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Ovarian Cancer: Determining Factors That Influence Referral to Genetics

THESIS

submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in Genetic Counseling

by

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ABSTRACT OF THE THESIS

Ovarian Cancer: Determining Factors which Influence Referral to Genetics

By

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Master of Science in Genetic Counseling

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In 2014, NCCN guidelines for ovarian cancer were updated to include genetic risk assessment for all women diagnosed with ovarian cancer, following the introduction of PARP inhibitors for targeted treatment*. Despite the advancements made in cancer genetics knowledge and the availability of cancer predisposition testing, little information has been gathered regarding the decision-making of providers in the referral process of their patients for cancer genetic risk evaluation.

We aimed to determine characteristics of the population of patients referred for genetics consultation upon receiving a diagnosis of ovarian cancer that distinguish them from those who are not referred. Data collected at the University of California, Irvine Medical Center covering a two-year time span following the NCCN update was analyzed. Our study found that women with ovarian cancer continue to be under-referred to cancer genetics; only 59% (95% CI 51-67%) of the study sample had documentation of referral following their diagnosis. This suggests a general unmet need to further educate providers on the importance of referral for genetics evaluation in the context of ovarian cancer. Of the

four patient characteristics studied, ethnicity, insurance type and age at diagnosis were not found to be statistically significant potential predictors for genetics referral. Patients with "unknown" stage at diagnosis had a lower percent of documented referral than patients with known stage cancer. Further research is needed to identify why a significant proportion of women with ovarian cancer are not being referred for genetics evaluation.

*National Comprehensive Cancer Network 2014.

1 INTRODUCTION

1.1 Overview

In the United States, more than 20,000 women annually are diagnosed with ovarian cancer, making it the tenth most common cancer and the fifth leading cause of cancer death in this population (National Cancer Institute 2014, CDC 2014). Ovarian cancer is the leading cause of death among gynecological malignancies, and while the impact of current early detection methods has been unclear, women with early stage ovarian cancer have been documented to have notably better survival rates than women diagnosed with cancer at later stages (Walsh et al. 2011, Partridge et al. 2009). Furthermore, studies have shown that risk-reducing salpingo-oophorectomy in women found to carry mutations in ovarian-related cancer predisposition genes has significantly reduced the incidence of ovarian cancer and overall mortality in these women (Cragun and Pal 2013, Walsh et al. 2011, Domchek et al. 2006).

Genetic risk assessment and testing have become widely used tools in cancer prevention and treatment, with applications in pre-symptomatic risk assessment as well as in diagnosis, prognosis and targeted therapies in the medical management of individuals with cancer diagnoses (Weitzel et al. 2011, Rosenthal et al. 2017). As scientific and technological advances continue to revolutionize the field of clinical cancer genetics, the role of genetic cancer risk assessment has grown increasingly important in helping patients understand their risk for disease, making decisions about genetic testing, and aiding in medical management (Cragun and Pal 2013, Petzel et al. 2014, Weitzel et al. 2011).

Although the advantages of cancer genetic risk assessment and testing have been well documented, women diagnosed with ovarian cancer continue to be under-referred to genetics professionals (Bellcross et al. 2009, Sussner et al 2011, Metcalfe et al. 2009, Sweet et al. 2002). According to the most recent guidelines by the National Comprehensive Cancer Network (NCCN), genetic counseling is recommended for all women diagnosed with ovarian cancer (NCCN 2017). Thus, primary care providers have an influential role in identifying and referring cancer patients who may benefit from genetic assessment (Petzel et al. 2014, Brandt et al. 2008, Shannon et al. 2002). The purpose of this study is to review the medical records of patients who were seen at the University of California, Irvine Medical Center and were diagnosed with ovarian cancer over a two-year time period and to determine what proportion of these patients were referred for genetics consultation. We performed an internal comparison within the group of patients to elucidate any common patient characteristics or differentiators between the patients who were referred to genetics versus those who were not. We anticipated that this data would aid in influencing provider education regarding the implications of genetics in the context of ovarian cancer.

1.2 Cancer and Genetics

Cancer is a disease of uncontrolled cell growth. While the etiology of cancer is thought to be multifactorial, meaning that genetic, environmental and lifestyle factors can play a role in its development, cancer is fundamentally a genetic disease. The human genome includes many types of genes that control cell growth and function. When these genes have an alteration in their coding, these genetic changes can lead to tumor formation

and malignancy over time. However, genetic causes of cancer are not all hereditary. The vast majority of cancers result from the interaction of acquired genetic changes with environmental and lifestyle factors, while about 5 to 10% of cancers result from an inherited cancer predisposition (Schneider 2012).

Knudson hypothesized that two "hits," or mutations, at a gene involved in a critical pathway could cause cancer. Since each individual typically has two copies of every gene – one from the egg and one from the sperm at fertilization – this means that cancer-causing mutations in both copies of a gene that normally regulates cell growth could cause an individual to develop cancer (Knudson 2001). Specifically, genes that lead to cancer when they are inactivated are called tumor-suppressor genes. When an individual is born with one copy of a tumor suppressor gene already mutated, they have a higher predisposition to developing a certain type(s) of cancer than someone in the general population who was born with two normal copies of the gene. This is not to say that an individual with an inherited mutation will certainly develop cancer in their lifetime, but that person would be at an increased risk since an acquired mutation in the second copy of the gene can lead to malignancy.

Insight into genetic information can be helpful in several ways. It can help to identify asymptomatic individuals who have an increased risk of developing cancer, such as family members of the affected patient; it can also help to elucidate the most efficient medical management options for an affected patient, such as appropriate treatments and therapies and/or prevention measures for additional cancers and appropriate screening (Schneider 2012).

1.3 Ovarian Cancer

Ovarian cancer refers to the uncontrollable growth of abnormal cells that originate inside, near, or on the outer layer of the ovaries (NCCN 2017). Three main cell types make up the ovaries: epithelial, germ, and stromal cells. Epithelial cells cover the outer lining of the ovaries, germ cells are the cells that differentiate to form eggs, and stromal cells release female hormones (estrogen and progesterone) and connect the structures of the ovaries (National Ovarian Cancer Coalition).

About 90% of ovarian cancers start in the epithelial cells, making epithelial ovarian cancer the most common subtype (Jones et al. 2017). Most epithelial tumors are benign and do not metastasize. Benign epithelial cancers include serous cystadenomas, mucinous cystadenomas, and Brenner tumors. Borderline epithelial tumors of low malignant potential (LMP) also start in the epithelial cells. While LMP tumors may spread and grow on the surface of nearby tissues and organs, they rarely metastasize in the manner in which fully cancerous cells do. Types of malignant epithelial tumors include serous, mucinous, endometrioid, and clear cell, all of which have different clinical courses and survival rates (Jones et al. 2017). Undifferentiated epithelial ovarian tumors look different than the aforementioned subtypes and tend to metastasize more quickly than the other types (American Cancer Society 2016).

Other cancers with a similar prognosis to epithelial ovarian cancer include primary peritoneal carcinoma (PPC) and fallopian tube cancer. PPC is a rare cancer that seemingly originates from cells in the pelvic and abdominal lining and spreads along the surfaces of

the pelvis and abdomen. Fallopian tube cancer originates in the fallopian tube and has a slightly better prognosis than ovarian cancer (American Cancer Society 2016, NCCN 2017).

Ovarian germ cell tumors account for fewer than 2% of ovarian cancers and have an overall good prognosis, with a patient survival rate of 90% for at least 5 years after diagnosis. While most germ cell tumors are benign, some are malignant. The most common types of germ cell tumors are teratomas, dysgerminomas, endodermal sinus tumors, and choriocarcinomas (American Cancer Society 2016, National Ovarian Cancer Coalition).

Ovarian stromal tumors make up about 1% of ovarian cancers, with more than half found in women 50 years and older. Benign stromal tumors are classified as thecomas and fibromas, and malignant stromal tumors include granulosa cell tumors, granulosa-theca tumors, and Sertoli-Leydig tumors. These tumors are usually detected at earlier stages and have a good prognosis, with a long-term survival rate of more than 75% (American Cancer Society 2016).

1.4 Risk Factors for Ovarian Cancer

A woman's risk for developing ovarian cancer is ultimately determined by a combination of genetic and epidemiological risk factors (Jones et al. 2017). Empirically, the lifetime risk for a woman to develop ovarian cancer is 1 in 75, with a risk of dying as a result of the disease of 1 in 100 (Howlader et al. 2016).

As Jones et al. note in their 2017 paper on the genetic epidemiology of ovarian cancer, several epidemiologic studies have suggested that hormone exposure plays an important role in ovarian cancer etiology (Risch 1998, Reid et al. 2017). Oral contraceptive

use, parity, breastfeeding, tubal ligation, hysterectomy, and bilateral prophylactic oophorectomy are all associated with a decreased epithelial ovarian cancer risk, while increasing age, younger age at menarche, endometriosis and use of post-menopausal hormone therapy is associated with an increased risk (Jones et al. 2017, Reid et al. 2017, Trabert et al. 2012, Sayasneh et al. 2011, Beral et al. 2008, Domchek and Rebbeck 2007). The impact of spontaneous or induced abortions on ovarian cancer risk is unclear (Reid et al. 2017). Some risk factors have also been reported to be associated with specific histological subtypes of ovarian cancer (Jones et al. 2017). For example, Olsen et al. found a weak correlation between obesity and risk of low-grade serous invasive tumors but no association with invasive high-grade serous disease; they also found high body mass index to increase the risk of borderline serous, invasive endometrioid, and invasive mucinous ovarian cancer histotypes (Olsen et al. 2013). Factors for which the effect on ovarian cancer risk remain unrefined and/or unresolved include diet and nutrition, exercise, and other lifestyle factors such as cigarette smoking, alcohol consumption, drug use, and exposure to asbestos and talcum powder (Reid et al. 2017).

Family history of epithelial ovarian cancer remains one of the strongest risk factors for the disease (Jones et al. 2017). Various classes of genes that confer varying risks for ovarian cancer have been and continue to be discovered. However, the susceptibility genes and risk alleles for ovarian cancer that have been identified to date characterize less than half of the heritable component of epithelial ovarian cancer; the remaining risk is thought to be "due to multiple alleles including common genetic variants (>5% in the population) conferring weak effects (relative risks <1.2), and uncommon (1-5%) and rare variants (<1%) conferring weak to moderate effects with relative risks less than ten" (Jones et al.

2017).

