specific hereditary cancer syndrome, not including prominent breast-cancer related genes *CHEK2* (15%, n=22) and *ATM* (3%, n=5). Additionally, carriers of *APC* p.I1307K (4.0%, n=6) and *MUTYH* monoallelic mutations (5.4%, n=8) are represented, though they do not confer a risk for hereditary cancer. Consistency between patients' personal and family history with their reported gene is described in Figure 5. Firstly, 35% (n=52) of patients had a pathogenic gene variant consistent with only

their personal history of cancer. On the other hand, 17% (n=26) of patients had only a family history consistent with their pathogenic gene variant. About 26% (n=39) had a gene result consistent with both their personal and family histories. For 22% (n=32) of patients, neither a personal history nor a family history consistent was consistent with their reported gene. Additionally, over half the study population (69%, n=102) pursued Expanded Panel testing.

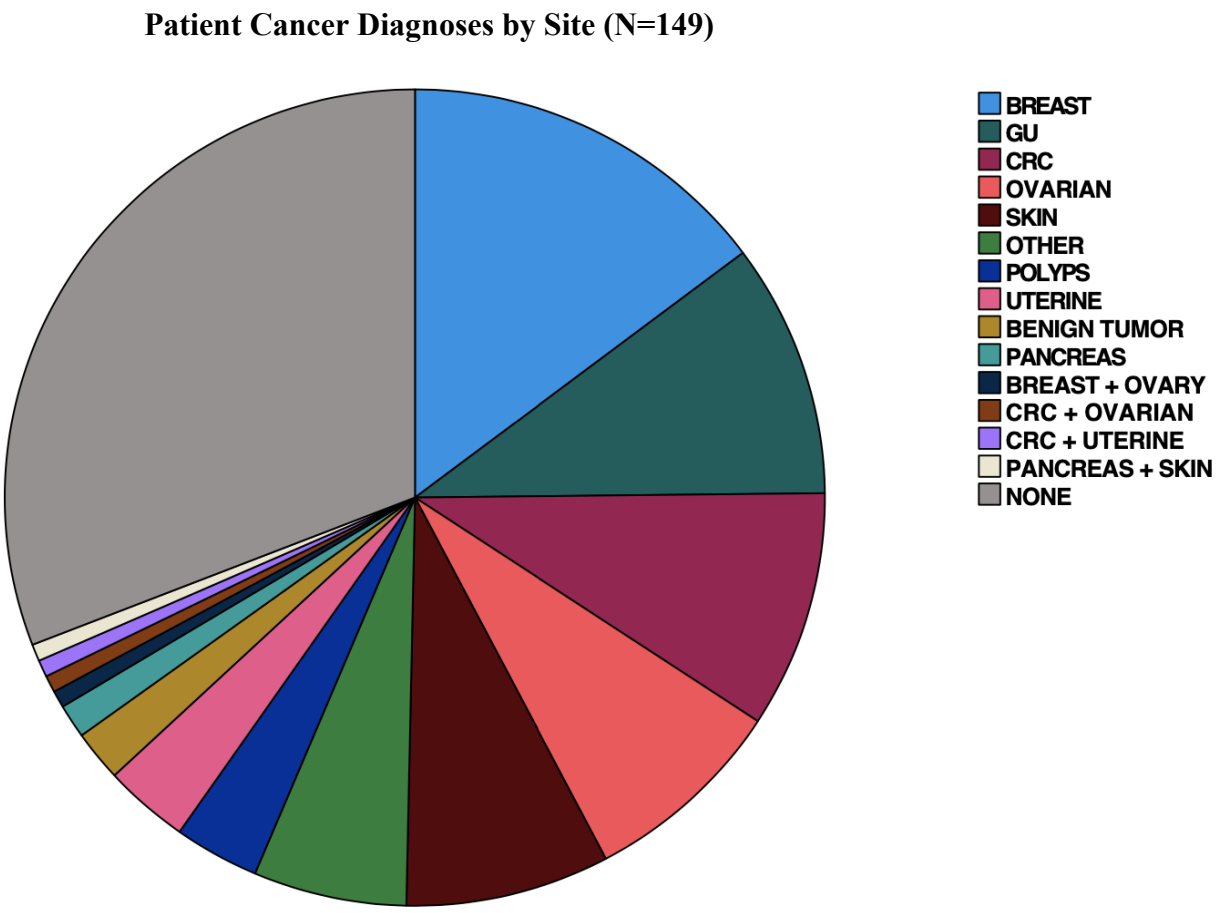

Figure 2. Distribution of patients' cancer diagnoses by site. N=149 patients with or without a personal history of cancer. For patients diagnosed with a second primary cancer in a different site, the cancer associated most closely with the patient's referral indication and/or their reported cancer gene was included in the analysis. When the second cancer was also relevant to the initial referral indication and/or was also associated with the reported cancer gene, both cancers were paired for analysis. CRC: Colorectal Cancer, GU: Genitourinary

Table 2. Frequencies of patients' cancer diagnoses by cancer site

Patient Cancer Diagnosis by Site (N=149)		
	n	%
Breast	22	15
GU	15	10
CRC	14	9
Ovarian	12	8
Skin	12	8
Polyps	5	3
Uterine	5	3
Benign Tumor	3	2
Pancreas	2	1
Breast + Ovary	1	1
CRC + Ovarian	1	1
CRC + Uterine	1	1
Pancreas + Skin	1	1
Other	9	6
None	46	31

CRC: Colorectal Cancer, GU: Genitourinary

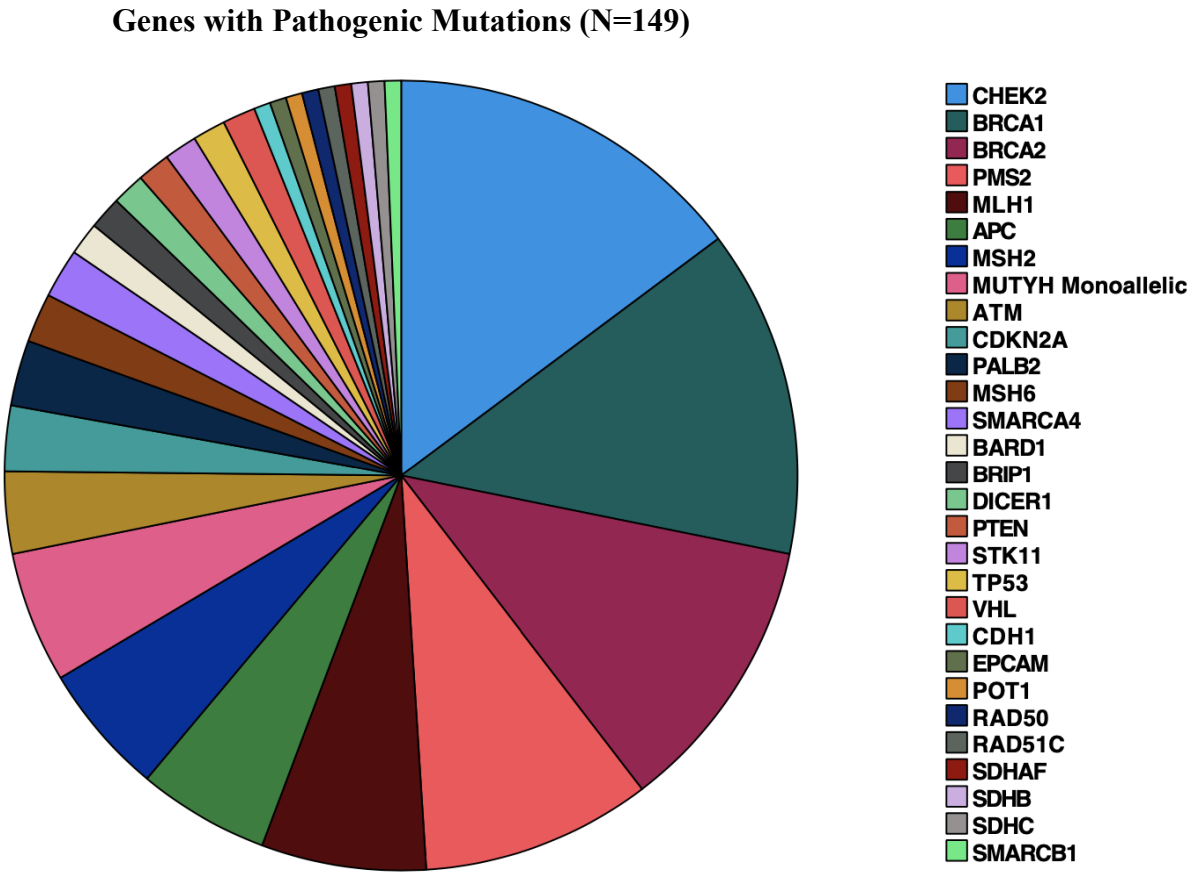

Figure 3. Genes in which pathogenic mutations were found. N=149 patients with a pathogenic variant reported in one of 29 resulted cancer-associated genes

Table 3. Frequencies of genes for which pathogenic mutations were found

Genes with Pathogenic Mutations (N=149)		
	n	%
CHEK2	22	15
BRCA1	20	13
BRCA2	17	13
PMS2	14	9
MLH1	10	7
APC	8	5
MSH2	8	5
MUTYH Monoallelic	8	5
ATM	5	3
CDKN2A	4	3
PALB2	4	3
MSH6	3	2
SMARCA4	3	2
BARD1	2	1
BRIP1	2	1
DICER1	2	1
PTEN	2	1
STK11	2	1
TP53	2	1
VHL	2	1
CDH1	1	1
EPCAM	1	1
POT1	1	1
RAD50	1	1
RAD51C	1	1
SDHAF	1	1
SDHB	1	1
SDHC	1	1
SMARCB1	1	1

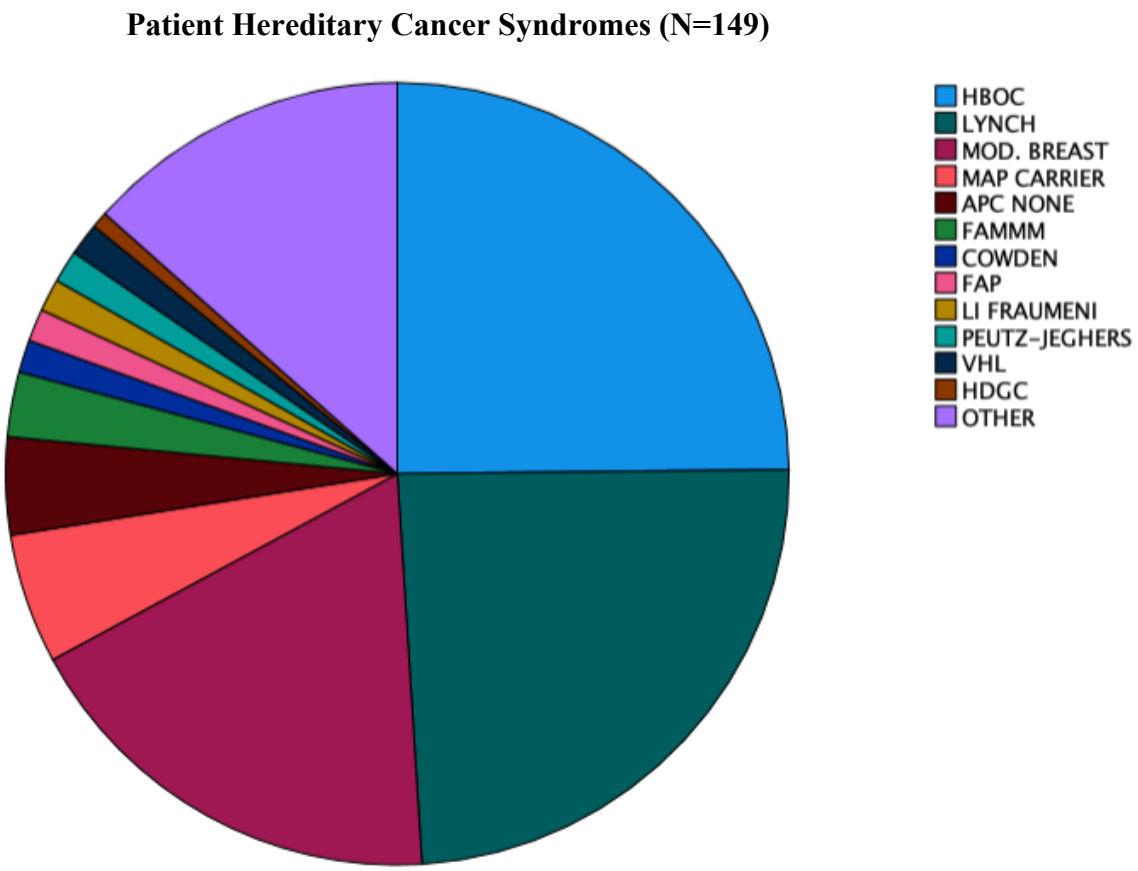

Figure 4. Distribution of patients' hereditary cancer syndromes. N=149 patients with a hereditary cancer syndrome confirmed by genetic testing. HBOC: Hereditary Breast and Ovarian Cancer syndrome, Mod. Breast: Moderate Breast (*ATM, CHEK2*), MAP: *MUTYH*-associated Adenomatous Polyposis syndrome, FAMM: Familial Atypical Multiple Mole Melanoma syndrome, FAP: Familial Adenomatous Polyposis syndrome, VHL: Von Hippel-Lindau syndrome, HDGC: Hereditary Diffuse Gastric Cancer.

Table 4. Frequencies of hereditary cancer syndromes for which patients were found to carry a pathogenic variant in an associated gene

Patient Hereditary Cancer Syndromes (N=149)		
	n	%
HBOC	37	25
LYNCH	36	24
Moderate Breast (*ATM a*nd *CHEK2*)	27	18
MAP Carrier	8	6
APC None	6	5
FAMMM	4	3
Cowden	2	1
FAP	2	1
Li Fraumeni	2	1
Peutz-Jeghers	2	1
VHL	2	1
HDGC	1	1
Other	20	13

HBOC: Hereditary Breast and Ovarian Cancer syndrome, MAP: *MUTYH*-associated Adenomatous Polyposis syndrome FAMM: Familial Atypical Mole Melanoma Melanoma syndrome, FAP: Familial Adenomatous Polyposis syndrome, VHL: Von Hippel-Lindau syndrome, HDGC: Hereditary Diffuse Gastric Cancer.

Consistency of Genetic Test Results with Personal and/or Family Histories (N=149)

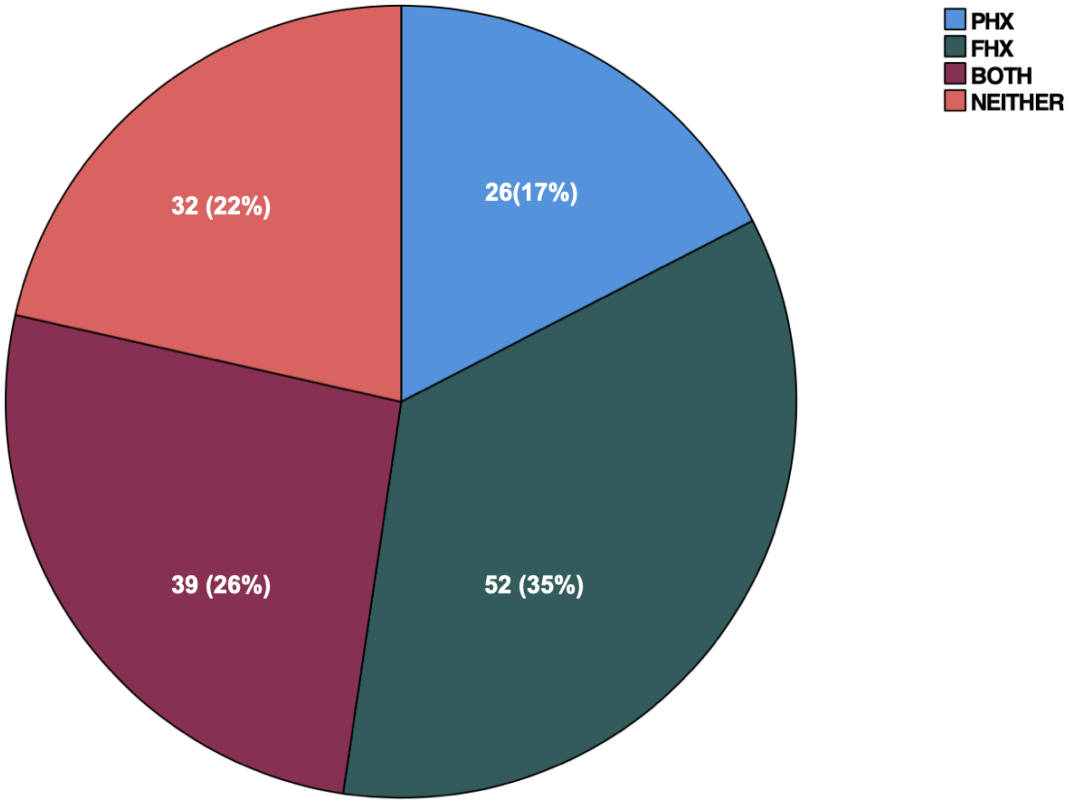

Figure 5. Consistency of genetic test results with personal and/or family histories. N=149 for patients whose genetic test result was compared to their personal or family history of cancer to determine consistency. PHX: Personal History, FHX: Family History

3.1.3 Patient Family History

Patients in this cohort most often had 2-5 family members with cancer, 60% (n=90). 12.1% (n=18) of patients had either one or no relatives with cancer (Figure 6A). The majority of patients in this cohort had at least one living child (70%, n=104), over two times as many as those without children (30%, n=45) (Figure 6B). A proportion of patients had knowledge of a previously identified familial variant at the time of genetic counseling (26%, n=39) (Figure 6C). The majority of patients with a known familial mutation pursued site-specific genetic testing, for which analysis of additional whole genes was not performed by the laboratory. Additionally, 19% (n=28) of patients had a limited family history which could not be thoroughly assessed (Figure 6D). Genetic counseling notes revealed 102 (69%) of patients had a family history suggestive of a hereditary cancer syndrome as determined by a genetic counselor. These family histories are not unique; some patients in this study are related to each other.

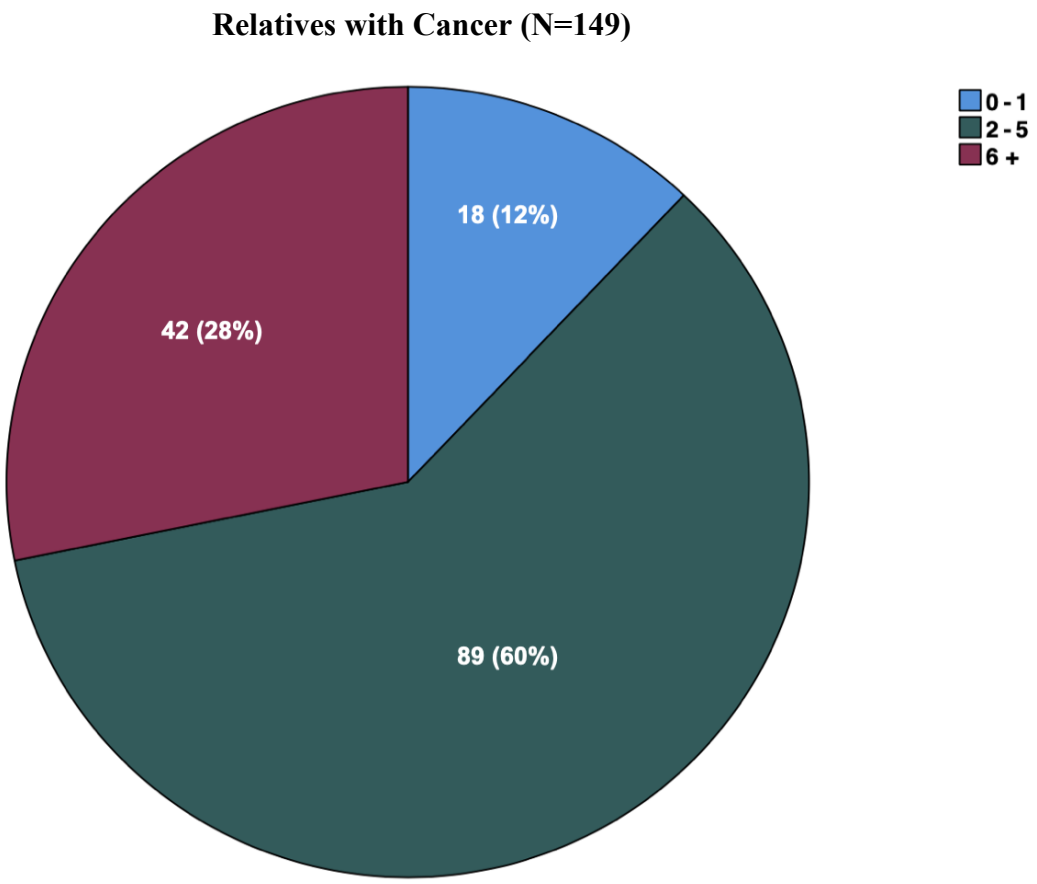

Figure 6A. Number of relatives affected with cancer. N=149 patients whose family histories included or did not include relatives diagnosed with any cancer.

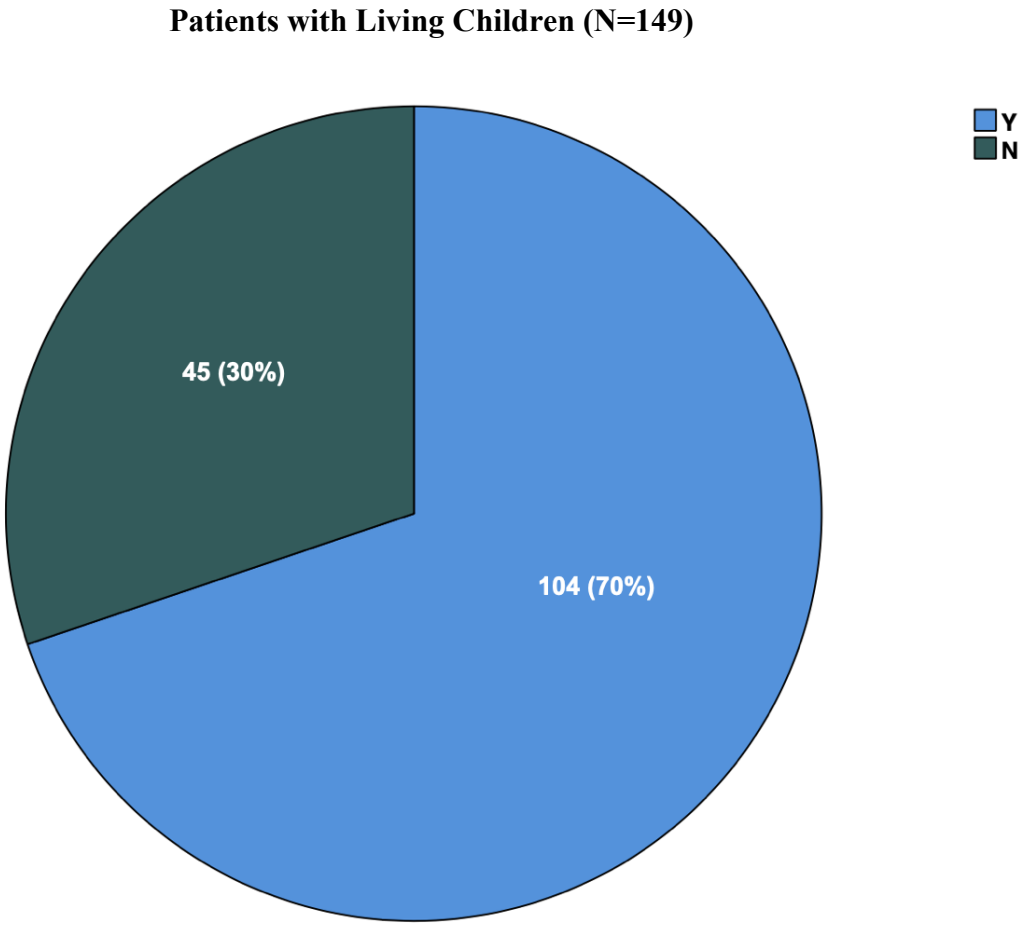

Figure 6B. Number of patients with living children. N=149 patients who were determined to either have (Y) or not have (N) living children, as documented in pedigree and genetic counseling notes.

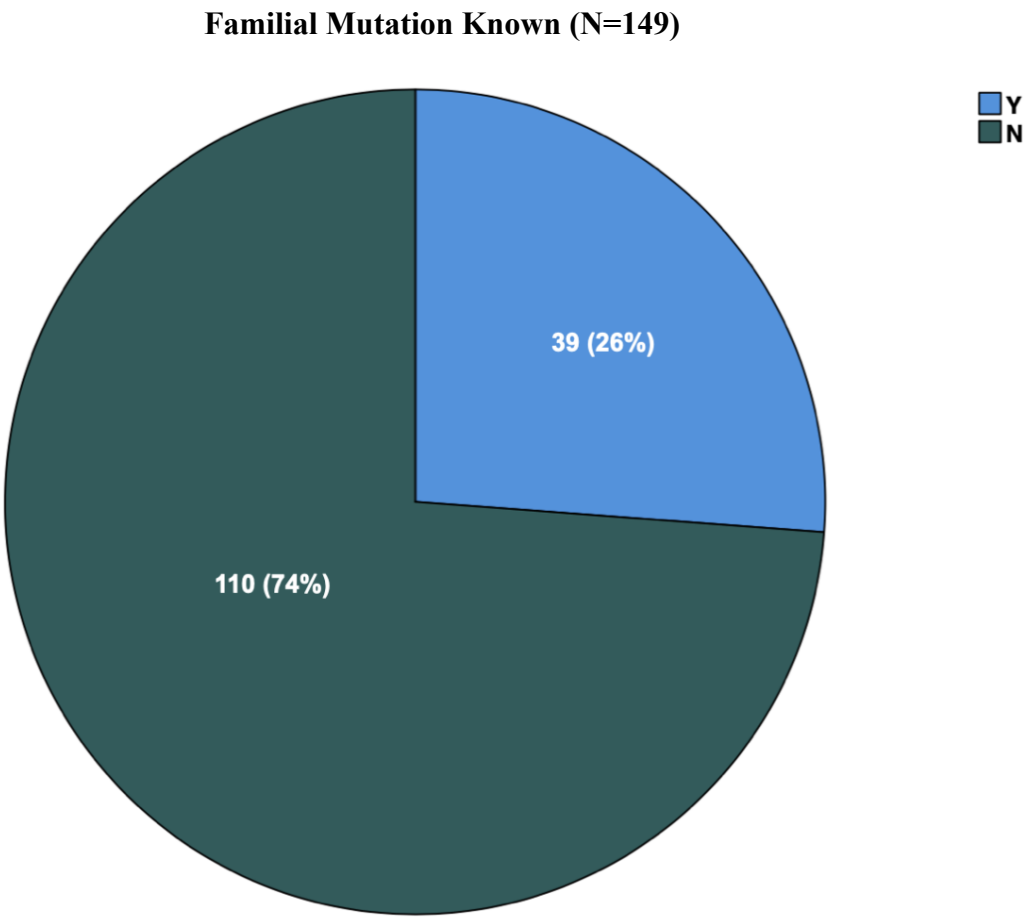

Figure 6C. Patients' knowledge of a familial mutation prior to genetic counseling N=149 patients who did (Y) or did not (N) report a familial variant previously identified in a relative, prior to genetic counseling appointment.