While much more must be learned about ovarian cancer risk factors in order to impact clinical risk prediction and prevention to ultimately reduce mortality of the disease, identification of germline variants that are known to increase susceptibility to ovarian cancer over recent years have proven to be clinically valuable. An example of this utility is demonstrated by the fact that prophylactic bilateral salpingo-oophorectomy is now a commonly used intervention to reduce the risk of mutation carriers to develop ovarian cancer and is generally offered to *BRCA1* (breast cancer susceptibility gene 1) carriers by age 40 and to *BRCA2* (breast cancer susceptibility gene 2) carriers by age 45 (NCCN Guidelines 2.2017, Jones et al. 2017). The limiting factors to more refined risk prediction strategies, including imprecise estimates of disease penetrance in the literature, the lack of functional proof that germline genetic variants are disease-causing, and the variable penetrance of different genetic variants in the same gene, will have to be resolved through further collection and examination of targeted genetic sequencing and epidemiological data in large population studies.

As Reid et al. concluded in their 2017 review of ovarian cancer epidemiology, "It is important to emphasize that the established risk factors aside from highly penetrant gene mutations confer neither large increases in risk nor account for all the variability in the incidence of this disease. Thus, additional causes of OC are yet to be identified. Additional research is needed to better understand the heterogeneous etiology of this deadly disease, with a view to better prevention and early detection strategies."

1.5 Screening for Ovarian Cancer

There are estimated to be over 225,000 new cases of ovarian cancer globally each year with 140,000 annual deaths from the disease, making ovarian cancer the leading cause of death among gynecological malignancies (Razi et al. 2016, Ferlay et al. 2010). One contributing factor to the high fatality rate of ovarian cancer is that over 70% women who are diagnosed are diagnosed with advanced disease (Buys et al. 2011, Rauh-Hain et al. 2011, Jones et al. 2017). Screening tests are examinations that can be used to detect a disease, such as cancer, in asymptomatic individuals in early stages and when the cancer is most likely to respond to treatment. While studies to find the optimal combination of screening tests for ovarian cancer are ongoing, there are currently no tests that can help diagnose ovarian cancer early (Jones et al. 2017, Clarke-Pearson 2009, Rosenthal et al. 2006).

Women who are at a higher risk for ovarian cancer than the general population, such as women with a strong family history of breast or ovarian cancer in multiple relatives, may consider ultrasonography, a blood test to look at cancer antigen 125 (CA 125) tumor marker levels, or a combination of both tests (Clarke-Pearson 2009, Rauh-Hain et al. 2011). Transvaginal ultrasound allows for detailed imaging of the ovaries and may detect changes that signify a developing malignancy. However, an important limitation to this screening is the variation in the interpretation and scoring of the results across observers (Rauh-Hain et al. 2011). CA 125 has been established as a tumor marker in epithelial ovarian cancer; however, it is also elevated in other common conditions that may be less serious and is not elevated in every individual with ovarian cancer. For these

reasons, the sensitivity and specificity of CA 125 testing are poor. Combining these two testing methods may achieve higher specificity but does not eliminate the chance of a false-positive result (Rauh-Hain et al. 2011). Thus, there is currently no evidence that these tests reduce the risk of dying from ovarian cancer in affected individuals (Buys et al. 2011, Clarke-Pearson 2009).

1.6 Cancer Predisposition Genes and Genetic Testing for Ovarian Cancer

In his 2014 paper reviewing the benefits of genetic testing of cancer predisposition genes, Rahman discusses the two ways in which gene mutations contribute to cancer: oncogenic mutations occur after birth within a specific cell and are known as 'somatic cancer mutations,' while mutations that are present in every cell due either to inheritance or to occurrence during conception are called 'germline mutations.' Genes in which germline mutations lead to an increased risk of developing cancer are thus referred to as cancer predisposition genes.

The scientific community's understanding of the role that genetic predisposition plays in cancer susceptibility has led to the development of prevention, targeted treatment, and pre-symptomatic screening strategies that continue to improve the precision and outcomes of patient care.

In their 2016 review article, Nielsen et al. compiled a timeline of events that were important in Hereditary Breast and Ovarian Cancer (HBOC) syndrome discovery and the identification of HBOC predisposition genes. These milestones include the first reported case of hereditary breast cancer in 1866, the proposal of Knudson's 'two-hit' model for

carcinogenesis in 1971, the introduction of Sanger Sequencing in 1977, identification of the *BRCA1* gene in 1994 and of *BRCA2* in 1995, ovarian cancer molecular subtyping in 2003, the proposal of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibition for *BRCA1*- and *BRCA2*- deficient tumors in 2005, the first report of exome sequencing in 2009, and the identification of various other pathogenic germline mutations in over 25 genes to date that have been associated with familial breast and/or ovarian cancer.

While about 5-10% of all cancers are hereditary, in the context of ovarian cancer specifically, studies have found that approximately 15-23% of cases result from contributions of cancer predisposition genes (Gayther 2010, Walsh et al. 2011) and that greater than 40% of mutation carriers have no known family history of breast and ovarian cancer (Eccles et al. 2016). Furthermore, in 65-85% of hereditary cases, the genetic abnormality is a germline mutation in one of the *BRCA* genes (Toss et al. 2012). Thus, identifying an underlying cancer predisposition gene mutation can provide information that can aid in the diagnosis, prognosis and medical management of patients as well as possibly providing a better understanding of the pathogenesis of their tumors (Rahman 2014). This information can also be helpful in preventing cancers in patients with a primary cancer diagnosis who may be at risk for additional cancers as well as for their unaffected relatives, since it offers an opportunity to implement appropriate surveillance and risk-reducing measures that may facilitate early detection and treatment (Rahman 2014, Vergote et al. 2016). Examples include personalized surveillance programs, chemo-preventative approaches, and/or prophylactic surgery that might not have been recommended given family history alone (Toss et al. 2015, Vergote et al. 2016).

With the rapid evolvement of DNA sequencing technology, genetic testing has become an affordable and efficient tool to sequence multiple genes in parallel by means of gene panels that range anywhere from two to one hundred or more cancer predisposition genes (Shendure and Ji 2008). In their 2012 paper on the genetics and pathogenesis of ovarian cancer, Liliac et al. provide a compilation of at least 16 known genes whose contribution to the mechanism of hereditary ovarian tumorigenesis has been recognized, as well as several additional unknown mutations that cannot yet be detected by specific genetic tests. These genes include *BRCA1* and *BRCA2*, genes involved in DNA double-strand break repair, mismatch repair *(MMR)* genes, *TP53*, and an 'unknown gene' category. Next-generation sequencing (NGS) technology continues to optimize the molecular diagnosis of sporadic and hereditary ovarian cancers by allowing the simultaneous analysis of multiple cancer predisposition genes at more rapid turnaround times and reduced costs (Toss et al. 2015).

As these discoveries continue to uncover nuanced information that aids in more accurate risk assessment for individuals based on their genetic status and personal and/or family history of cancer, referrals for genetic counseling and evaluation of these patients becomes increasingly important to risk management and decision-making for themselves and their families (Nielsen et al. 2016, Vergote et al. 2016). Following their review of newly-updated guidelines and up-to-date evidence in their 2016 study, Vergote et al. concluded that "all ovarian cancer patients with invasive epithelial ovarian cancer (excluding borderline and mucinous), including fallopian tube and peritoneal cancers, should be considered for referral for *BRCA* genetic testing, irrespective of age; genetic testing should ideally be offered at diagnosis, although patients can be referred at any

stage; retrospective testing should be offered to long-term follow-up patients because of family member implications and individual future breast cancer risk; and germline *BRCA* testing of a blood/saliva sample should initially be conducted and, if negative, a tumor tissue sample testing to identify non-germline *BRCA* PARPi therapy candidates".

1.7 PARP Inhibitor Introduction

Rahman concluded in his 2014 paper on mainstreaming genetic testing of cancer predisposition genes that such an approach offers unprecedented opportunities to improve the quality and equity of care provided to patients with cancer and the wider population. Perhaps one of the most relevant applications of this in the context of ovarian cancer diagnosis is identifying potential targets for specific drugs such as poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors.

Genomic integrity and survival is maintained through various repair pathways that repair damaged DNA at the cellular level (Hoejimakers 2001). These DNA repair pathways can aid in tumor cell survival when DNA damage is induced by chemotherapeutic treatments; thus, the inhibition of specific repair pathways can be helpful when used in combination with such treatments to selectively target for tumor cell destruction (Helleday et al. 2008).

PARP proteins are key enzymes that are activated in response to DNA single-strand breaks. The inhibition of PARP leads to an accumulation of double-strand DNA breaks, which activates homologous recombination as a mechanism for repair (Ledermann 2015, Chen 2011). Studies have shown that cells with *BRCA* mutations cannot use homologous

recombination to repair double-strand breaks in their DNA; as such, they are heavily dependent on the PARP pathway to initiate repair following detection of DNA damage (Ledermann 2016, Chen 2011, Fong et al. 2009, Bryant et al. 2005, Farmer et al. 2005). In their 2008 study on DNA repair pathways as targets for cancer therapy, Helleday et al. labeled the process by which PARP inhibition leads to cell death in the presence of homologous recombination deficiency 'synthetic lethality.'

In 2014, olaparib became the first PARP inhibitor to be approved by the European Medicines Agency "as maintenance therapy for responding ovarian cancer patients found to have a *BRCA1/2* mutation following chemotherapy." It was also the first to receive accelerated approval by the US Food and Drug Administration (FDA) for advanced ovarian cancers with a *BRCA1/2* mutation while confirmatory trials are completed (Brown et al. 2016). Exploration of PARP inhibitor activity has since expanded to include non-*BRCA* mutation-related ovarian cancer as well as other types of cancers and continues to be an area of great interest among geneticists and oncologists (Meehan and Chen 2016).

1.8 National Comprehensive Cancer Network Guidelines

As genomic research continues to expand our knowledge base of cancer predisposition genetics, the translation of this information into clinical practice guidelines that can be applied on a widespread basis becomes increasingly more important as it relates to patient care. The National Comprehensive Cancer Network (NCCN) is a non-profit coalition of cancer experts that publishes annually updated surveillance and treatment guidelines for patient care in the context of various types of cancer.

The NCCN guidelines were updated in 2014 to recommend genetic risk evaluation in patients with possible ovarian tumors for evaluation of the potential benefits of targeted treatment with PARP inhibitors (National Comprehensive Cancer Network, 2014). Current NCCN guidelines for patients affected with or at high risk for ovarian cancer include strong recommendations for genetic consultation, including genetic counseling, as part of initial testing for all patients and subsequent genetic risk evaluation (National Comprehensive Cancer Network, 2017). However, despite the availability of NCCN guidelines for cancer prevention, screening, and treatment, the extent to which they are adhered to by oncologists, as well as across clinical specialties, is unclear (Dhar et al. 2011). Some recent provider-based survey studies show that there is room for improvement in provider compliance with these guidelines (Cragun et al. 2013, Dhar et al. 2011). Since improving the cost effectiveness and quality of patient care continue to be main objectives of current healthcare practices, the issues of provider education and compliance with practice guidelines will become of increasing importance (Pal et al. 2013).

1.9 Study Aims and Hypothesis

In spite of the advancements made in cancer genetics knowledge and the availability of cancer predisposition testing, little information has been gathered regarding providers' decision-making regarding referring their patients for genetics consultations and cancer genetic risk evaluation. Our study aims to determine whether there are any common patient characteristics (age at diagnosis, ethnicity, stage of cancer, and insurance type) of the population of patients referred for genetics consultation after receiving a diagnosis of

ovarian cancer compared with those who are not referred. To address this aim, data was collected from a large academic medical center for analysis that should be, for the most part, generalizable to other medical centers as well. Data collected at the University of California, Irvine Medical Center covering a two-year time span from January 2015 to January 2017 was analyzed. We theorized that younger patients with HMO/PPO insurance plans would be more likely to receive a referral for genetics consultation, while ethnicity and cancer staging would not have significant effects on likelihood for patient referral for genetics consultation.

These findings may elucidate a population of eligible patients who could benefit from genetics involvement in their care and possibly may provide new insight into the genetic contributions to ovarian cancer if these patients are included in the referred population in the future. The results of this study may also be used to influence provider education regarding the importance of genetics referrals in the context of ovarian cancer.

2 MATERIALS AND METHODS

2.1 Study Sample

A list of patients diagnosed with ovarian cancer at UCI Medical Center (UCIMC) between January 1, 2015 and January 1, 2017 was obtained from the California Cancer Registry (CCR), a statewide population-based cancer surveillance program of the California Department of Public Health's Chronic Disease Surveillance and Research Branch. Inclusion criteria comprised the following: a diagnosis of ovarian cancer was made at UCIMC between the specified dates, and patients included must have been 18 years or older.

A total of 162 records were included in the CCR data sample. Seven of these records were outside of the date of diagnosis range, and two were duplicate entries; these records were excluded from the study sample. Two records had duplicate and triplicate entries in the CCR, respectively, with different staging and primary cancer site information in each. The entries with the higher-staged tumors for these records were included, and the duplicate entries were excluded from the study sample. This reasoning was driven by the logic that a patient's medical management in the context of cancerous tumor presence would be based on the higher-staged primary cancer. A final count of 150 records from the CCR were de-identified and used for analysis.

A list of patients seen in the UCI Cancer Genetics Clinic from January 1, 2015 onward was obtained from the clinic's Cancer Genetics database (CaGen). Inclusion criteria were the same as for the CCR patient list. Follow-up appointments were excluded from the CaGen entries so that the study sample included only new patient consultations. However,

subsequent visits to cancer genetics clinic were included, if applicable, for patients who were seen for repeat consultation (i.e., one patient's testing was denied by her insurance in 2016, and she returned to cancer genetics clinic in 2018, at which time she re-elected to undergo genetic testing, which was then covered). Any results of genetic testing that was done on patients from the CaGen database was recorded from the patient charts prior to de-identification of the records; this included the specific test ordered, the results of the testing (positive/pathogenic mutation, likely pathogenic mutation [variant, likely pathogenic, VLP], negative/no mutation, or variant of unknown significance [VUS]), and the genes in which mutations were identified, if applicable. A total of 106 records making up the CaGen study sample were then de-identified and used for analysis.

2.2 Comparisons Between Study Sample Groups

The de-identified list of patients from the CCR and CaGen study samples were combined and cross-referenced to comprise two groups: ovarian cancer patients from the CCR who *were* scheduled in cancer genetics clinic at UC Irvine, and ovarian patients from the CCR who *were not* scheduled in cancer genetics clinic at UC Irvine.

The electronic medical records (EMR) of patients from the CCR who appeared not to have been scheduled in the cancer genetics clinic at UC Irvine were reviewed for documentation of referral for genetics consultation. This included review of the referral orders, laboratory orders, and provider notes. Patients who were found to have documentation of referral for genetics consultation were then combined with the group of patients from the CCR who had been scheduled in the cancer genetics clinic at UC Irvine to

comprise the group of ovarian cancer patients with "Documented Referral to Genetics." The remaining ovarian cancer patients from the list of CCR patients were classified as patients with "No Documented Referral to Genetics."

Age, ethnicity, cancer stage, and insurance type were the only variables evaluated in this study by comparison between the two groups of ovarian cancer patients in the study sample. These variables were previously recorded upon entry into the CCR and CaGen databases. Age subgroups were created by quartiles. Subgroups by cancer stage were created to include pathology stages 1 through 4 as well as an "other/unknown" category. One entry with a cancer stage of zero was excluded from the study sample. Subgroups by ethnicity were created using the categories for ethnicity as entered for each patient into CCR and stratifying into the following groups: White/Non-Hispanic, Hispanic, Black, and Asian. The ethnicities of patients with unspecified ethnicity in the CCR were determined by cross-referencing this information using the CaGen data, if applicable. Subgroups for insurance type were created by combining the types of insurance into the following groups: (1) "Low-Income Insurance" includes Medicaid/Medicare/Medicare+Medicaid Supplement/County-Funded/Tricare/No insurance; (2) "Managed Care Insurance" includes Managed Care/Medicare+Managed Care Supplement/HMO; (3) "Private Insurance" includes PPO/Medicare+Supplement/Medicare+Private Supplement; and (4) "Unknown Insurance."

The association between known versus unknown pathology and the other demographic variables (age at diagnosis, ethnicity, and insurance type) for patients who were referred to genetics as well as for patients who had no documentation of referral to genetics was analyzed to determine whether any of these associations was statistically

significant. Histology was also analyzed to determine whether referral rate differs across histological subtypes of tumors. Subgroups for histology were created by combining subtypes with similar behavior codes, as documented in the CCR data, into the following categories: clear cell, endometrioid, serous, mucinous, sex-chord stromal, germ cell, and other/not otherwise specified (NOS)/unknown.

Additionally, genetic testing information, including the specific test ordered, the results of the testing, and the genes in which mutations were identified, if applicable, were evaluated for patients from the CCR who also appeared in the CaGen database.

2.3 Statistical Analysis

All analyses were run using IBM SPSS Version 24 (Hearne Software). All variables were categorical. The Pearson Chi-Square test was used to determine the statistical significance of the association between a given demographic variable and whether or not a patient was found to have documentation of referral to genetics. Statistical significance was defined as a p-value less than 0.05.

2.4 Ethical Considerations

This study consisted of a retrospective analysis of existing data from the California Cancer Registry (CCR) Database, electronic medical records (EMR), and the UC Irvine Cancer Genetics (CaGen) Clinic Database. All subjects were de-identified prior to analysis. This study was approved by the University of California Irvine's Institutional Review Board

as “exempt status” protocol (HS#2017-4098), and no consent was required from participants whose records were included.

3 RESULTS

3.1 Patient Referral to Cancer Genetics: Documentation of Referral vs. No Documentation of Referral

A total of 150 patients were diagnosed with ovarian cancer at the University of California, Irvine Medical Center between January 1, 2015 and January 1, 2017, according to the California Cancer Registry database. This study sample of 150 patients is described in terms of age at diagnosis, stage at diagnosis, ethnicity, and insurance type (Table 1). The average age at diagnosis of patients in the study sample was 58 years (SD=14, Range: 18-92). At diagnosis, 12.7% (19/150) of patients had Stage 1 ovarian cancer, 11.3% (17/150) had Stage 2, 31.3% (47/150) had Stage 3, 12.0% (18/150) had Stage 4, and 32.7% (49/150) had Other/Unknown Stage. The ethnicities of the patients in the study sample were as follows: 54.7% (82/150) patients were White/Non-Hispanic, 20.7% (31/150) were Hispanic, 1.3% (2/150) were Black, and 23.3% (35/150) were Asian. The Insurance types of the patients in the study sample were as follows: 15.3% (23/150) patients had Medicaid, 6.0% (9/150) patients had Medicare, 6.7% (10/150) patients had Medicare with Medicaid Supplement, 5.3% (8/150) had County-Funded insurance, 0.7% (1/150) had Tricare, 0.7% (1/150) had no insurance, 13.3% (20/150) had Managed Care, 4.7% (7/150) had Medicare with Managed Care Supplement, 2.0% (3/150) had HMO, 10.0% (15/150) had PPO, 5.3% (8/150) had Medicare with Supplement, 6.0% (9/150) had Medicare with Private Supplement, and 24.0% (36/150) had unknown insurance.

Of the 150 patients with ovarian cancer diagnosed identified through the CCR database, 88 patients (59%) were found to have documentation of referral to cancer genetics and 62 patients (41%) were not found to have documentation of referral to cancer genetics.

Table 1. Demographic Characteristics of Study Sample

	Frequency (N)	Percent (%)
Age at Diagnosis		
≤48	38	25.3
49-58	39	26.0
59-69	40	26.7
70+	33	22.0
Total	*150*	*100.0*
Ethnicity		
White/Non-Hispanic	82	54.7
Hispanic	31	20.7
Black	2	1.3
Asian	35	23.3
Total	*150*	*100.0*
Stage at Diagnosis		
1	19	12.7
2	17	11.3
3	47	31.3
4	18	12.0
Other/Unknown	49	32.7
Total	*150*	*100.0*
Insurance Type		
Medicaid	23	15.3
Medicare	9	6.0
Medicare + Medicaid Supplement	10	6.7
County Funded	8	5.3
Tricare	1	0.7
No Insurance	1	0.7
Managed Care	20	13.3
Medicare + Managed Care	7	4.7
HMO	3	2.0
PPO	15	10.0
Medicare + Supplement	8	5.3
Medicare + Private Supplement	9	6.0
Unknown Insurance	36	24.0
Total	*150*	*100.0*

3.2 Age at Diagnosis

Age at diagnosis of ovarian cancer patients from the CCR with documentation of referral to cancer genetics was compared to age at diagnosis in those with no documentation of referral to cancer genetics (Table 2, Figure 1).

Patients were grouped into age categories by quartile. For the youngest quartile including patients aged ≤48, 57.9% (22/38) of ovarian cancer patients had documentation of referral to cancer genetics, while 42.1% (16/38) had no documentation of referral to cancer genetics. In the second quartiles including patients aged 49-58, 64.1% (25/39) of ovarian cancer patients had documentation of referral to cancer genetics, while 35.9% (14/39) had no documentation of referral to cancer genetics. In the third quartile (ages 59-69), 52.5% (21/40) of ovarian cancer patients had documentation of referral to cancer genetics, while 47.5% (19/40) had no documentation of referral to cancer genetics. In the oldest quartile including patients aged 70 or older, 60.6% (20/33) of ovarian cancer patients had documentation of referral to cancer genetics, while 39.4% (13/33) had no documentation of referral to cancer genetics.