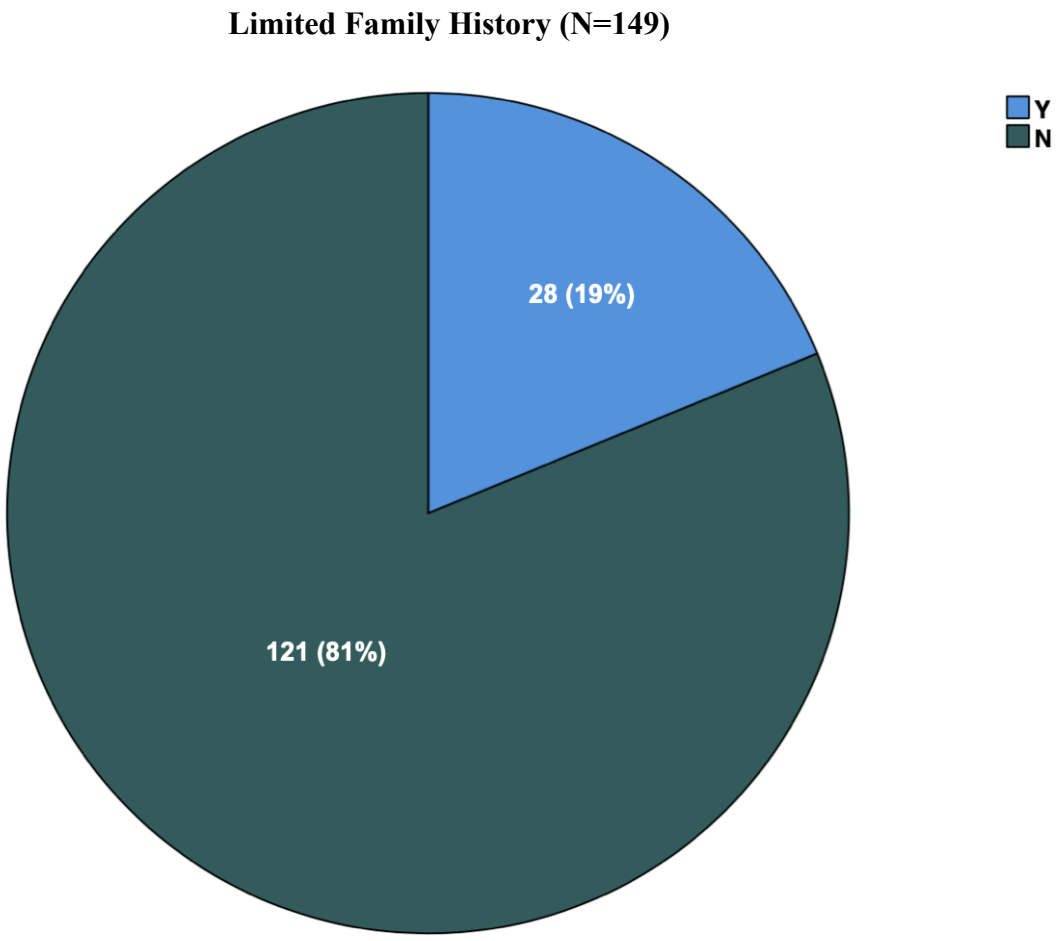

Figure 6D. Distribution of patients with a limited family history N=149 patients who were (Y) or were not (N) determined to have a family history which was incomplete for accurate risk assessment, as documented in pedigree and/or genetic counseling notes as no contact with family, small family structure, or adoption with no information on biological family.

3.1.4 Patient Visit Details

A total of 49% (n=73) of patients had a personal history of cancer as their primary referral indication, regardless of family history (Figure 7). An estimated 21% (n=31) of patients had a known personal genetic variant as their primary indication. The proportion of patients referred due only to family history of cancer was 16% (n=24). The remaining 14% (n=21) of patients were referred due to a family history of genetic testing.

A limited number of patients had a significant number of cancellations and scheduled appointments which they did not attend, leading to these variables not being chosen for analysis. Overall, wait times between first referral and pre-/post-test genetic counseling appointments did not significantly exceed 5 months, and therefore were not included in analysis. Generally, most appointments were held In-Person prior to 2020, presumably due to COVID-19 restrictions starting in March 2020. The format of the visit was not included in the final analysis. The proportions of patients who completed a follow-up genetics visit around 6 months (5%,8) or 1 year (12%,18) after receiving results and recommendations by a genetic counselor were determined.

Of all patients, 81% (n=121) were referred by a provider, while 16% (n=24) self-referred. New patients establishing care for the first time at UCI for their genetic counseling appointment were 42% (n=63). Additionally, 15% (n=22) of patients had testing ordered outside of UCI prior to their genetic counseling appointment. These patients may or may not have been tested again after meeting with a genetic counselor. A total of 10 patients (7%) pursued a re-test after meeting with a UCI genetic counselor. A total of 30% (n=45) of patients only received post-test counseling from a UCI genetic counselor. Only 6% (n=9) had pre-test counseling only. The majority of patients received both pre- and post-test counseling at UCI (63.8%, n=95).

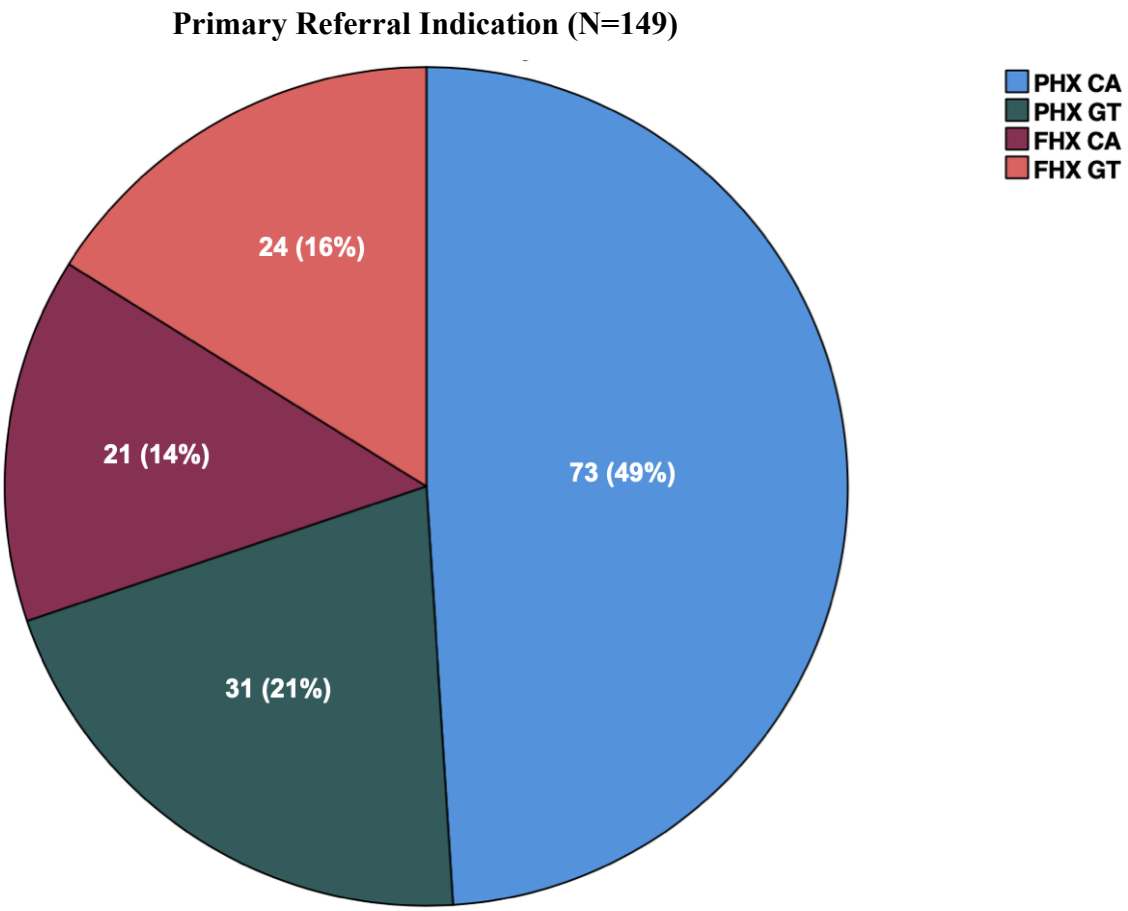

Figure 7. Distribution of patients' primary referral indication. N=149 patients with one of four primary referral indications based on history of cancer and/or genetic testing. PHX: Personal History, FHX: Family History, CA: Cancer, GT: Genetic Testing

3.2 Univariate Analysis of Predictors for Uptake of Recommendations

3.2.1 Uptake of Referral to Specialists

In total, 76 patients in this study were referred to a non-genetics specialist, for a total of 111 referrals (Figure 8). Patients were recorded to have seen all, any (for 2 referrals), or none of the referred non-genetics specialists at UC Irvine. Approximately 28% (n=41) of patients were referred to at least one specialist. Four of the patients from this group did not have records available to review (NA). Ultimately, 63% (n=26) of patients referred to one specialist were able to see that specialist, while 27% (n=11) did not see their recommended specialist. Of note, 24% of patients were referred to two different specialists.

For patients referred to two specialists, 65% (n=23) saw both specialists, 17% (n=6) saw, one specialist, and 14% (n=5) did not reach any recommended UCI specialist according to available records. It is possible that patients for whom we did not have documentation of a visit to their referred specialist actually did follow up with an outside provider not at UCI.

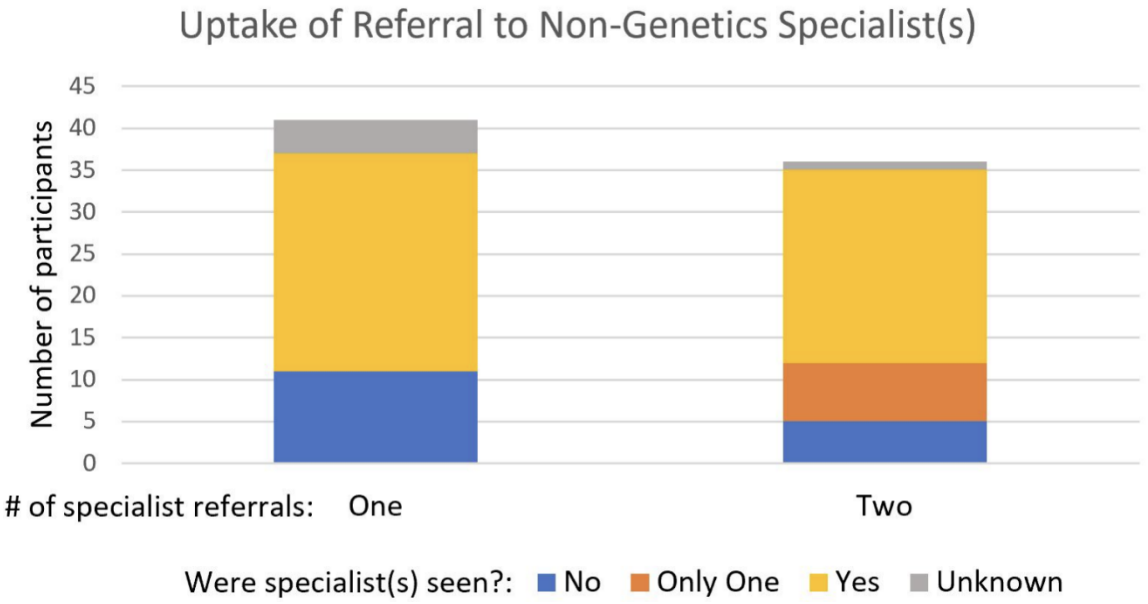

Figure 8. Uptake of referral to non-genetics specialist(s) N=76 patients who were referred to either 1 or 2 non-genetics specialist(s), recorded as having visited No specialists, Only One specialist, or Yes (all specialists to whom they were referred). Total referrals n=111. Some records of visit to referred specialist were not available (Unknown).

3.2.2 **Predictors for Uptake of Screening Recommendations**

In total, 130 (87.2%) of individuals in this study received screening recommendations from a genetic counselor (Figure 9A). For records available (patients continuing care at UCI after genetics appointment), 73% (n=96) of patients were able to complete some degree of screening, while 12% (n=16) did not have documentation of any screening (Figure 9B). A total of 14% (n=18) of patients recommended for screening did not continue care at UCI, and did not have further records available to review.

Patients who successfully completed any recommended screening and those who failed to complete screening were compared based on their demographic and clinical characteristics using Fisher's exact tests (2-sided) and Chi-Square tests for association when Fisher's exact tests could not be completed due to insufficient computational ability. Overall, most selected patient and family health history factors and visit factors were not determined to be significant for predicting whether or not an individual would complete screening (Table 5A).

The outcome of these analyses may be confounded by missing data from the significant number of patient records (n=22, 14%) that were unavailable for review due to discontinued care at UCI. Evaluated factors remained insignificant and did not become predictors for screening behavior when analyses were run without inclusion of missing charts.

There was not a significant difference between the number of males and females who completed or did not complete recommended screening (p=0.491) (Table 5A). Within both sexes, most patients were able to complete screening (Female n=69 (75.8%); Male n=27 (69%)).

Patients under age 50 successfully completed the recommended screening nearly 76% of the time, while those age 50 and over completed screening 69% of the time, the difference between which was not significant (p=0.767). A slightly higher proportion of age ≥50 individuals (14%,

n=11), were able to complete screening than those age <50 (10%, n=5). Both age groups had a similar proportion of unavailable records, (<50: n=7 (14%); ≥50: n=11 (14%)).