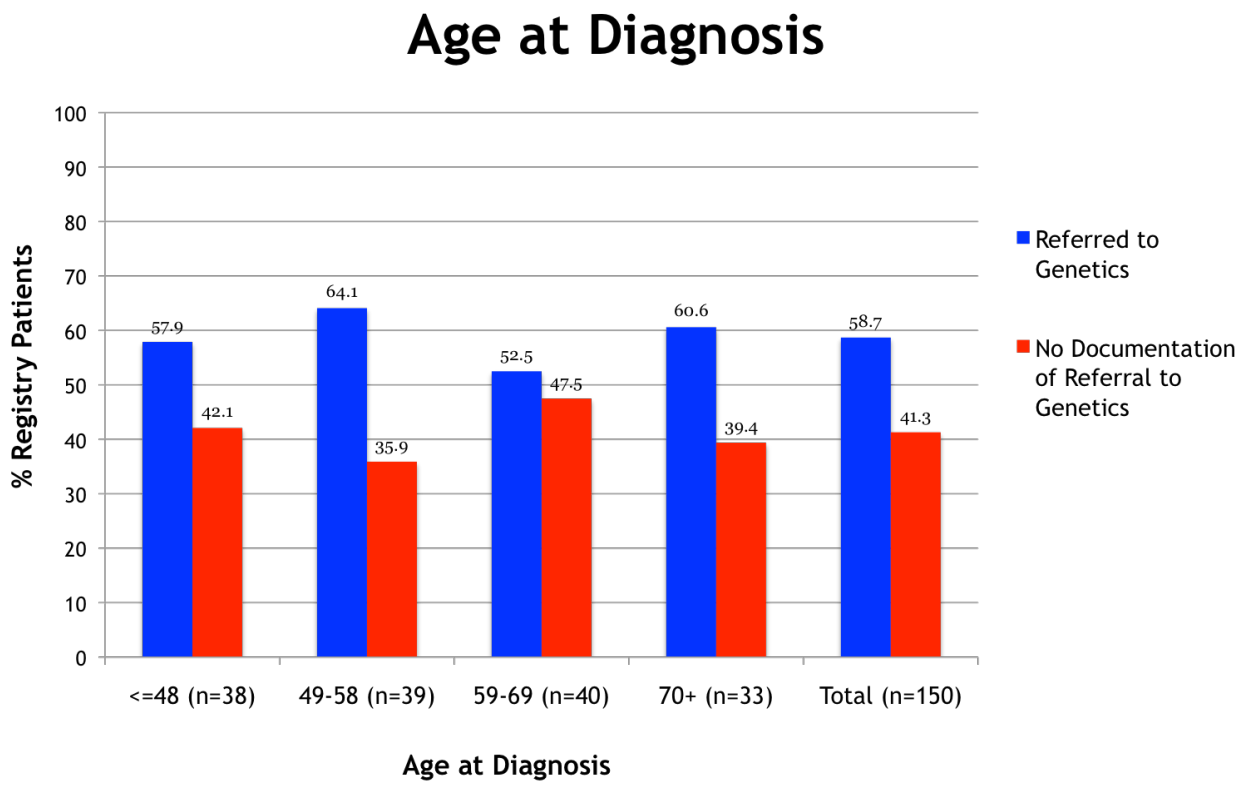
When rates for documentation of referral were compared across quartiles for age at diagnosis, differences were not statistically significant ($p=0.762$). There is no obvious trend toward higher or lower referral rates by age quartile. Although not statistically significant, slightly lower referral rates were seen for women in the third quartile (ages 59-69).

Table 2. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Age at Diagnosis

Age at Diagnosis	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Total Patients
	N	%	N	%	N
<=48	22	57.9	16	42.1	38
49-58	25	64.1	14	35.9	39
59-69	21	52.5	19	47.5	40
70+	20	60.6	13	39.4	33
Total	*88*	*58.7*	*62*	*41.3*	*150*

Table 2. p=0.762; not statistically significant.

Figure 1. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Age at Diagnosis



3.3 Ethnicity

The ethnicity of ovarian cancer patients from the CCR with documentation of referral to cancer genetics was compared to ethnicity of those with no documentation of referral to cancer genetics (Table 3, Figure 2).

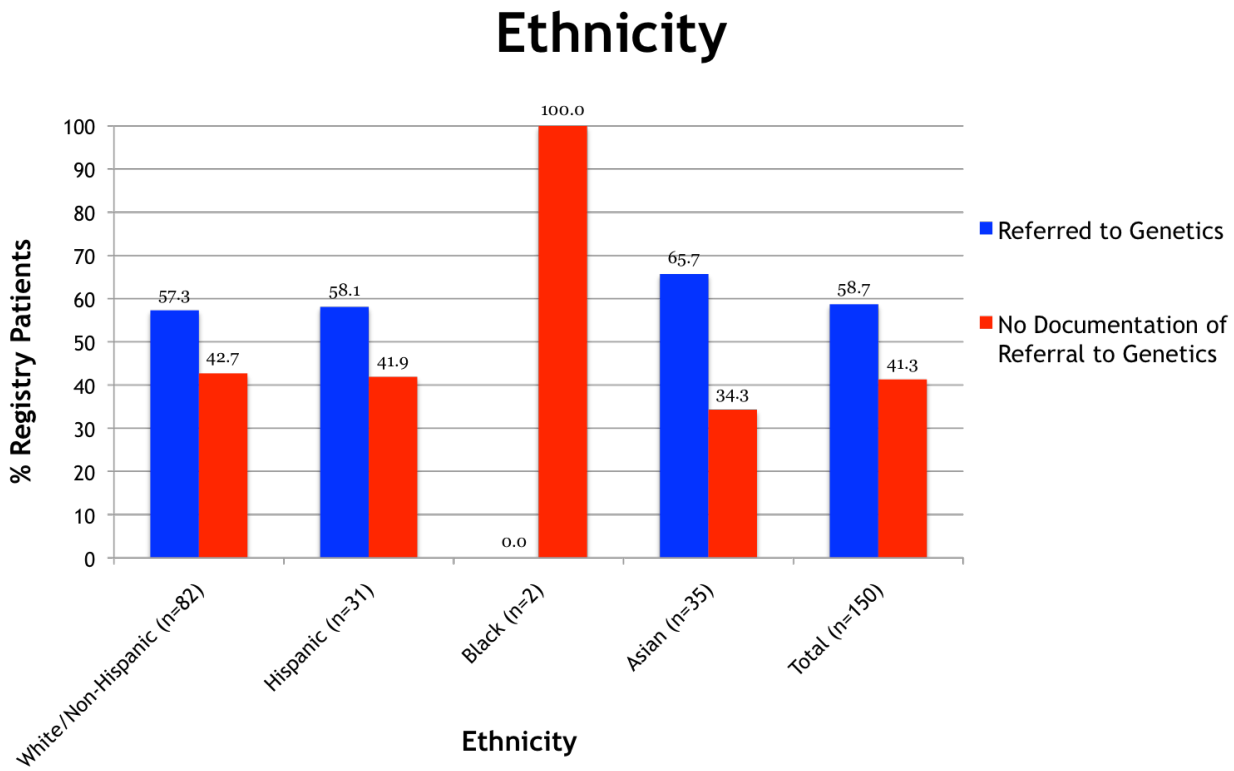
Of the White/Non-Hispanic ovarian cancer patients, 57.3% (47/82) had documentation of referral to cancer genetics, while 42.7% (35/82) had no documentation of referral to cancer genetics. Of the Hispanic ovarian cancer patients, 58.1% (18/31) had documentation of referral to cancer genetics, while 41.9% (13/31) had no documentation of referral to cancer genetics. Of the Black ovarian cancer patients, 0.0% (0/2) had documentation of referral to cancer genetics, while 100.0% (2/2) had no documentation of referral to cancer genetics. Of the Asian ovarian cancer patients, 65.7% (23/35) had documentation of referral to cancer genetics, while 34.3% (12/35) had no documentation of referral to cancer genetics. When rates for documentation of referral were compared across ethnicity, differences were not statistically significant (p=0.305).

Table 3. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Ethnicity

Ethnicity	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Total Patients
	N	%	N	%	N
White/Non-Hispanic	47	57.3	35	42.7	82
Hispanic	18	58.1	13	41.9	31
Black	0	0.0	2	100.0	2
Asian	23	65.7	12	34.3	35
Total	*88*	*58.7*	*62*	*41.3*	*150*

Table 3. p=0.305; not statistically significant.

Figure 2. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Ethnicity



3.4 Stage at Diagnosis

Stage of diagnosis of ovarian cancer patients from the CCR with documentation of referral to cancer genetics was compared to stage of diagnosis in those with no documentation of referral to cancer genetics (Table 4, Figure 3).

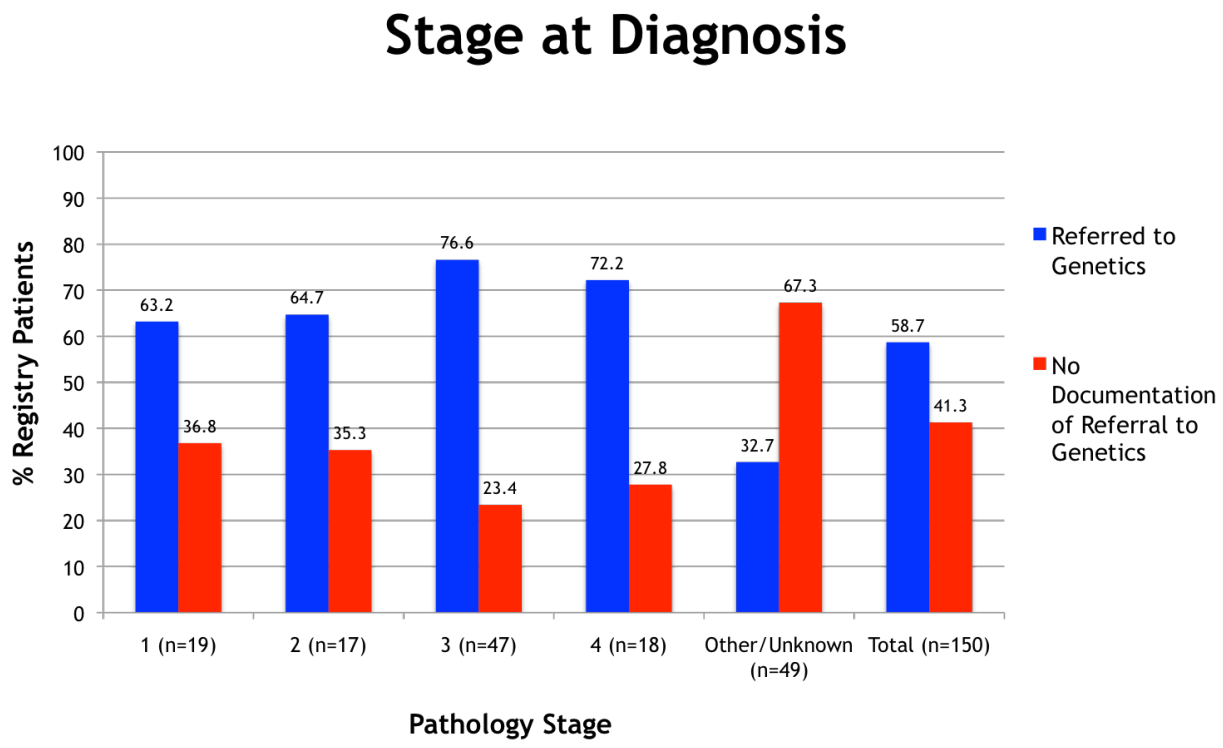
Of the Stage 1 ovarian cancer patients, 63.2% (12/19) of patients had documentation of referral to cancer genetics, while 36.8% (7/19) had no documentation of referral to cancer genetics. Of the Stage 2 ovarian cancer patients, 64.7% (11/17) of patients had documentation of referral to cancer genetics, while 35.3% (6/17) had no documentation of referral to cancer genetics. Of the Stage 3 ovarian cancer patients, 76.6% (36/47) of patients had documentation of referral to cancer genetics, while 23.4% (11/47) had no documentation of referral to cancer genetics. Of the Stage 4 ovarian cancer patients 72.2% (13/18) of patients had documentation of referral to cancer genetics, while 27.8% (13/18) had no documentation of referral to cancer genetics. Of the Other/Unknown Stage ovarian cancer patients, 32.7% (16/49) of patients had documentation of referral to cancer genetics, while 67.3% (33/49) had no documentation of referral to cancer genetics. When rates for documentation of referral were compared across stage at diagnosis, differences were statistically significant ($p<0.0005$). This significant difference is primarily due to the lower referral rates in patients with unknown stage.

Table 4. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Stage of Diagnosis (All Stages)

Stage at Diagnosis	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Total Patients
	N	%	N	%	N
1	12	62.3	7	36.8	19
2	11	64.7	6	35.3	17
3	36	76.6	11	23.4	47
4	13	72.2	5	27.8	18
Other/Unknown	16	32.7	33	67.3	49
Total	*88*	*58.7*	*62*	*41.3*	*150*

Table 4. p<0.0005; statistically significant association between cancer stage and no documentation of referral to cancer genetics.

Figure 3. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Stage of Diagnosis (All Stages)



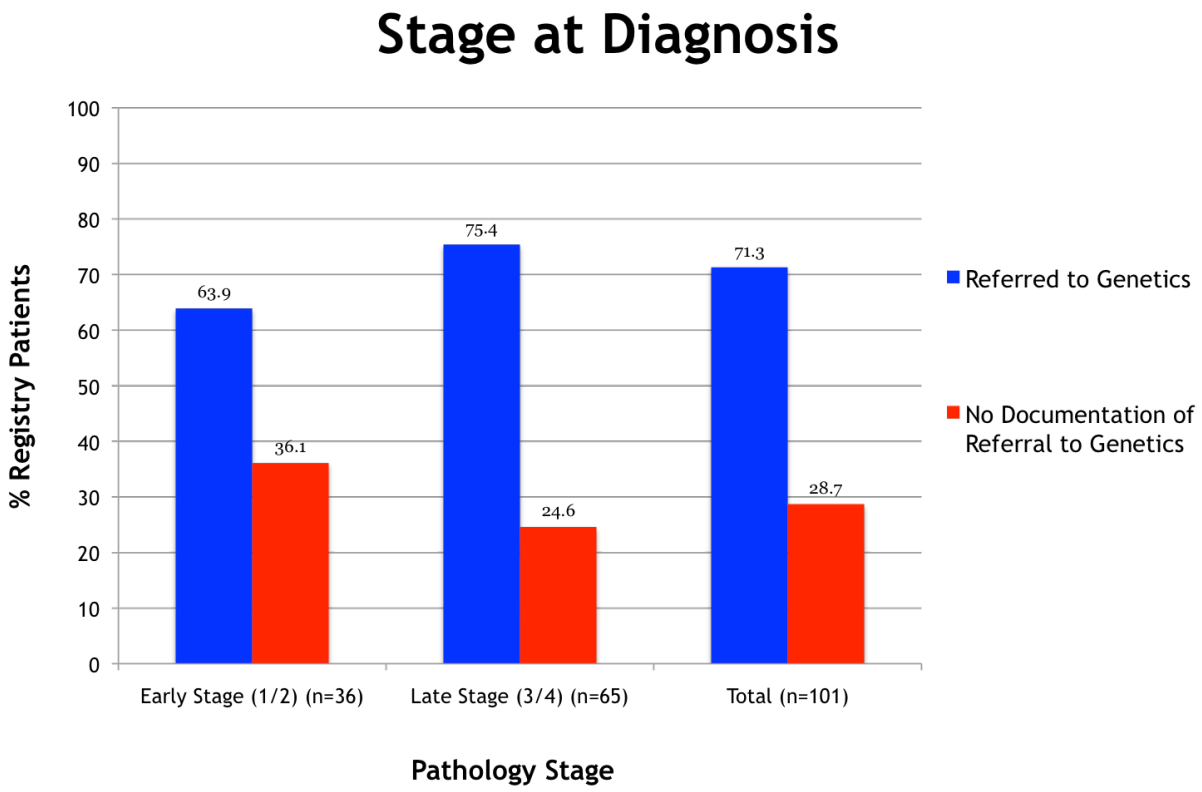
To determine if referral rates differed by early vs. late stage, patients in the study sample were then categorized into two subgroups: “Early Stage (1/2)” and “Late Stage (3/4)” cancer, excluding patients with “Other/Unknown” stage cancer (Table 5, Figure 4). Of the subgroup of patients from the study sample, 63.9% (23/36) of patients with Early Stage (1/2) ovarian cancer were found to have documentation of referral to cancer genetics, and 75.4% (49/65) of patients with Late Stage (3/4) ovarian cancer were found to have documentation of referral to cancer genetics. While rates for documentation of referral were higher for late stage patients compared to early stage patients, this difference did not reach statistical significance (p=0.221).

Table 5. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Stage of Diagnosis (Early Stage vs. Late Stage, Other/Unknown Excluded)

Stage at Diagnosis	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Total Patients
	N	%	N	%	N
Early Stage (1/2)	23	63.9	13	36.1	36
Late Stage (3/4)	49	75.4	16	24.6	65
Total	*72*	*71.3*	*29*	*28.7*	*101*

Table 5. p=0.221; not statistically significant.

Figure 4. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Stage of Diagnosis (Early Stage vs. Late Stage, Other/Unknown Excluded)



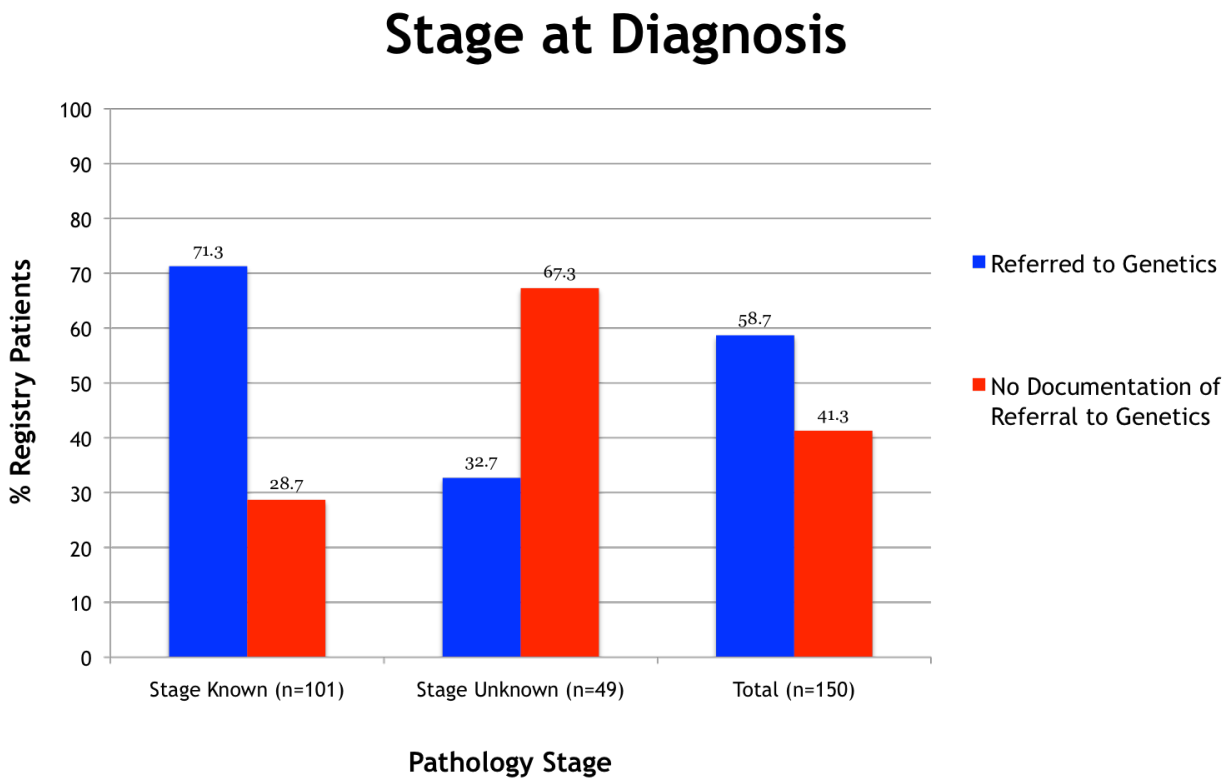
To confirm that the significant difference seen by stage at diagnosis was primarily due to the lower referral rates in patients with unknown stage, patients in the study sample were then categorized into two subgroups: “Known Stage” and “Unknown Stage” cancer (Table 6, Figure 5). Of the subgroup of patients from the study sample, 71.3% (72/101) of patients with Known Stage ovarian cancer were found to have documentation of referral to cancer genetics, and 32.7% (16/49) of patients with Unknown Stage ovarian cancer were found to have documentation of referral to cancer genetics. When rates for documentation of referral were compared across known vs. unknown stage at diagnosis, differences were statistically significant ($p<0.0005$).

Table 6. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Stage of Diagnosis (Known Stage vs. Unknown Stage)

Stage at Diagnosis	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Total Patients
	N	%	N	%	N
Known Stage	72	71.3	29	28.7	101
Unknown Stage	16	32.7	33	67.3	49
Total	*88*	*58.7*	*62*	*41.3*	*150*

Table 6. p<0.0005; statistically significant association between unknown cancer stage and no documentation of referral to cancer genetics.