Ultimately, patient ancestry was not a significant predictor for completion of screening (p=0.301) (Table 5A). For each chosen ancestral group, patients were more likely to complete screening than not. Individuals marking "Other" ancestry demonstrated the highest rate of missed screening, while White were the least likely to miss screening (8%, 5) when records were available. For only the Black/African American group, the number of charts unavailable (67%, 2) exceeded the number available to review (33%, 1), which yielded no missed screenings. The Asian group had the fewest unavailable charts (5%, 1), while White (14%, 9), Hispanic/Latino (13%, 2) and Other (13%, 2) groups had similar rates of unavailable charts.

The range of cancer indications amongst this patient cohort did not appear to be associated with screening recommendations, although the number of categories was too large to allow a statistical comparison in this small data set (Table 5B). All individuals in the following groups were fully compliant for recommended screening (100%): Benign Tumor, Breast+Ovarian, CRC+Ovarian, Pancreas, Pancreas+Skin, Polyps, and Uterine. All records were available to review for screening compliance for individuals diagnosed with Benign Tumor, Breast+Ovarian, CRC+Ovariant, Ovarian, Pancreas, Pancreas+Skin, Polyps, Skin, Uterine, and Other cancers.

There also did not appear to be a difference in screening uptake across the wide range of hereditary cancer syndromes represented in this data set, although again the number of categories was too large to allow a statistical comparison (Table 5B). For major syndromes HBOC (60%, 21) and Lynch (78%, 25) over 50% of recommended patient completed recommended screening, when results were available. This was also true for the third largest group of Moderate-risk Breast (70%, 19). Records were available to review for all patients with the following molecular

diagnoses: FAMM, FAP, Li Fraumeni, MAP carrier, Peutz-Jeghers, and VHL. At least 5 individuals were diagnosed with these syndromes, and all patients (except those with FAMM), were able to complete their recommended screening. All records were available for "Other" syndromes, where all individuals but 1 were able to complete screening (92.9%, 3). One individual with a FAP-causing mutation in *APC* was able to complete screening, while 60% of individuals with the low-risk p.I1307K mutation.

Patients' genetic test result and its consistency with their family and/or personal history was not a predictor for their screening uptake (p=0.752), as compliance was high across all groups regardless of consistency (Table 5B). The number of relatives with cancer was not a predictor for patients' compliance with screening (p=0.673). For all groups, the majority of patients had screening (Table 5C). A sizable number of records were unavailable for each group. Similarly, whether or not a patient has children did not predict whether screening was completed (p=0.353) (Table 5C). In both groups, the majority of patients were able to complete screening.

When a family mutation was known, 77% (n=27) of patients were able to complete the recommended screening (Table 5C). The rate of screening for those without a familial variant was comparable at 73% (n=69). A similar distribution for unsuccessful screening and unavailable charts was found between each group. Knowledge of familial mutation was not a conclusive predictor for screening compliance (p=0.901). Limited family history was not a predictor for low screening compliance when compared to sufficient family history (p=0.158) (Table 5C). Over half of patients in either group were able to complete screening.

Of the four possible primary referral indications, screening compliance was highest within the "FHx Cancer" group, in which all individuals were able to complete screening, for available records (89%, n=16) (Table 5D). The screening rate for the most common primary indication,

"PHx Cancer", had a screening rate of 72% (n=46). The majority of individuals with a known familial variant were able to complete screening (85%, 17). This was also true of those who previously had genetic testing themselves (61%, 17). Overall, there was not a significant difference in screening between referral indications ($p<0.284$).

The majority of patients who-self referred to genetic counseling completed screening (68%, n=15) (Table 5D). Similarly, those who were referred by a provider were able to screen at a rate of 68% (n=15). Ultimately, referral source was not a predictor for whether or not a patient would follow through with screening ($p=0.491$). There was no significant difference in screening uptake between patients who were or were not new patients at UCI establishing care for genetics ($p=0.216$) (Table 5D). Screening uptake was comparable between the groups when records were available.

There seemed to be a significant difference between those who had testing ordered or completed outside of UCI and those whose testing was initiated at UCI ($p=0.002$) (Table 5D). Patients whose testing was initiated at UCI had a higher documented screening uptake (78%, n=86) than those with previously ordered tests (50%, n=10) (Figure 10A, 10B). Additionally, those who had testing initiated externally had a higher rate of unavailable records to review for uptake of screening (40%, n=8). The apparent difference in screening uptake may be primarily due to the higher rate of unavailable records to review post-counseling screening behaviors, for those who had testing ordered or completed outside of UCI. Patients who pursued additional testing after meeting with a genetic counselor were not more likely to have completed screening than those who had testing for the first time at UCI ($p=0.836$) (Table 5D).

There was a nearly significant difference ($p=0.052$) in screening compliance between those who received only post-test counseling (62%, n=26) and those who had both pre- and post-test

counseling (75%, n=91) (Table 5D) (Figure 11A, 11B). We did not have documentation for whether a patient had pre-test counseling outside of UCI.

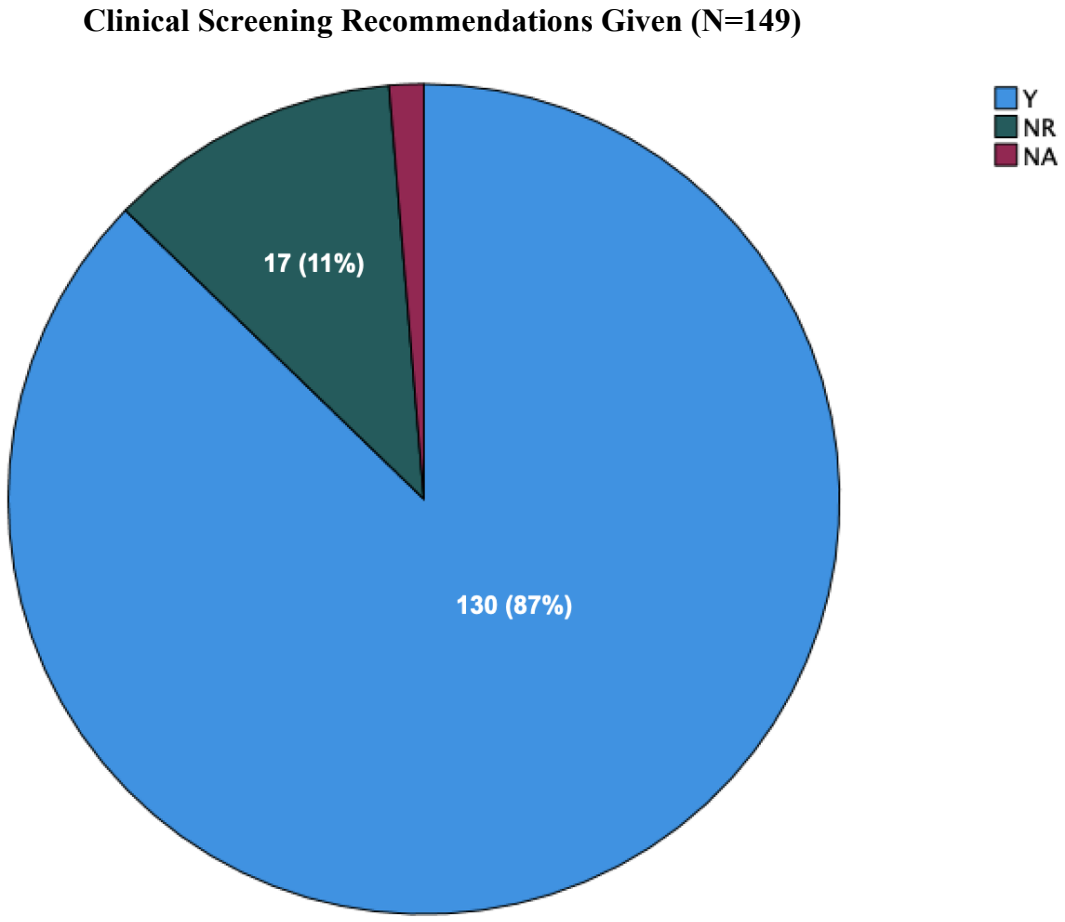

Figure 9A. Number of patients given clinical screening recommendations N=149 for patients who were either given (Y) or not given (NR) specific clinical screening recommendations by a genetic counselor based on their genetic test result. NA: Not Available

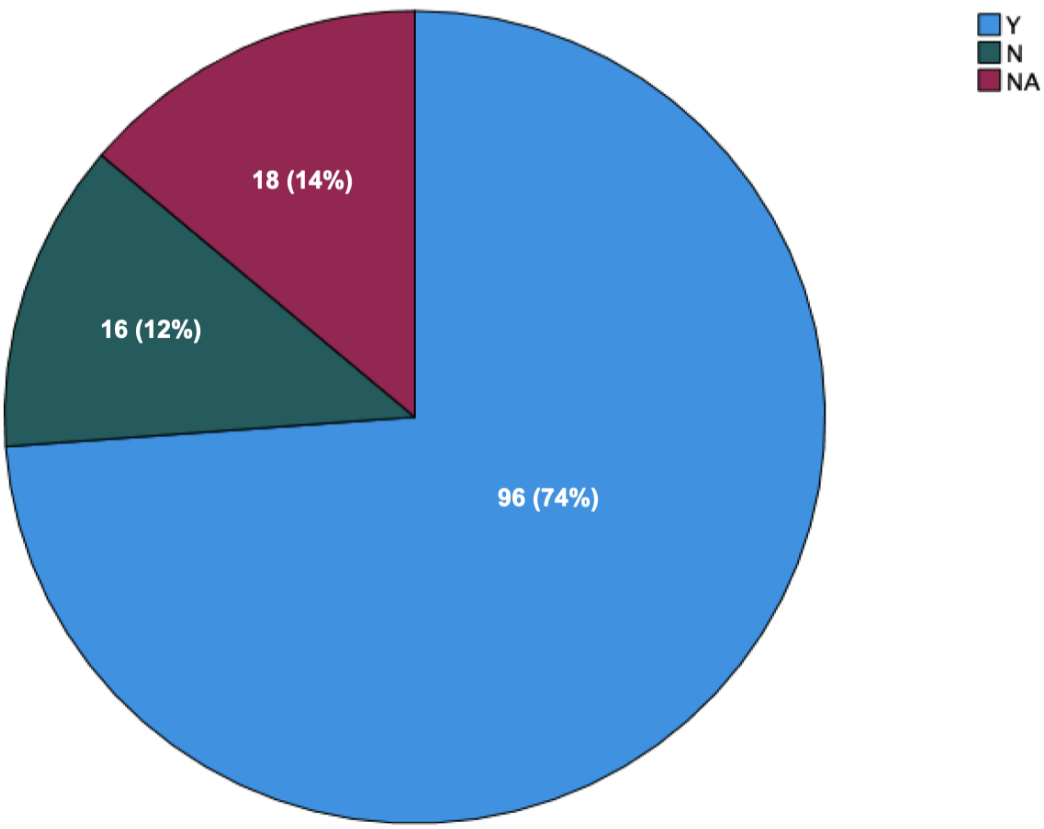

Figure 9B. Uptake of clinical screening recommendations following genetic counseling. N=130 for patients determined to have completed genetic counselors' clinical screening recommendations (Y), or not have documentation of screening uptake though they continued care at UCI after their genetic counseling appointment (N). Those who did not continue care and had no documentation of screening at UCI were marked as NA (Not Available).

Table 5A. Frequencies of Screening Uptake by Patient Demographics

Predictor	SCREENING PERFORMED			Total N (%)
	Y N(%)	N N(%)	NA N(%)	
Total	96 (74%)	16 (12%)	18 (14%)	130 (100%)
Patient Demographics				
Sex				*2 d.f., p=0.491*
Female	69 (76%)	9 (10%)	13 (14%)	91 (70%)
Male	27 (69%)	7 (18%)	13 (13%)	39 (30%)
Age at Report (years)				*2 d.f., p=0.767*
<50	39 (76%)	5 (10%)	7 (14%)	51 (39%)
50/+	57 (72%)	11 (14%)	11 (14%)	79 (61%)
Ancestry				*10 d.f., p=0.301*
Ashkenazi	8 (66%)	2 (17%)	2 (17%)	12 (9%)
Asian	15 (75%)	4 (20%)	1 (5%)	20 (15%)
Black/African-American	1 (33%)	0 (0%)	2 (67%)	3 (2%)
Hispanic/Latino	11 (74%)	2 (13%)	2 (13%)	15 (12%)
White	51 (78%)	5 (8%)	9 (14%)	65 (50%)
Other	10 (67%)	3 (20%)	2 (13%)	15 (12%)

Table 5B. Frequencies of Screening Uptake by Patient Health History

Predictor	SCREENING PERFORMED			Total N (%)
	Y N(%)	N N(%)	NA N(%)	
Total	96 (74%)	16 (12%)	18 (14%)	130 (100%)
Patient Health History				
Cancer Diagnosis				
Benign Tumor	3 (100%)	0%	0%	3 (2%)
Breast	9 (50%)	2 (11%)	7 (39%)	18 (13%)
Breast + Ovarian	1 (100%)	0%	0%	1 (1%)
CRC	8 (62%)	3 (23%)	2 (15%)	13 (10%)
CRC + Ovarian	1 (100%)	0%	0%	1 (1%)
CRC + Uterine	0%	0%	1 (100%)	1 (1%)
GU	10 (77%)	2 (15%)	1 (8%)	13 (10%)
Ovarian	10 (91%)	1 (10%)	0%	11 (9%)
Pancreas	2 (100%)	0%	0%	2 (2%)
Pancreas + Skin	1 (100%)	0%	0%	1 (1%)
Polyps	4 (100%)	0%	0%	4 (3%)
Skin	8 (80%)	2 (20%)	0%	10 (8%)
Uterine	3 (100%)	0%	0%	3 (2%)
Other	6 (75%)	2 (25%)	0%	8 (6%)
None	30 (73%)	4 (10%)	7 (17%)	41 (31%)
Syndrome				
APC None	3 (60%)	2 (40%)	0%	5 (4%)
Moderate breast (*ATM, CHEK2*)	19 (70%)	4 (15%)	4 (15%)	27 (21%)
Cowden	1 (50%)	0%	1 (50%)	2 (1%)
FAMM	3 (75%)	1 (25%)	0%	4 (3%)
FAP	1 (100%)	0%	0%	1 (1%)
HBOC	21 (60%)	5 (14%)	9 (26%)	35 (27%)
Li-Fraumeni	1 (100%)	0%	0%	1 (1%)
Lynch	25 (77%)	3 (10%)	4 (13%)	32 (25%)
MAP Carrier	5 (100%)	0%	0%	5 (4%)
Peutz-Jeghers	2 (100%)	0%	0%	2 (1%)
VHL	2 (100%)	0%	0%	2 (1%)
Other	13 (93%)	1 (7%)	0%	14 (11%)
Result Consistent with Clinical History				*6 d.f., p=0.752*
Personal History	19 (76%)	2 (8%)	4 (16%)	25 (19%)