Figure 5. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Stage of Diagnosis (Known Stage vs. Unknown Stage)



3.5 Histology

Tumor histology of ovarian cancer patients from the CCR with documentation of referral to cancer genetics was compared to tumor histology of those with no documentation of referral to cancer genetics (Table 7).

Of the patients with clear cell tumors, 55.6% (5/9) had documentation of referral to cancer genetics, while 44.4% (4/9) had no documentation of referral to cancer genetics. Of the patients with endometrioid tumors, 70.6% (12/17) had documentation of referral to cancer genetics, while 29.4% (5/17) had no documentation of referral to cancer genetics. Of the patients with serous tumors, 60.8% (48/79) had documentation of referral to cancer genetics, while 39.2% (48/79) had no documentation of referral to cancer genetics. Of the patients with mucinous tumors, 75.0% (3/4) had documentation of referral to cancer genetics, while 25.0% (1/4) had no documentation of referral to cancer genetics. Of the patients with sex-chord stromal tumors, 0.0% (0/2 had documentation of referral to cancer genetics, while 100.0% (2/2) had no documentation of referral to cancer genetics. Of the patients with germ cell tumors, 0.0% (0/1) had documentation of referral to cancer genetics, while 100.0% (1/1) had no documentation of referral to cancer genetics. Of the patients with other/NOS/unknown tumors, 52.6% (20/38) had documentation of referral to cancer genetics, while 47.4% (18/38) had no documentation of referral to cancer genetics.

When rates for documentation of referral were compared across tumor histology, differences were not statistically significant (p=0.375).

Table 7. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Histology

Histology	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Total Patients	
	N	%	N	%	N	%
Clear Cell	5	55.6	4	44.4	9	100.0
Endometrioid	12	70.6	5	29.4	17	100.0
Serous	48	60.8	31	39.2	79	100.0
Mucinous	3	0.0	1	100.0	4	100.0
Sex-Chord Stromal	0	0.0	2	100.0	2	100.0
Germ Cell	0	0.0	1	100.0	1	100.0
Other/NOS/Unknown	20	52.6	18	47.4	38	100.0
Total	*88*	*58.7*	*62*	*41.3*	*150*	*100.0*

Table 7. p=0.375; not statistically significant.

To determine whether tumor histology was associated with referral rate, patients in the study sample were then categorized into two subgroups: "Known Histology" and "Unknown Histology" (Table 8). Of the subgroup of patients from the study sample, 60.7% (68/112) of patients with Known Histology had documentation of referral to cancer genetics, and 52.6% (20/38) of patients with Unknown Histology had documentation of referral to cancer genetics. When rates for documentation of referral were compared across known vs. unknown histology, differences were not statistically significant (p=0.382).

Table 8. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Histology (Known Histology vs. Unknown Histology)

Histology	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Total Patients
	N	%	N	%	N
Known Histology	68	60.7	44	39.3	112
Unknown Histology	20	52.6	18	47.4	38
Total	*88*	*58.7*	*62*	*41.3*	*150*

Table 8. p=0.382; not statistically significant.

To determine whether tumor histology was associated with known vs. unknown stage at diagnosis, patients in the study sample were categorized into two subgroups: "Known Histology" and "Unknown Histology," and "Known Stage" and "Unknown Stage" (Table 9). Of the subgroup of patients from the study sample, stage was known for 74.1% (83/112) of patients with Known Histology and for 47.4% (18/38) of patients with Unknown Histology.

The percent of patients with known vs. unknown stage differed significantly by known versus unknown histology ($p<0.0005$), signifying that patients with known stage were also more likely to have known histology (74.1% vs. 25.9% in those with unknown stage). This difference may partially explain the slightly lower observed referral rates (although not statistically significant) in those with unknown histology compared to those with known histology.

Table 9. Known vs. Unknown Stage at Diagnosis Compared to Known vs. Unknown Histology

Stage at Diagnosis vs. Histology	Stage Known		Stage Unknown		Total Patients
	N	%	N	%	N
Known Histology	83	74.1	29	25.9	112
Unknown Histology	18	47.4	20	52.6	38
Total	*101*	*67.3*	*49*	*32.7*	*150*

Table 9. p=0.002; statistically significant.

3.6 Insurance Type

The type of insurance held by ovarian cancer patients from the CCR with documentation of referral to cancer genetics was compared to the type of insurance held by those with no documentation of referral to cancer genetics (Table 10, Figure 6).

Of the patients with Medicaid insurance, 65.2% (15/23) had documentation of referral to cancer genetics while 34.8% (8/23) had no documentation of referral to cancer genetics. Of the patients with Medicare insurance, 66.7% (6/9) had documentation of referral to cancer genetics while 33.3% (3/9) had no documentation of referral to cancer genetics. Of the patients with Medicare with Medicaid Supplement insurance, 30.0% (3/10) had documentation of referral to cancer genetics while 70.0% (7/10) had no documentation of referral to cancer genetics. Of the patients with County Funded insurance, 75.0% (6/8) had documentation of referral to cancer genetics while 25.0% (2/8) had no documentation of referral to cancer genetics. Of the patients with Tricare insurance, 0.0% (0/1) had documentation of referral to cancer genetics while 100.0% (1/1) had no documentation of referral to cancer genetics. Of the patients with no insurance, 100.0% (1/1) had documentation of referral to cancer genetics while 0.0% (0/1) had no documentation of referral to cancer genetics. Of the patients with Managed Care insurance, 55.0% (11/20) had documentation of referral to cancer genetics while 45.0% (9/20) had no documentation of referral to cancer genetics. Of the patients with Medicare with Managed Care insurance, 57.1% (4/7) had documentation of referral to cancer genetics while 42.9% (3/7) had no documentation of referral to cancer genetics. Of the patients with HMO insurance, 66.7% (2/3) had documentation of referral to cancer

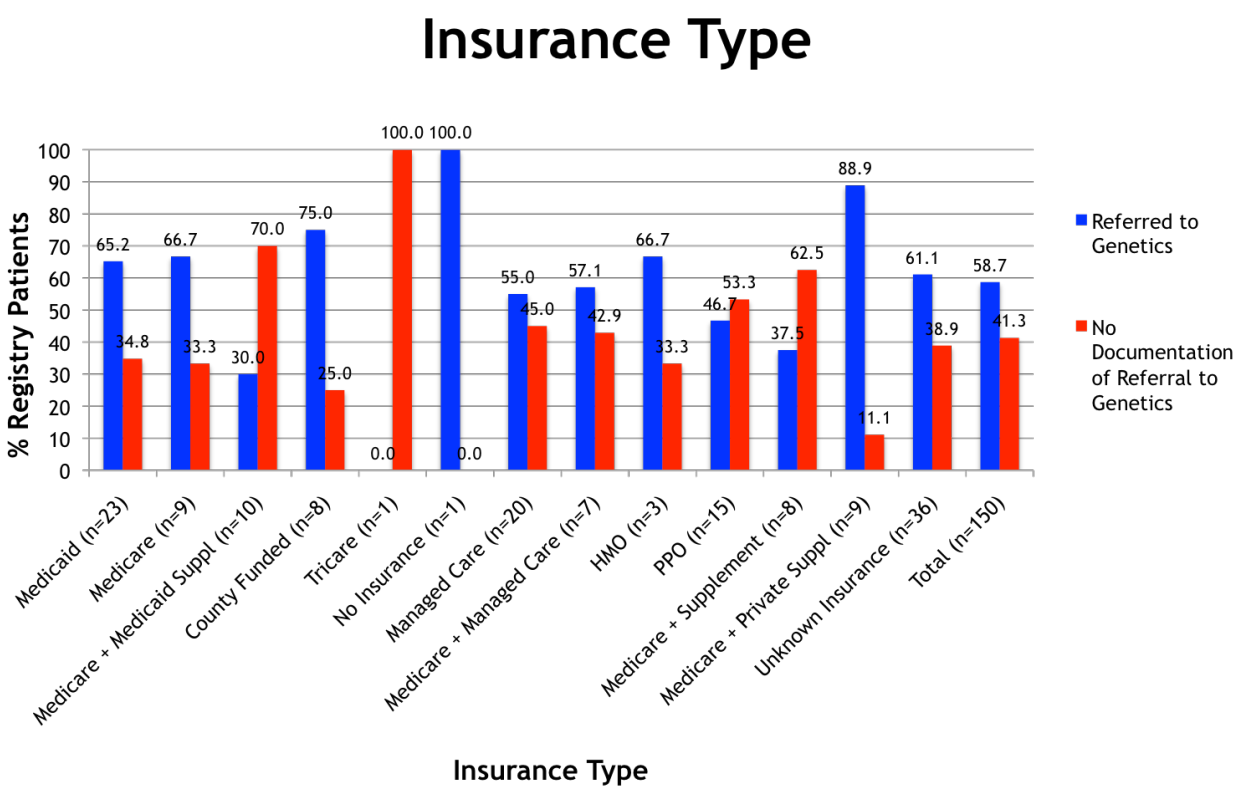
genetics while 33.3% (1/3) had no documentation of referral to cancer genetics. Of the patients with PPO insurance, 46.7% (7/15) had documentation of referral to cancer genetics while 53.3% (8/15) had no documentation of referral to cancer genetics. Of the patients with Medicare with Supplemental insurance, 37.5% (3/8) had documentation of referral to cancer genetics while 62.5% (5/8) had no documentation of referral to cancer genetics. Of the patients with Medicare with Private Supplemental insurance, 88.9% (8/9) had documentation of referral to cancer genetics while 11.1% (1/9) had no documentation of referral to cancer genetics. Of the patients with unknown insurance, 61.1% (22/36) had documentation of referral to cancer genetics while 38.9% (14/36) had no documentation of referral to cancer genetics.

The highest referral rates were seen for patients with Medicare with Private Supplement insurance (89%); the lowest referral rates were seen for patients with Medicare with Medicaid Supplement (30%) and Medicare with Supplement (unspecified) (38%). Numbers in each category were small; thus, statistical testing for differences in referral rates by all CCR insurance categories was not possible.

Table 10. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Insurance Type (All Insurance Types)

Insurance Type	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Total Patients
	N	%	N	%	N
Medicaid	15	65.2	8	34.8	23
Medicare	6	66.7	3	33.3	9
Medicare + Medicaid Supplement	3	30.0	7	70.0	10
County Funded	6	75.0	2	25.0	8
Tricare	0	0.0	1	100.0	1
No Insurance	1	100.0	0	0.0	1
Managed Care	11	55.0	9	45.0	20
Medicare + Managed Care	4	57.1	3	42.9	7
HMO	2	66.7	1	33.3	3
PPO	7	46.7	8	53.3	15
Medicare + Supplement	3	37.5	5	62.5	8
Medicare + Private Supplement	8	88.9	1	11.1	9
Unknown Insurance	22	61.1	14	38.9	36
Total	*88*	*58.7*	*62*	*41.3*	*150*

Figure 6. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Insurance Type (All Insurance Types)



Patients in the study sample were then categorized into four subgroups to further analyze whether there was an association between insurance type and documentation of referral to cancer genetics: (1) "Low-Income Insurance" includes Medicaid/Medicare/Medicare+Medicaid Supplement/County-Funded/Tricare/No insurance; (2) "Managed Care Insurance" includes Managed Care/Medicare+Managed Care Supplement/HMO; (3) "Private Insurance" includes PPO/Medicare+Supplement/Medicare+Private Supplement; and (4) "Unknown Insurance." Documentation of referral to cancer genetics was then compared across these four subgroups (Table 11, Figure 7).