Family History	33 (72%)	6 (13%)	6 (13%)	45 (35%)
Both	25 (69%)	4 (12%)	7 (19%)	36 (28%)
Neither	19 (79%)	4 (17%)	1 (4%)	24 (18%)

CRC: Colorectal Cancer, GU: Genitourinary

FAMM: Familial Atypical Multiple Mole Melanoma syndrome, FAP: Familial Adenomatous Polyposis syndrome, HBOC: Hereditary Breast and Ovarian Cancer syndrome, MAP: *MUTYH*-associated Adenomatous Polyposis syndrome, VHL: Von Hippel-Lindau syndrome

Table 5C. Frequencies of Screening Uptake by Patient Family History

Predictor	SCREENING PERFORMED			Total N (%)
	Y N(%)	N N(%)	NA N(%)	
Total	96 (74%)	16 (12%)	18 (14%)	130 (100%)
Family History				
Number of Relatives with Cancer				*4 d.f., p=0.673*
0-1	10 (59%)	3 (18%)	4 (24%)	17
2-5	58 (76%)	9 (12%)	9 (12%)	76
6+	28 (76%)	4 (11%)	5 (14%)	37
Any Children				*3 d.f., p=0.353*
Yes	69 (78%)	10 (11%)	10 (11%)	89 (68%)
No	27 (65%)	6 (15%)	8 (20%)	41 (32%)
Known Family Mutation				*2 d.f., p=0.901*
Yes	27 (77.1%)	4 (11.4%)	4 (11.4%)	27%
No	69 (72.6%)	12 (12.6%)	14 (14.7%)	73%
Limited Family History				*2 d.f., p=0.158*
Yes	12 (60%)	5 (25%)	3 (15%)	20 (15%)
No	84 (76%)	11 (10%)	15 (14%)	110 (85%)

Table 5D. Frequencies of Screening Uptake by Patient Visit Details

Predictor	SCREENING PERFORMED			Total N (%)
	Y N(%)	N N(%)	NA N(%)	
Total	96 (74%)	16 (12%)	18 (14%)	130 (100%)
Visit Details				
Primary Referral Indication				*6 d.f., p=0.284*
Personal History of Cancer	46 (71%)	8 (13%)	10 (16%)	64 (49%)
Personal History of Genetic Testing	17 (61%)	6 (21%)	5 (18%)	28 (22%)
Family History of Cancer	16 (89%)	0%	2 (11%)	18 (14%)
Family History of Genetic Testing	17 (85%)	2 (10%)	1 (5%)	20 (15%)
Referral Source				*6 d.f., p=0.284*
Self-Referred	15 (68%)	2 (9%)	5 (23%)	22 (17%)
Provider	79 (75%)	13 (13)%	12 (12%)	104 (80%)
NA	2 (50%)	1 (25%)	1 (25%)	4 (3%)
New to UCI				*6 d.f., p=0.284*
Yes	38 (73%)	4 (8%)	10 (19%)	52 (40%)
No	58 (75%)	12 (15%)	8 (10%)	78 (60%)
Tested Before UCI				*2 d.f., p=0.002,*
Yes	10 (50%)	2 (10%)	8 (40%)	20 (15%)
No	86 (79%)	14 (12%)	10 (9%)	110 (85%)
Re-Tested at UCI				*1 d.f., p=0.836*
Yes	5 (62%)	1 (13%)	2 (25%)	8 (6%)
No	91 (75%)	15 (12%)	16 (13%)	122 94%)
Post-Test Counseling Only				*2 d.f., p=0.052*
Yes	26 (62%)	6 (14%)	10 (24%)	42 (32%)
No	70 (80%)	10 (11%)	8 (9%)	88 (68%)

Clinical Screening Uptake by Patients Tested Before UCI (N=20)

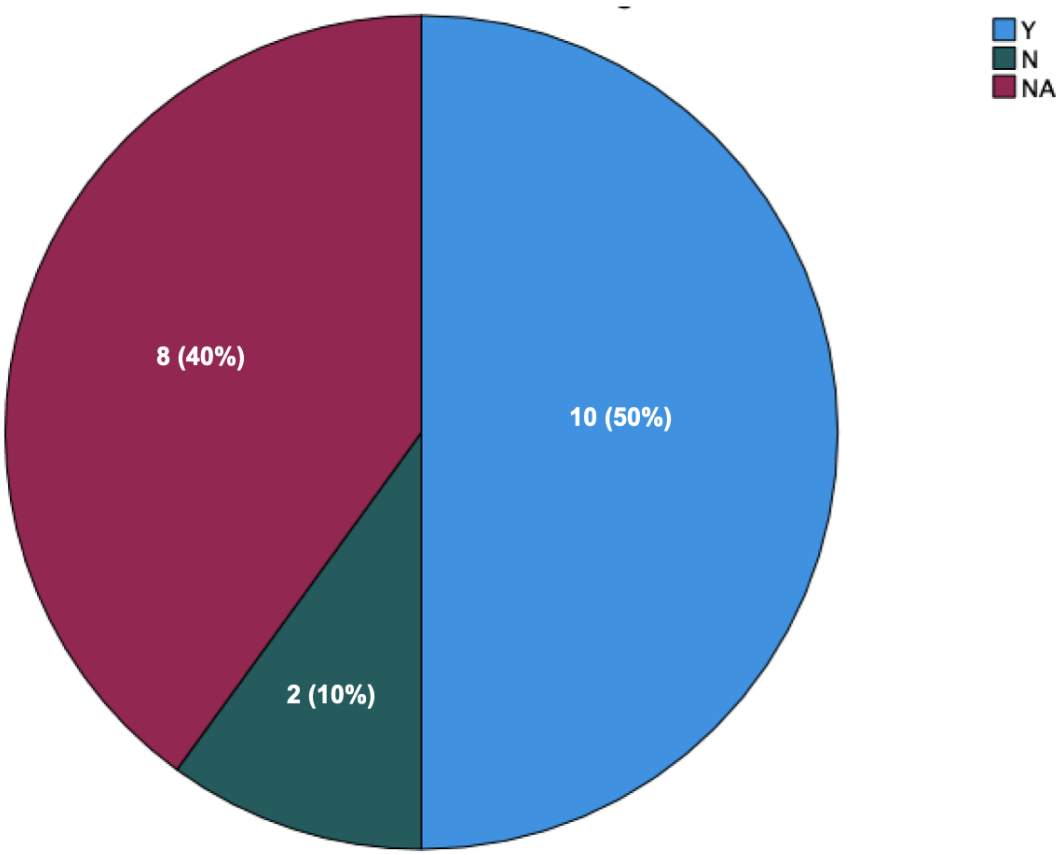

Figure 10A. Clinical screening uptake by patients with genetic testing ordered prior to UCI genetic counseling N=20 patients who had testing initiated outside of UCI before their genetic counseling appointment who either did (Y) or did not (N) complete screening. NA: Not Available

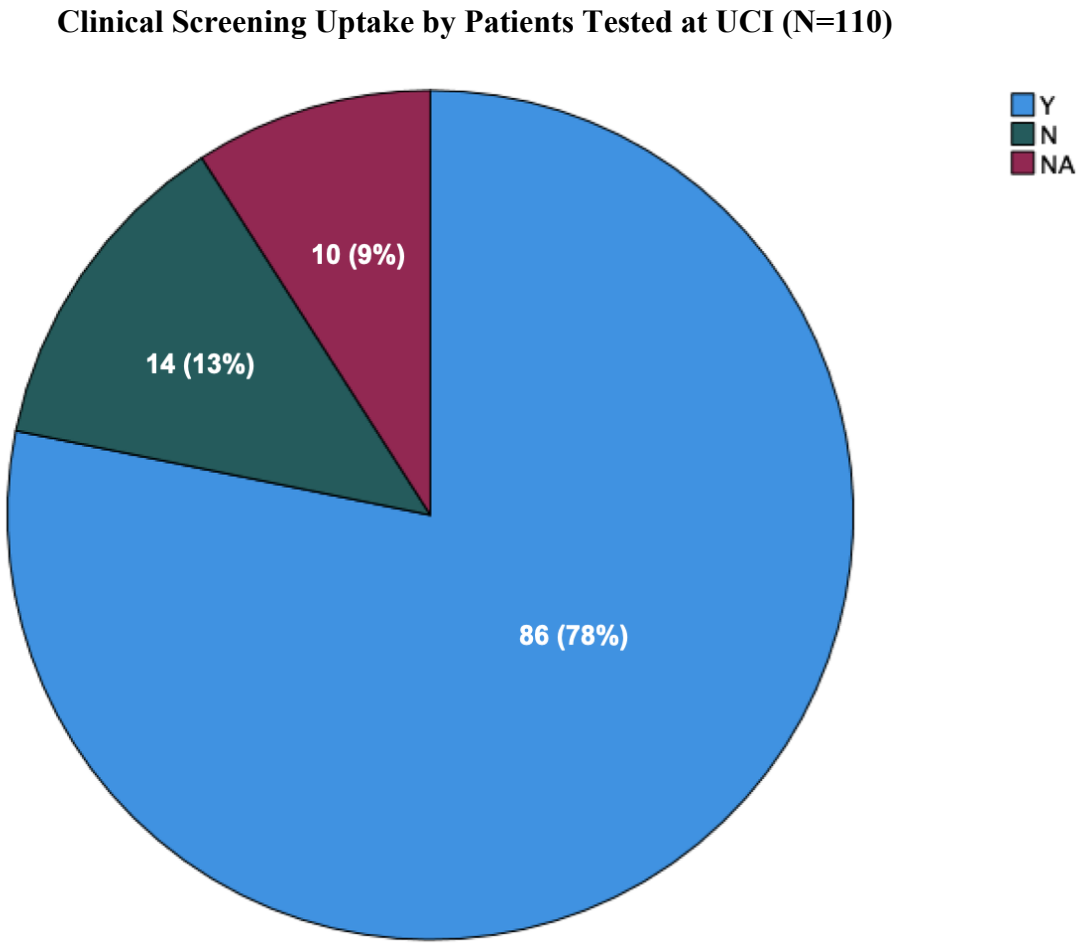

Figure 10B. Clinical screening uptake by patients with genetic testing ordered after UCI genetic counseling N=110 patients who had testing at UCI after their genetic counseling appointment who either did (Y) or did not (N) complete screening. NA: Not Available

Clinical Screening Uptake by Patients with Only Post-Test Counseling (N=42)

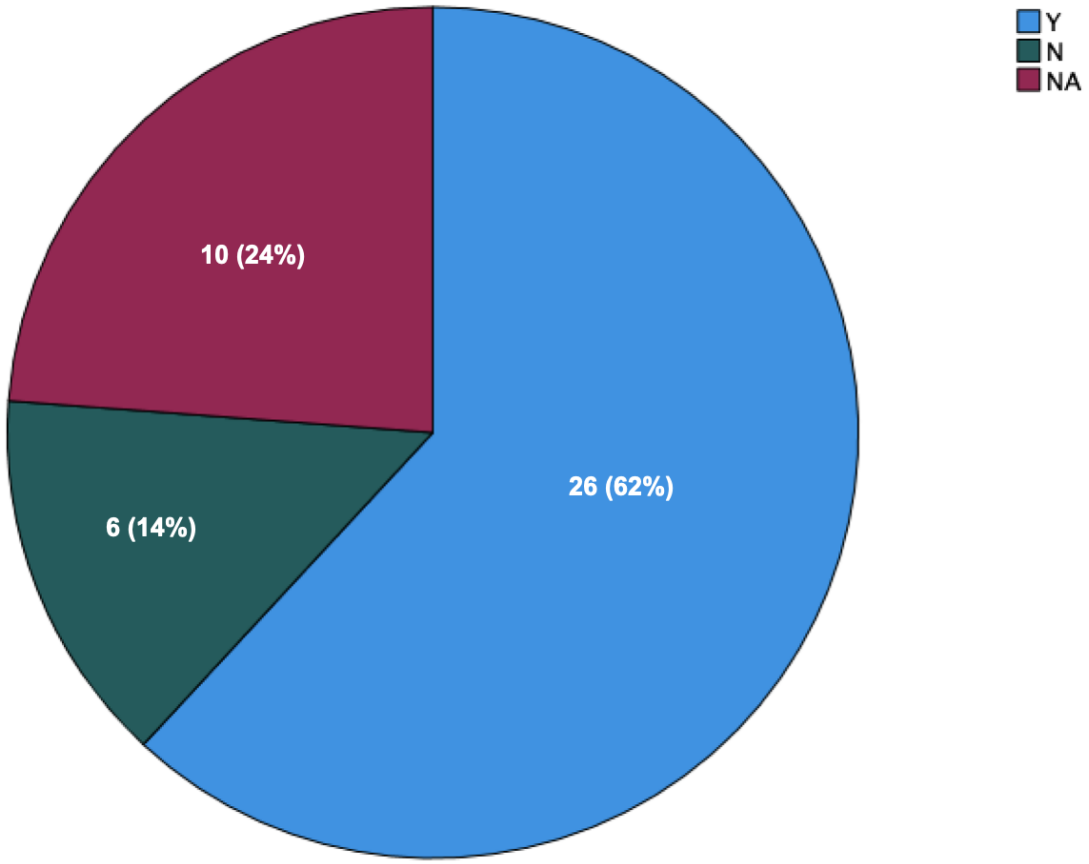

Figure 11A. Clinical screening uptake by patients receiving post-test genetic counseling only Patients who had only post-test genetic counseling at UCI (N=42) either did (Y) or did not (N) complete recommended clinical screening. NA: Not Available

Clinical Screening Uptake by Patients with Pre-Test Counseling with/without Post-Test Counseling (N=88)

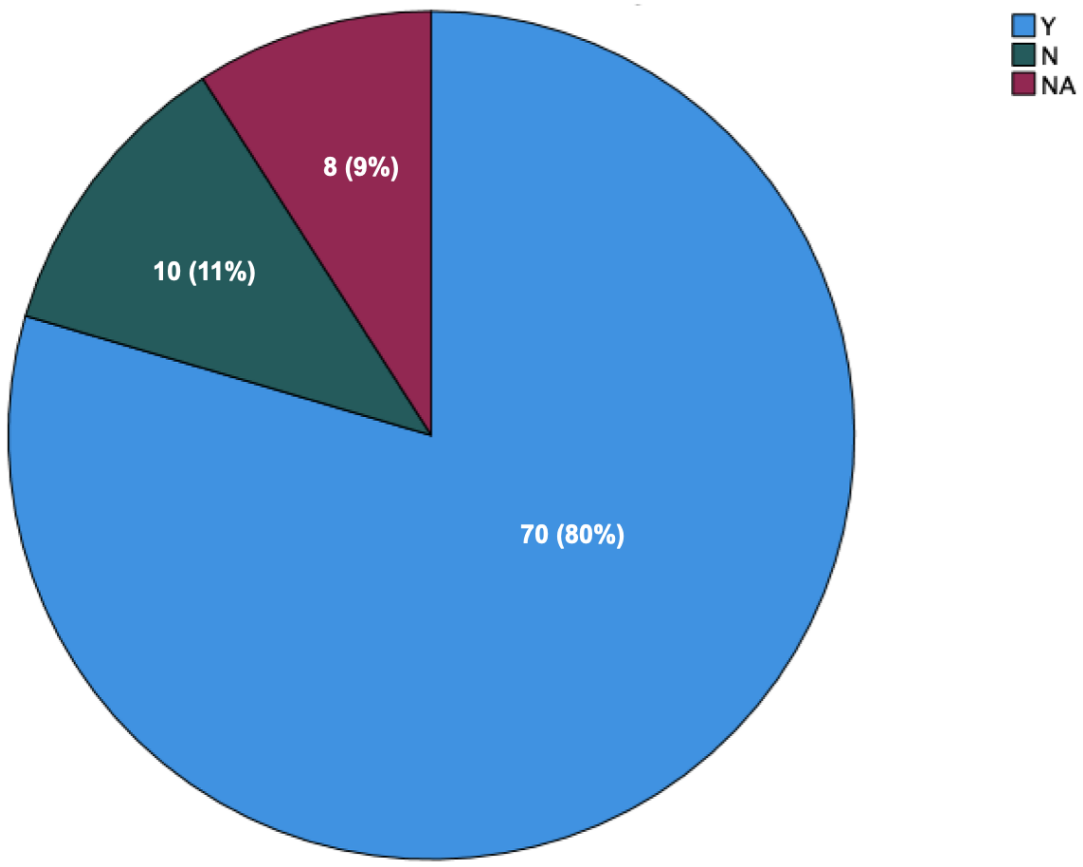

Figure 11B. Clinical screening uptake by patients Receiving pre- and post-test genetic counseling, or only post-test counseling N=88 patients who had pre-test genetic counseling at UCI (either with or without post-test counseling) either did (Y) or did not (N) complete recommended clinical screening. NA: Not Available

3.2.3 Predictors for Uptake of Surgical Intervention

A total of 55 (37%) individuals had a documented discussion with their genetic counselor about possible surgical interventions based on their genetic test result (Figure 12A). Not every patient in this group was an eligible candidate for surgery, as described in Discussion, but still received counseling that surgery is an option that is discussed based on their result. These patients may have also had additional screening recommendations.

Of these 55 individuals, 16 (29%) had already had an appropriate surgery performed prior to post-test genetic counseling and had no further surgical options available. Analyses were performed for the 39 (71%) individuals receiving surgery recommendations who had never had a relevant surgery before counseling. 36% (n=14) of those receiving discussion ultimately chose surgery for risk management (Figure 12B).. Additionally, 44% (n=17) did not undergo surgery, and 21% (n=8) of this group did not have further records available for review.

The outcome of these analyses may be confounded by missing data from the significant number of patient records that were unavailable for review due to discontinued care at UCI. Evaluated factors remained insignificant and did not become predictors for screening when analyses were run without inclusion of missing charts.

Female patients comprised the majority of this group (97%, n=38). Approximately 37% (n=14) of females chose surgical intervention, while 42% (n=16) did not (Table 6A). Sex could not be evaluated as a possible predictor for uptake of surgery, because there was only one male who had surgical discussion as part of counseling. The one male (3%) who had surgical discussion for his CHEK2 mutation ultimately did not pursue surgery (p=1.0). A significant difference was not found between the under and over 50 age group for uptake of surgery after discussion (p=0.595). An equal number of patients were found in each age category (<50: 37%, n=7; ≥50: 35.0%, n=7).

Ancestry was not a significant predictor for uptake of surgical intervention (p=0.900). The largest group, White, had a screening uptake of 31% (n=5). The Asian group had the highest relative uptake at 33.3% (n=2). For each group, there was a sizable proportion of unavailable records. For Asian, Hispanic/Latino, and White groups, an equal number of records were available and unavailable. The smallest group, Black/African-American (n=1), had no records available.

Diagnosis of cancer was not a major predictor for choice of surgery, as the significance was just over p=0.05 (p=0.056) (Table 6B). Interestingly, individuals with two cancer diagnoses included for analyses did not have a surgical discussion. Of all groups, the largest was of those never diagnosed with cancer, for which 29.4% (n=5) did pursue surgery and 41.2% (n=7) did not. The largest group of individuals diagnosed with cancer were those with Breast cancer, only 12.5% (1) of which pursued surgery. Records were available for review for all cancer groups except for Breast (37.5%, 3) and None (29.4%, 5).

A significant difference in uptake between patients' hereditary cancer syndromes was not found (p=0.334). However, there was limited power to detect differences between subgroups, given the small sample size. Individuals in the largest syndrome group, HBOC, were found to pursue surgery 33% (n=7) of the time, while 38% (n=8) did not. Similarly, for patients with mutations in the moderate-risk breast cancer gene *CHEK2*, a comparable uptake of surgery was found (33%, n=2). The proportion of individuals not pursuing surgery was greater than those who did, for both these groups. The other most prominent group, Lynch syndrome, saw a 67% (n=2) rate of surgery uptake, while only one person declined surgery (33%, n=1).

Analyzing consistency between the patient's genetic test result and their reported personal and family health history did not yield a significant difference in surgery uptake (p=0.390). The

majority of patients with a personal cancer history completed surgery (66.8%, n=4), while an equal proportion of patients did not get surgery, or had unavailable records (n=1, 16.7%). Interestingly, most patients with only a family history did not pursue screening (n=9, 56.3%). Half of patients with both a consistent personal and family history ultimately underwent surgery (50%, n=4). Patients with neither a personal nor a familial history did not pursue testing (56%, n=5) as often as others did (33%, n=3).

A trend was not found for surgical uptake with greater number of affected relatives (p=0.353) (Table 6C). For patients with 2-5 relatives with cancer, 29.2% (n=7) pursued surgery and 54.2% (n=13) declined surgery. The greatest proportion of declined surgery was also found in this group (54.2%, n=13). For patients with 6 or greater relatives, the uptake was 50% (n=5). Patients with 1 or no affected relative had an uptake of 40% (n=2). Whether or not a patient had any living children was not a significant predictor for the decision of surgical intervention (p=0.420). Those who did have children pursued surgery 42.3% (n=11) of the time, while those without did so 23.1% (n=3) of the time.

Patients pursued surgery at a statistically similar rate regardless of their prior knowledge of a familial mutation (p=0.420). When patients had a previously detected familial variant, 60% (n=12) pursued surgery. Similarly, patients who did not have this information pursued surgery 76.4% (=84) of the time. Complete knowledge of family history did not make a significant difference to uptake of surgery (p=0.582). Those with complete knowledge pursued surgery at a rate of 50% (n=5), while those who had incomplete history did so at 31% (n=9).

Referral indication was not a major predictor for a patient's likelihood to complete surgery after discussion with a genetic counselor (p=0.219) (Table 6D). Those with a personal history of cancer (47.4%, n=9) sought out surgery at a rate slightly higher than those with only a family

history (40%, n=2). Patients who had a previously detected variant were more likely to have surgery (16.7%, n=1) than those with a known family variant but unknown personal status (22%, n=2). Individuals who self-referred were not more likely to pursue testing than those referred by a provider (p=0.219). In fact, self-referred patients sought (33%, n=3) and declined surgery at a similar rate (33%, n=3).

A significant difference in surgery uptake was not found between patients who were new UCI patients and those continuing previously established care (p=0.154). Interestingly, those who were newly established UCI patients at their genetics visit had a higher rate of surgery (50.0%, n=9) than those who were not (23.8%, n=5), although this was not a statistically significant difference. An equal number of charts (n=4) were unavailable for both groups.

There was a suggested association between a patient's test ordered outside of UCI prior to their genetics visit and their likelihood to complete surgery (p=0.040) (Table 6D). Those coming into genetics with testing completed were found to have 38% (n=3) uptake of surgery, while 36% (n=11) of those initiating testing at UCI (most of this sample) pursued surgery (Figure 13A, 13B). The main factor underlying the significant association for this variable may be that there was a larger proportion for whom records were unavailable to review among those who came to genetics with testing completed (unavailable records for 50%, n=4) in comparison to those who had testing ordered following genetic counseling at UCI (unavailable records for 13%, n=4)

Amongst patients who had previously had genetic testing prior to their UCI genetics visit, there was no significant difference between those who did or did not pursue a re-test (p=0.564). Only one individual who chose to be re-tested had a discussion of surgery, which they ultimately pursued. There was a 34% (n=13) uptake of surgery for patients who did not retest, and 45% (n=17) did not undergo surgery.

Patients were evaluated for uptake of surgery when they had only post-test counseling (23%, n=3) compared to those who had pre- and post-test counseling. (42%, n=11). A significant difference between the groups was not found (p=0.122).

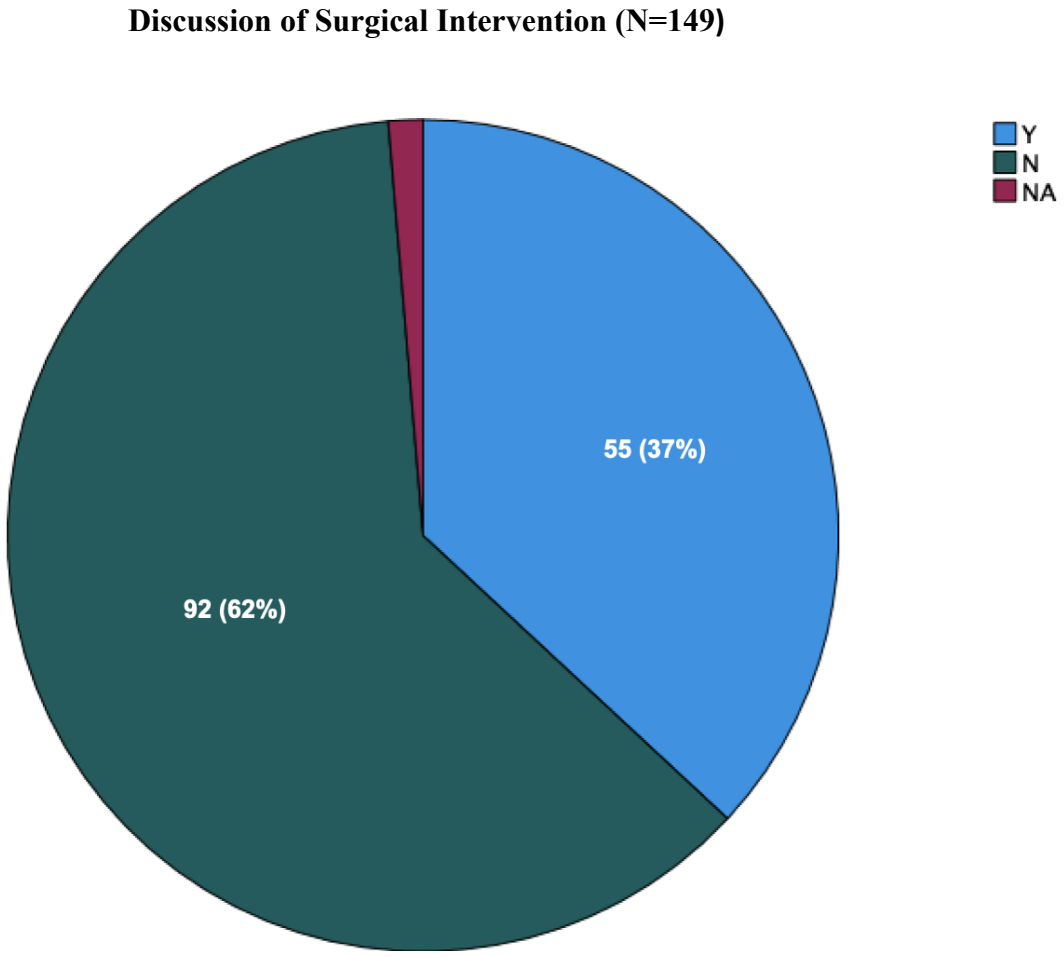

Figure 12A. Number of patients who discussed Surgery with a genetic counselor N=149 for patients who either did (Y) discuss possible surgical interventions relevant to their genetic test results or did not discuss surgery/discussed that surgery was not a risk management option for them (N). Those who did not have documentation of a surgery discussion were marked NA: Not Available.