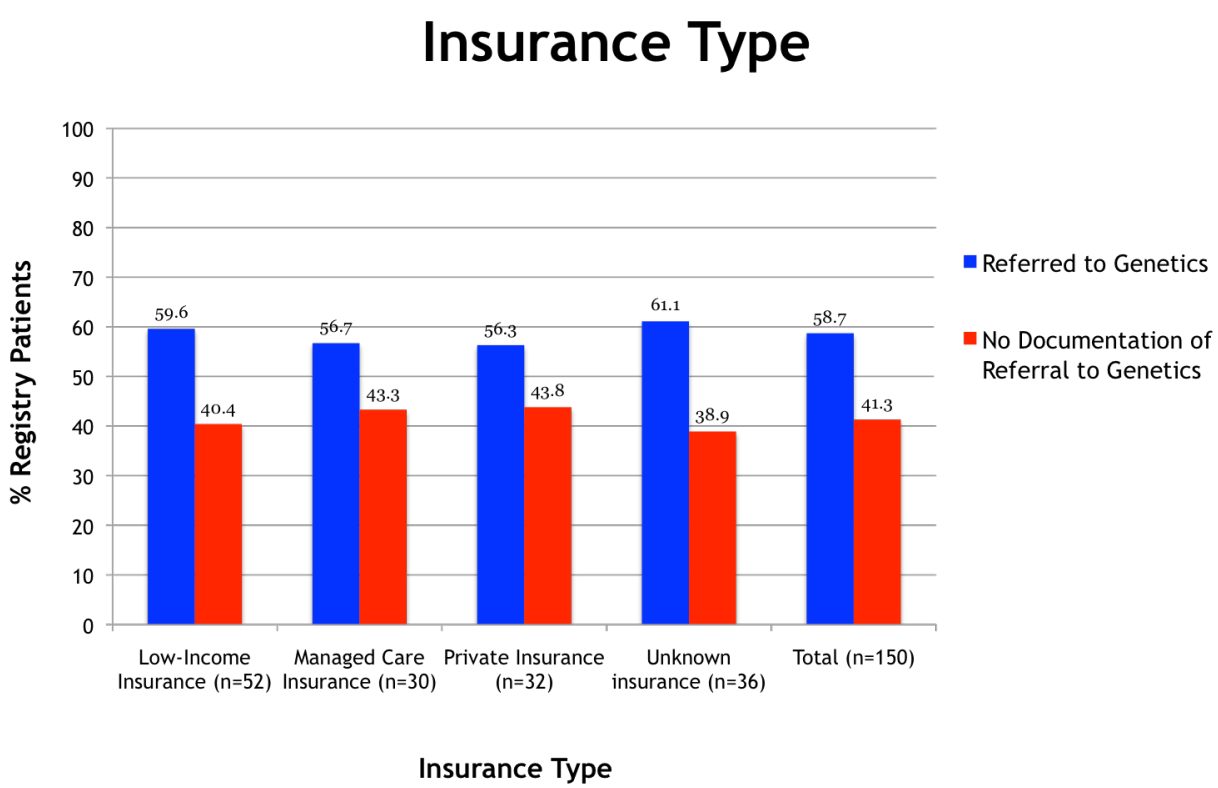
Of the subgroup of patients with "Low-Income Insurance," 59.6% (31/52) had documentation of referral to cancer genetics while 40.4% (21/52) had no documentation of referral to cancer genetics. Of the patients with "Managed Care Insurance," 56.7% (17/30) had documentation of referral to cancer genetics while 43.3% (13/30) had no documentation of referral to cancer genetics. Of the patients with "Private Insurance," 56.3% (18/32) had documentation of referral to cancer genetics while 43.8% (14/32) had no documentation of referral to cancer genetics. Of the patients with "Unknown Insurance," 61.1% (22/36) had documentation of referral to cancer genetics while 38.9% (14/36) had no documentation of referral to cancer genetics. Differences in referral rates between patients classified by insurance type were not statistically significant ($p=0.972$).

Table 11. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Insurance Type (Insurance Subgroups)

Insurance Type	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Total Patients
	N	%	N	%	N
Low-Income Insurance	31	59.6	21	40.4	52
Managed Care Insurance	17	56.7	13	43.3	30
Private Insurance	18	56.3	14	43.8	32
Unknown insurance	22	61.1	14	38.9	36
Total	*88*	*58.7*	*62*	*41.3*	*150*

Table 11. p=0.972; not statistically significant.

Figure 7. Referred to Cancer Genetics vs. No Documentation of Referral to Cancer Genetics by Insurance Type (Insurance Subgroups)



3.7 Known vs. Unknown Stage Compared with Other Demographic Characteristics

Chi-square analysis was used to examine the association between stage (known versus unknown) and referral rate after adjusting for the other variables in the analysis (age at diagnosis, ethnicity, and insurance type) (Table 12). Differences due to age, ethnicity, and insurance type were not found to be associated with the significantly lower referral rates when patients were stratified by known vs. unknown stage at diagnosis [Known Stage: p=0.948 (Age at Diagnosis), p=0.696 (Ethnicity), p=0.642 (Insurance Type); Unknown Stage: p=0.376 (Age at Diagnosis), p=0.692 (Ethnicity), p=0.716 (Insurance Type)].

Patients with known stage had a significantly higher odds ratio for referral to genetics (OR-5.1, 95% CI 2.5-10.7). Differences in age at diagnosis, ethnicity and insurance type did not explain the difference in referral rates for patients with known vs. unknown stage.

Table 12. Known vs. Unknown Stage for All Patients Compared with Other Demographic Characteristics and Referral Status

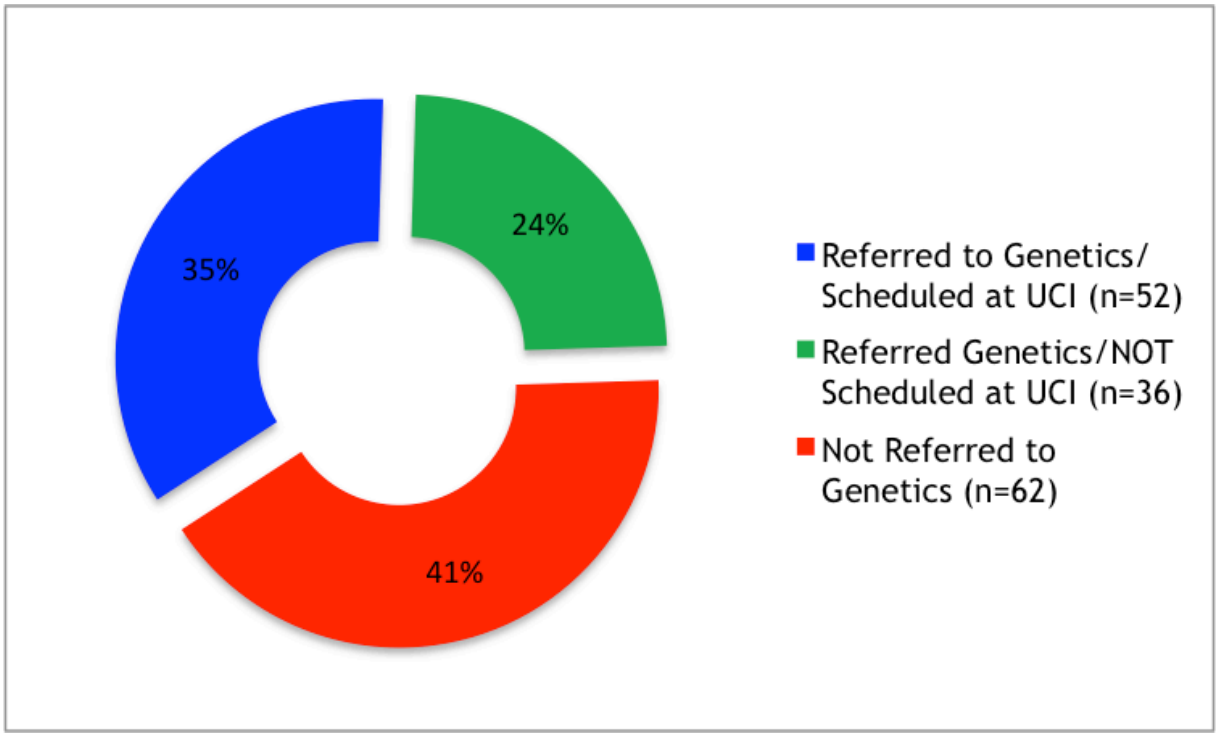
	Known Stage				Unknown Stage			
	Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics		Referred to Cancer Genetics		No Documentation of Referral to Cancer Genetics	
Age at Diagnosis	N	%	N	%	N	%	N	%
≤48	21	67.7	10	32.3	1	14.3	6	85.6
49-58	22	73.3	8	26.7	3	33.3	6	66.7
59-69	12	63.2	7	36.8	4	19.0	17	81.0
70+	12	75.0	4	25.0	8	47.0	9	52.9
Total	*67*	*69.8*	*29*	*30.2*	*16*	*29.6*	*38*	*70.4*
Ethnicity	N	%	N	%	N	%	N	%
White/Non-Hispanic	39	69.6	17	30.4	8	30.8	18	69.2
Hispanic	15	68.2	7	31.8	3	33.3	6	66.7
Black	0	0.0	0	0.0	0	0.0	2	100
Asian	18	78.3	5	21.7	5	41.7	7	58.3
Total	*72*	*71.3*	*29*	*28.7*	*16*	*32.7*	*33*	*67.3*
Insurance Type	N	%	N	%	N	%	N	%
(1) Low Income Insurance	25	73.5	9	26.5	6	33.3	12	66.7
(2) Managed Care Insurance	12	63.2	7	36.8	5	45.5	6	54.5
(3) Private Insurance	16	66.7	8	33.3	2	25.0	6	75.0
(4) Unknown Insurance	19	71.3	5	20.8	3	25.0	9	75.0
Total	*72*	*71.3*	*29*	*28.7*	*16*	*32.7*	*33*	*67.3*

Table 12. Chi-Square values for Known Stage: p=0.948 (Age at Diagnosis), p=0.696 (Ethnicity), p=0.642 (Insurance Type); Chi-Square values for Unknown Pathology: p=0.376 (Age at Diagnosis), p=0.692 (Ethnicity), p=0.716 (Insurance Type).