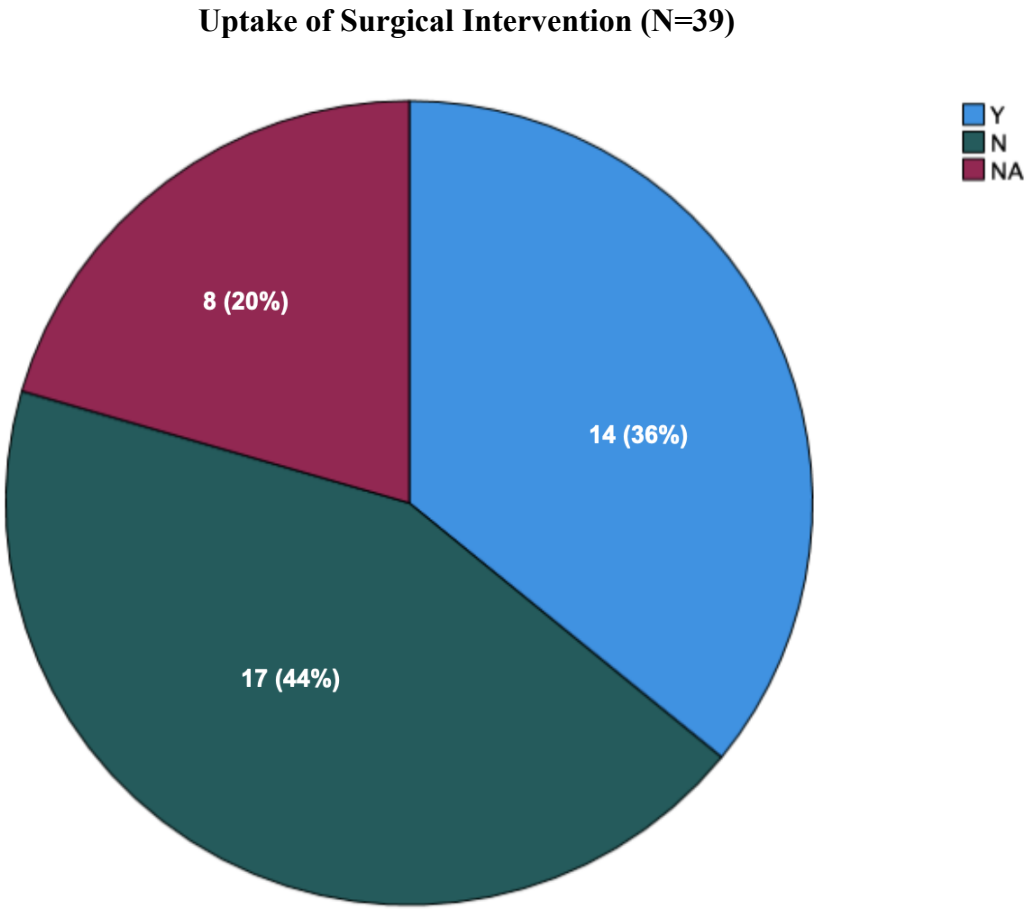

Figure 12B. Uptake of surgery by eligible patients who discussed surgery with a genetic counselor N=39 for patients who were eligible to pursue surgical intervention (as described in Methods). Patients who had already performed a relevant surgery prior to genetic counselors' recommendations were not included in this analysis.

Table 6A. Frequencies of Surgery Uptake by Patient Demographics

	SURGERY PERFORMED			
PREDICTOR	**Y N(%)**	**N N(%)**	**NA N(%)**	**Total N (%)**
Total	14 (35%)	17 (46%)	8 (19%)	39 (100%)
Patient Demographics				
Sex				*2 d.f., p=1.0*
Female	14 (36%)	16 (42%)	8 (22%)	38 (97%)
Male	0%	1 (100%)	0%	1 (3%)
Age at Report (Years)				*2 d.f., p=0.595*
<50	7 (37%)	7 (37%)	5 (26%)	19 (49%)
50/+	7 (35%)	10 (50%)	3 (15%)	20 (51%)
Ancestry				*10 d.f., p=0.900*
Ashkenazi	4 (50%)	3 (38%)	1 (12%)	8 (21%)
Asian	2 (34%)	3 (50%)	1 (16%)	6 (15%)
Black/African-American	0%	0%	1 (100%)	1 (3%)
Hispanic/Latino	1 (25%)	2 (50%)	1 (25%)	4 (10%)
White	5 (31%)	8 (50%)	3 (19%)	16 (41%)
Other	2 (50%)	1 (25%)	1 (25%)	4 (10%)

Table 6B. Frequencies of Surgery Uptake by Patient Health History

	SURGERY PERFORMED			
PREDICTOR	**Y N(%)**	**N N(%)**	**NA N(%)**	**Total N (%)**
Total	14 (35%)	17 (46%)	8 (19%)	39 (100%)
Patient Health History				
Cancer Diagnosis				*14 d.f., p=0.056*
Breast	1 (12.5%)	4 (50%)	3 (37.5%)	8 (20%)
CRC	2 (100%)	0%	0%	2 (5%)
GU	0%	1 (100%)	0%	1 (3%)
Ovarian	5 (84%)	1 (16%)	0%	6 (15%)
Polyps	1 (100%)	0%	0%	1 (3%)
Skin	0%	1 (100%)	0%	1 (3%)
Other	0%	3 (100%)	0%	3 (8%)
None	5 (29%)	7 (41%)	5 (30%)	17 (43%)
Syndrome				*14 d.f., p=0.334*
APC None	0%	0%	4 (100%)	4 (10%)
Moderate breast (*CHEK2* only)	2 (33%)	3 (50%)	1 (17%)	6 (15%)
Cowden	0%	0%	1 (100%)	1 (3%)
FAP	1 (100%)	0%	0%	1 (3%)
HBOC	7 (33%)	8 (38%)	6 (29%)	21 (53%)
Lynch	2 (67%)	1 (33%)	0%	3 (8%)
MAP carrier	1 (100%)	0%	0%	1 (3%)
Other	1 (50%)	1 (50%)	0%	2 (5%)
Result Consistent with Clinical History				*6 d.f., p=0.390*
Personal History	4 (66%)	1 (17%)	1 (17%)	6 (15%)
Family History	3 (19%)	9 (56%)	4 (25%)	16 (42%)
Both	4 (50%)	2 (25%)	2 (25%)	8 (20%)
Neither	3 (33%)	5 (56%)	1 (11%)	9 (23%)

CRC: Colorectal Cancer, GU: Genitourinary
FAP: Familial Adenomatous Polyposis syndrome, MAP: *MUTYH*-associated Adenomatous Polyposis syndrome, HBOC: Hereditary Breast and Ovarian Cancer syndrome

Table 6C. Frequencies of Surgery Uptake by Patient Family History

	SURGERY PERFORMED			
PREDICTOR	**Y N(%)**	**N N(%)**	**NA N(%)**	**Total N (%)**
Total	14 (35%)	17 (46%)	8 (19%)	39 (100%)
Family History				
Number of Relatives with Cancer				*4 d.f., p=0.497*
0-1	2 (40%)	1 (20%)	2 (40%)	5 (12%)
2-5	7 (30%)	13 (54%)	4 (16%)	24 (62%)
6+	5 (50%)	3 (30%)	2 (20%)	10 (26%)
Any Children				*2 d.f., p=0.420*
Yes	11 (42%)	11 (42%)	4 (15%)	26 (66%)
No	3 (23%)	6 (46%)	4 (31%)	13 (33%)
Family Mutation Known				*2 d.f., p=0.096*
Yes	1 (10%)	7 (70%)	2 (20%)	10 (26%)
No	13 (45%)	10 (34%)	6 (21%)	29 (74%)
Limited Family History				*2 d.f., p=0.582*
Yes	5 (50%)	3 (30%)	2 (20%)	10 (26%)
No	9 (31%)	14 (48%)	6 (21%)	29 (74%)

Table 6D. Frequencies of Surgery Uptake by Patient Visit Details

	SURGERY PERFORMED			
PREDICTOR	**Y N(%)**	**N N(%)**	**NA N(%)**	**Total N (%)**
Total	14 (35%)	17 (46%)	8 (19%)	39 (100%)
Visit Details				
Primary Referral Indication				*6 d.f., p=0.753*
Personal History of Cancer	9 (47%)	7 (37%)	3 (16%)	19 (44%)
Personal History of Genetic Testing	2 (22%)	4 (44%)	3 (33%)	9 (23%)
Family History of Cancer	2 (40%)	2 (40%)	1 (20%)	5 (13%)
Family History of Genetic Testing	1 (17%)	4 (66%)	1 (17%)	6 (15%)
Referral Source				*4 d.f., p=0.219*
Self-Referred	3 (33%)	3 (33%)	3 (33%)	9 (23%)
Provider	11 (38%)	14 (48%)	4 (14%)	29 (74%)
NA	0%	1 (100%)	0%	1 (3%)
New to UCI				*2 d.f., p=0.154*
Yes	9 (50%)	5 (28%)	4 (22%)	18 (46%)
No	5 (24%)	12 (57%)	4 (19%)	21 (54%)
Tested Before UCI				*2 d.f., p=0.040*
Yes	3 (38%)	1 (12%)	4 (50%)	8 (21%)
No	11 (36%)	16 (51%)	4 (13%)	31 (79%)
Re-Tested at UCI				*2 d.f., p=0.546*
Yes	1 (100%)	0%	0%	1 (3%)
No	13 (34%)	17 (45%)	8 (21%)	38 (97%)
Post-Test Counseling Only				*2 d.f., p=0.122*
Yes	3 (24%)	5 (38%)	5 (38%)	13 (33%)
No	11 (42%)	12 (46%)	3 (12%)	26 (67%)

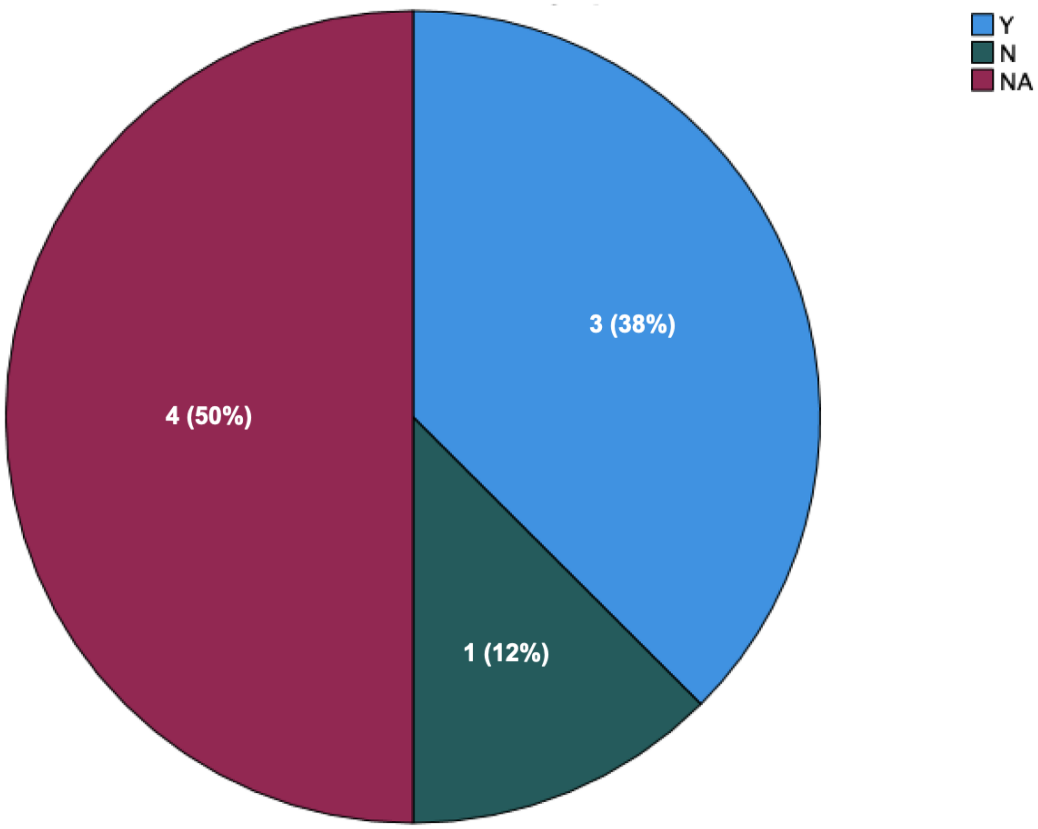

Figure 13A. Uptake of surgery by patients with genetic testing ordered prior to UCI genetic counseling Patients who had testing initiated outside of UCI (N=8) before their genetic counseling appointment, and either did (Y) or did not (N) pursue surgical intervention after genetic counseling

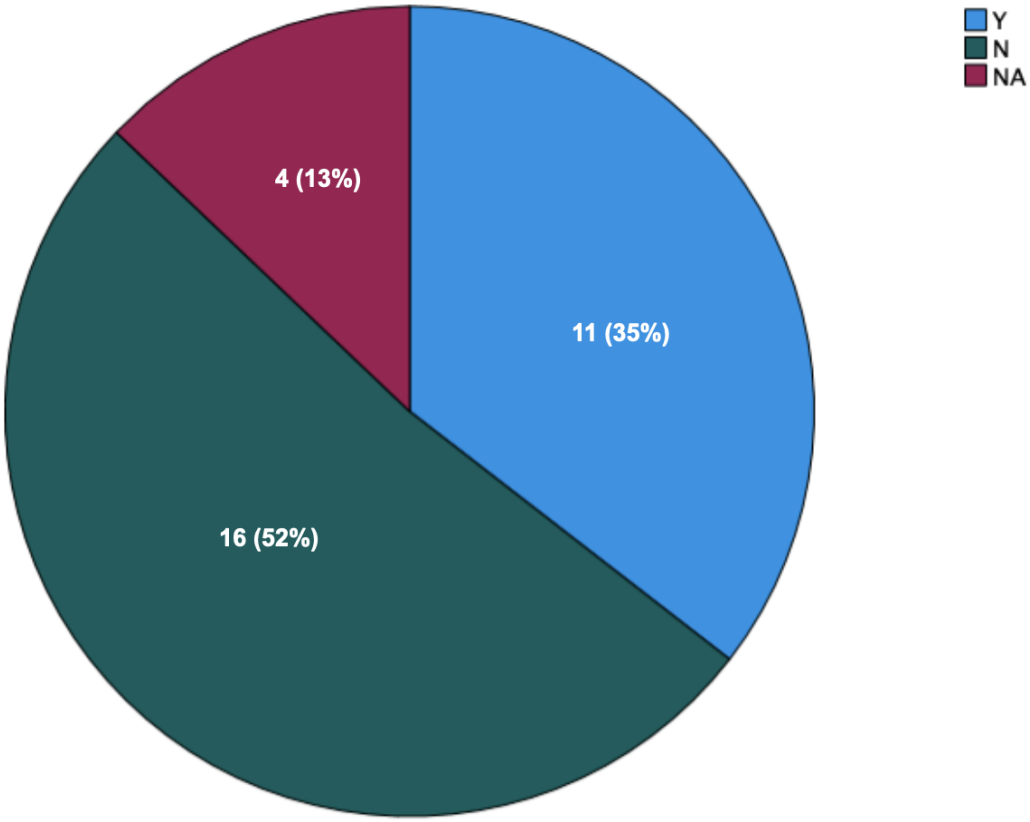

Figure 13B. Uptake of Surgery by Patients with Testing Ordered After UCI Genetic Counseling Patients who had testing initiated at UCI (N=31) after their genetic counseling appointment, and either did (Y) or did not (N) pursue surgical intervention after genetic counseling

CHAPTER 4: DISCUSSION

Discussion of risk management strategies is essential to genetic counseling for high-risk individuals harboring a pathogenic variant in a cancer-associated gene (Riley et. al, 2012). These individuals show a range of risk management behaviors after genetic counseling, influenced by various motivators and barriers. The utility of risk management as a means of early detection and prevention for high-risk mutation carriers lies in improved survival after cancer diagnosis and decreased mortality. Previous works have identified discrepancies in compliance with genetic counselors' recommendations between various patient demographics, personal health histories, and family histories (Schneider et. al, 2012). Cancer genetics clinics, especially those at well-resourced medical centers with comprehensive cancer care, can benefit from maintaining longitudinal documentation of mutation-positive patients' subsequent risk management after receiving positive genetic test results (Wagner et. al, 2005). This data can potentially inform targeted interventions and initiate systemic adjustments to improve uptake in patient groups with suboptimal compliance. Additionally, this can empower genetic counselors to redirect time and resources to patient high-risk groups needing special attention.

This study aimed to investigate the distribution of demographic, personal and family history, and clinical visits in mutation-positive patients at one medical center and identify any potential predictors for uptake of cancer genetic counselors' risk-management recommendation.

It is recognized that a patient with a negative or VUS genetic test result may still receive recommendations from a genetic counselor based on their personal and/or family history of cancer, as well as general population guidelines for cancer screening. This study was focused on mutation-positive patients who received clinical recommendations based on their specific pathogenic genetic result. Understanding long-term risk management behaviors for patients with

VUS results and genetic counseling recommendations will be a valuable area of future study. Further investigations can offer additional insight into differences in uptake between VUS and mutation-positive patients by comparing potential predictors for compliance.

4.1 Evaluation of completed referrals to specialist

In total, 76 patients in this study were referred to at least one non-genetics specialist, for a total of 111 referrals. Documentation for specialists seen was available for 71 (93.4%) of referred patients referred to either one or two patients. In total, 42% (n=32) of all referred patients were able to complete a consultation with at least one of the providers to which they were referred. The estimates presented in this study are conservative, as they are based on available records after genetic counseling recommendations were received. For patients with unavailable records, or patients who were identified as not having visited any referred UCI specialist, it is possible that they did continue risk management outside of UCI with a specialist of their choice. Thus, the non-compliance figures in this study are underestimates, limited to information available at UCI.

4.2 Evaluation of predictors for screening uptake

In total, 130 (87%) of individuals in this study received recommendations for screening to facilitate risk management (for example, imaging) from a genetic counselor, based on their identified P/VLP mutation and their personal or family history. From available documentation, screening uptake in this population was high, 96 of the 130 individuals (74%) who received screening recommendation did complete screening.

In this study sample, patients' sex, age at report, and ancestry did not significantly predict whether it would be more or less likely for a patient to complete at least one screening. This was also true of the collected patient health history (including cancer history and genetic status), family history, and visit details. Previously described trends in mutation carriers' screening

behavior were not reflected in this study. This small study sample, and limited number of available records for review, limits analysis for identifying strong predictors for screening. Thus, this study does not rule out the selected predictors for uptake of screening, and future investigations may reveal stronger predictors.

One outcome of univariate analysis identified a potentially significant relationships between patients' uptake of screening and whether they had testing initiated outside of UCI, where those who had outside testing seemingly had lower screening uptake than those who did not. A similar relationship was also suggested between screening uptake and whether patients had post-test counseling only or had both pre- and post- test counseling at UCI. The results suggested those who only had post-test counseling pursued screening at a lower rate. These findings, if real, would have important implications for patient care, and might suggest a differential approach to following up with patients in these groups to ensure they can access the recommended screening. However, another possible explanation for these findings is the high rate of unavailable records for one group. Of the 20 individuals who had testing initiated outside of UCI, 8 (40%) did not have available records to review with respect to whether they had followed up with screening. Of the 45 individuals who had post-test counseling only, 11 (24%) did not have available records. Hence, these factors may not be true predictors for screening behavior, but rather may be indicative of whether a patient continues their care at UCI after their post-test genetic counseling appointment.

This study did not consider patients' full extent of screening compliance. Compliance was recorded when at least one screening behavior was completed after post-test genetic counseling (e.g. one mammogram). As such, it was not recorded whether patients completed screening at the recommended time interval (e.g. annual mammogram). Further, if patients were recommended to

have two different screening types, it was not recorded whether only one or both types were performed (e.g. colonoscopy and/or transvaginal ultrasound). Although collecting these detailed records from patient charts may be time-consuming, the results could provide insight for a larger population of patients needing additional screening support within an academic medical center.

4.3 Evaluation of predictors for uptake of surgical intervention

A total of 55 (36.9%) individuals discussed possible surgical interventions with a genetic counselor based on their genetic test result. Not every patient was an eligible candidate for surgery after genetic counseling, but still received counseling based on their result. Patients may have been deemed ineligible for surgery based on previous relevant surgical history (not included in analysis), age, cancer stage, medical conditions, or other co-morbidities. These patients may have also had additional screening recommendations.

Of those individuals who discussed possible surgical interventions with a genetic counselor and had never had a relevant surgery in the past (n=39), there were 31 (79%) charts available to review, which revealed that 14 (35%) individuals of eligible patients completed surgery. Much like screening analyses, the analyses for predictors of surgery uptake did not yield significant or generalizable associations. This was true across the selected potential personal history, family history, and visit predictors.

We found that 36% (n=14) of female patients chose surgery following discussion of surgery with their genetic counselors, however the one male patient who had a documented discussion of surgery did not pursue surgery. This could possibly be explained by the additional sex-specific surgical options available to females with a *BRCA1/2* mutation, a large subset of this study population. While males with *BRCA1/2* mutations may elect prostatectomy, females have the option for mastectomy, hysterectomy, and/or oophorectomy to manage their risk.

Additionally, one factor that could influence female screening outcomes include the number of *BRCA1/2+* female patients of premenopausal age with a genetic mutation warranting breast screening, mastectomy, or hysterectomy who may have chosen breast screening over surgical interventions to retain reproductive abilities. We found that of all female patients under age 50 with a *BRCA1/2* mutation who were recommended for screening (N=13), all patients with available records (n=8) did complete their screening. Female patients of the same characteristics who discussed post-test surgery (N=13) were found to have elected surgery at a rate of 30.7% (n=4). The same number of female patients (n=4) declined surgery.

For those age 50 years and older with a *BRCA1/2* mutation with screening recommendations (n=16) and records available (n=13), 62.5% (n=10) completed screening, while 18.8% (n=3) did not. For the 8 females age 50 and older who had a discussion of surgery related to their *BRCA1/2* mutation, records were available for 7 patients. surgery pursued by 37.5% (n=3), and half the group did not pursue surgery (n=4, 50%).

The likelihood of an unaffected individual versus an affected individual to elect surgery could was not assessed in this study due to the small sample size. Of note, most cancers represented in this cohort did not have a surgical option for risk management. Cancer syndromes conferring high risk for breast cancer most commonly had recommendations available.

4.4 Study Limitations and Future Directions

The outcomes of these analyses are confounded by missing data from the significant number of patient records that were unavailable for review due to discontinued care at UCI, a major limitation to the study design. Due to this large proportion, significant conclusions regarding predictors for risk management could not be made. Any suggested associations can be attributed to the distribution of unavailable records between groups. As such, these factors may serve as

predictors for whether an individual was likely to continue medical care at UCI. This was true for the "Tested Before UCI" and "Post-Test Only" groups. One explanation for the large proportion of unavailable charts in these groups could be that these individuals only established care at UCI to receive genetics services, and continued their recommended risk management at an external site where they might have had genetic testing ordered.

This study demonstrates the limitations of retrospective chart review in collecting longitudinal data of interest. In the future, this study's original aims may be explored further using a research design that includes long-term follow up with patient populations. This approach to retrospective analysis of research data would also be enhanced by implementation of the recommendations by Conley, et. al (2020) for longitudinal follow-up within the clinic setting of all individuals who are identified as a mutation carrier, although it is understood that even in this setting, some individuals may be lost to follow up. This can be accomplished using direct-to-patient telephone interviews or questionnaires at regular intervals after post-test counseling which include the potential predictors considered in this study. This research design may also be implemented to explore the outcomes for patients who are encouraged to inform relatives about the identified familial variant for which they could be tested. The number of family members, and their degree of relation, with whom a patient has shared information with and encouraged to pursue testing may illustrate the extent of familial communication and testing beyond this clinic.

Another avenue for collection of data after the genetics visit may include communications with patients outside providers to glean screening compliance, which would require release of medical records for each patient. Perhaps a less laborious option would be an integrated shared electronic medical record across multiple institutions and providers which allows for linked charts. The

findings of this study underscore the importance of accessible, thorough documentation available between care sites to achieve more efficient and comprehensive care.

An additional limitation to this study was its relatively small sample size, including the small proportion of individuals who did not follow through with recommendations. The small number of individuals within comparison groups presented difficulty for drawing significant associations for predictors and risk management uptake. This was especially true for chosen predictors with multiple categories (e.g. cancer type, syndrome). Thus, findings in this study cannot be generalized to all patients in this clinic or other cancer clinics. This limitation may be mitigated by an increased sample size achieved by broadening inclusion criteria to include patients who received results prior to 2017, or who were seen at multiple centers.

This study did not explore psychosocial or socioeconomic predictors for adherence to genetic counselors' risk management recommendations. An investigation of patients' diverse feelings towards surgery and screening would provide insight to the facilitators and barriers of compliance, which could be addressed further during genetic counseling appointments. Previous studies have considered zip code, primary language, or insurance type to represent socioeconomic status. Considerations for patients' sources of anxiety, coping skills, and other facets of decision-making are valuable to collect in future studies. These data, combined with outcomes of risk management recommendations as explored in this study, may illustrate the need for additional financial or emotional support from a patient's medical institution.

It is recognized that the onset of the COVID-19 pandemic may influence the results of this study. The majority of charts reviewed were of individuals who had results reported before the clinic's frequent use of telemedicine as a service delivery model. It is proposed that stay-at-home orders throughout 2020 and 2021 may have influenced uptake of risk management or clinic attendance

and wait times. A growing body of literature comparing pre-pandemic factors with those during the pandemic will reveal its effect on multiple aspects of cancer clinics and its patients.

4.5 Conclusions

The present study identified a high rate of uptake for genetic counselors' risk management recommendations by high-risk individuals with a pathogenic variant in a hereditary cancer gene. Further analysis found that for individuals with a pathogenic cancer gene variant, uptake of follow-up clinical screening recommendations could not be strongly predicted by the selected patient demographic, personal and family history factors, and visit details. Significant associations between uptake of surgery and screening for patients who initiated genetic testing outside of UCI or those who had only post-test counseling were suggested. However, this significance is primarily driven by the large number of records unavailable between groups, which limited the number of charts available to review for adherence to recommendations. Limitations of this study include the inability to evaluate uptake for those without clearly documented outside records when care at UCI ceased after receiving genetic counseling. Additionally, the small sample size available for review diminished the study's power to make conclusions of significance. Ultimately, this study demonstrates the necessary considerations for future studies to best conduct long-term studies for patient's follow-up behavior. Additionally, the need for a unified electronic medical records system between institutions is apparent, implementation of which can potentially improve studies of this type along with improving comprehensive patient care.

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