3.8 Descriptive Analyses for CCR Patients Scheduled in UCI Cancer Genetics Clinic

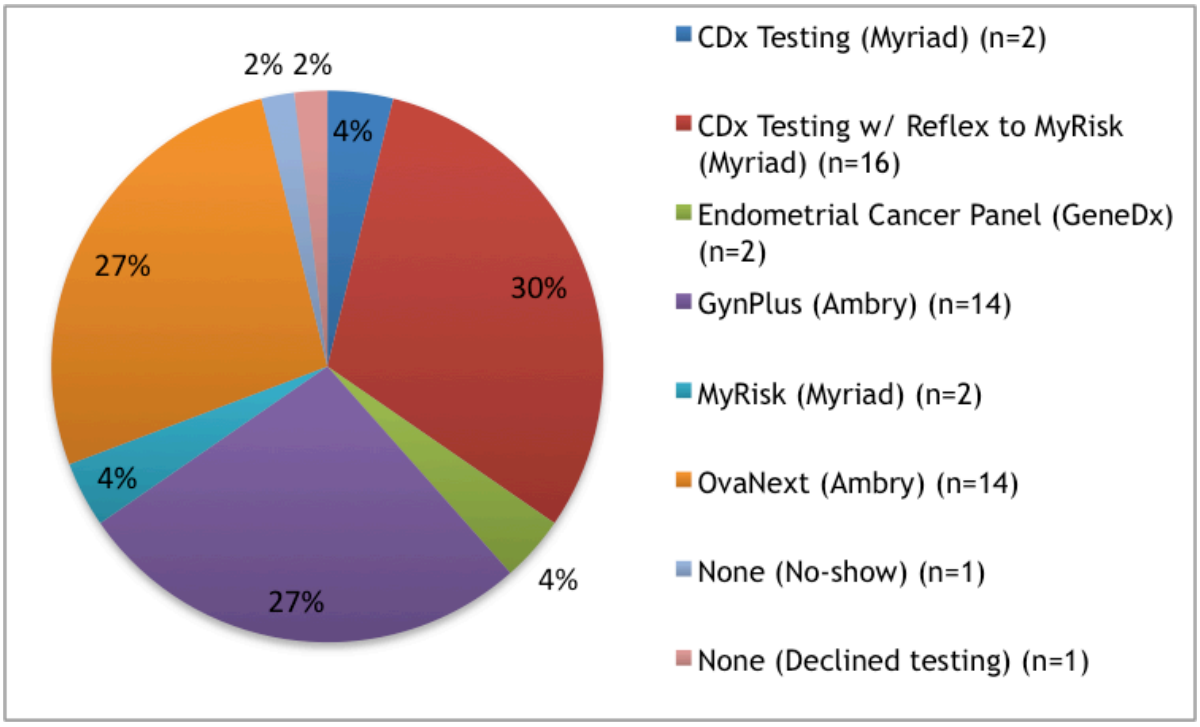
Of the 150 ovarian cancer patients in the study sample, 35% (52/150) were referred to cancer genetics and were scheduled in the cancer genetics clinic at UC Irvine, 24% (36/150) were referred to cancer genetics and were not scheduled in the cancer genetics clinic at UC Irvine, and 41% (62/150) had no documentation of referral to cancer genetics (Figure 8).

Figure 8. Total Registry Patient Breakdown for Study Sample



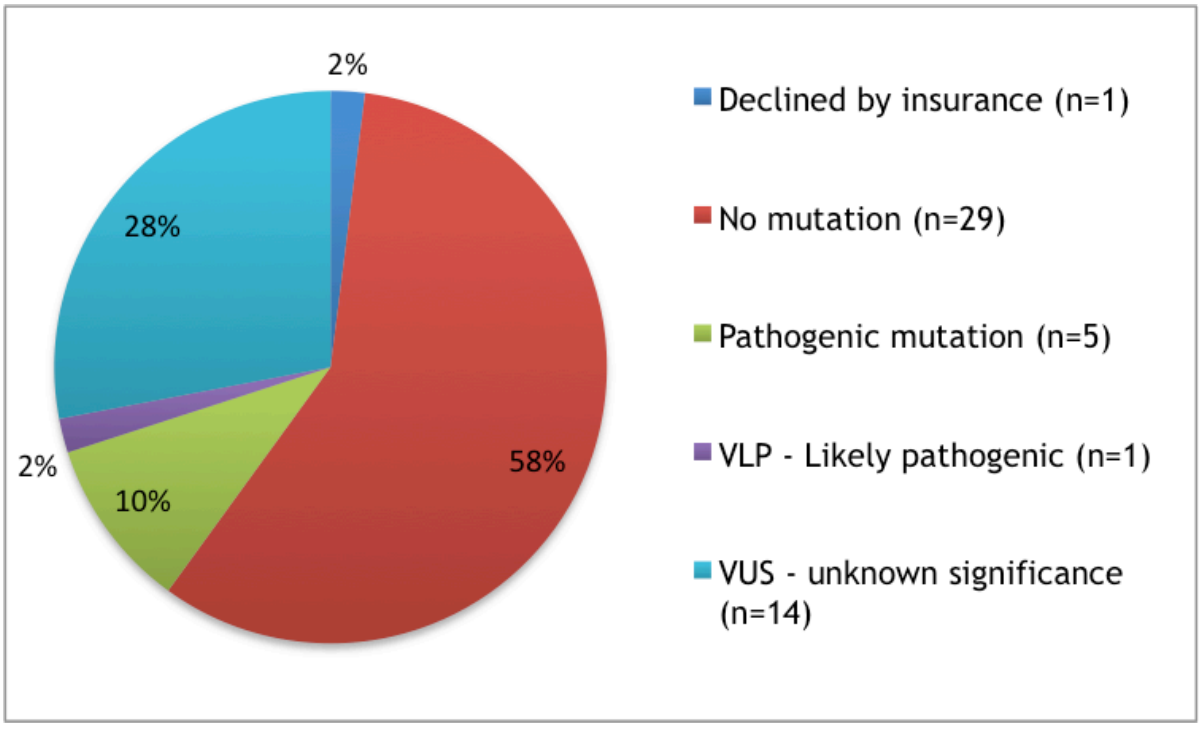
Of the patients in the study sample who were referred to cancer genetics and scheduled in the cancer genetics clinic at UC Irvine, 4% (2/52) had CDx Testing through Myriad Genetics, 30% (16/52) had CDx Testing with Reflex to the MyRisk panel through Myriad Genetics, 4% (2/52) had the Endometrial Cancer Panel through GeneDx, 27% (14/52) had the GynPlus panel through Ambry Genetics, 4% (2/52) had the MyRisk panel through Myriad Genetics, 27% (14/52) had the OvaNext panel through Ambry Genetics, 2% (1/52) did not show up to their appointment, and 2% (1/52) declined genetic testing (Figure 9).

Figure 9. Specific Test Ordered for N=52 Patients Scheduled in Cancer Genetics at UC Irvine



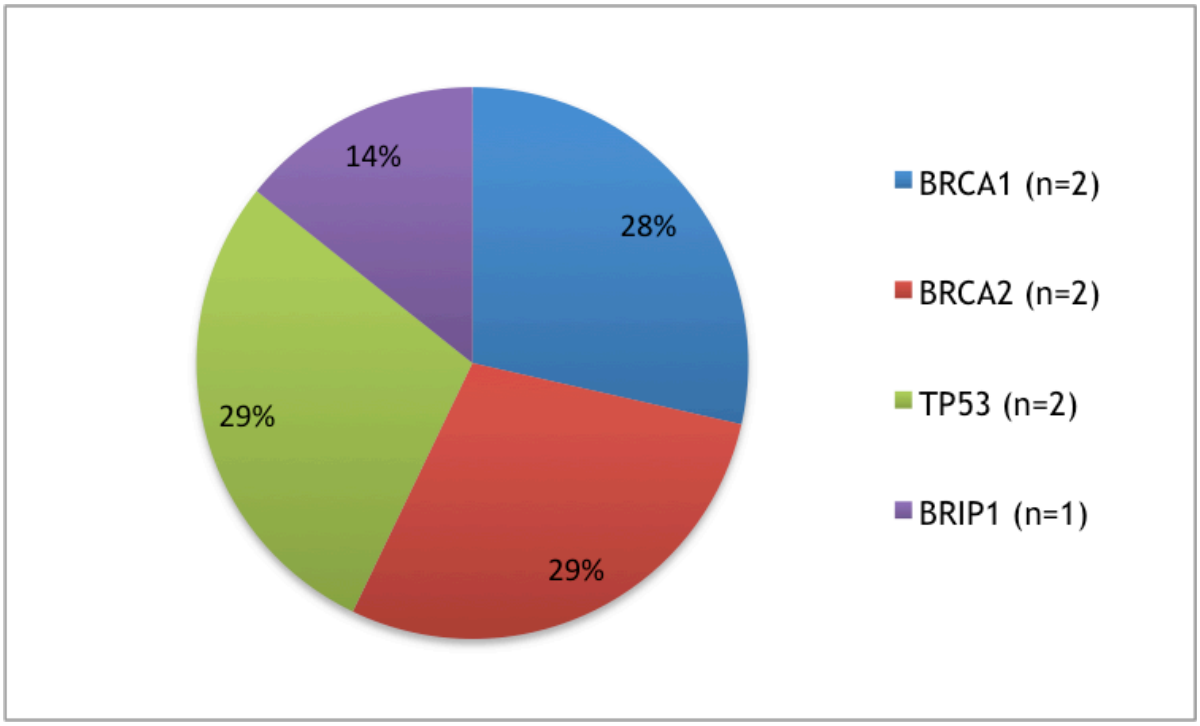
Of the patients in the study sample who were referred to cancer genetics, scheduled in the cancer genetics clinic at UC Irvine and chose to undergo genetic testing, 2% (1/50) had testing declined by their insurance, 58% (29/50) had no mutation identified, 10% (5/50) had a pathogenic mutation identified, 2% (1/50) had a likely pathogenic variant (VLP) identified, and 28% (14/50) had a variant of unknown significant (VUS) identified (Figure 10).

Figure 10. Test Results for N=50 Patients Scheduled in Cancer Genetics at UC Irvine



Of the patients in the study sample who were referred to cancer genetics, scheduled in the cancer genetics clinic at UC Irvine, chose to undergo genetic testing, and had a pathogenic mutation or likely pathogenic variant identified, 28% (2/7) had a pathogenic mutation or VLP identified in *BRCA1*, 29% (2/7) in *BRCA2*, 29% (2/7) in *TP53*, and 14% (1/7) in *BRIP1* (Figure 11).

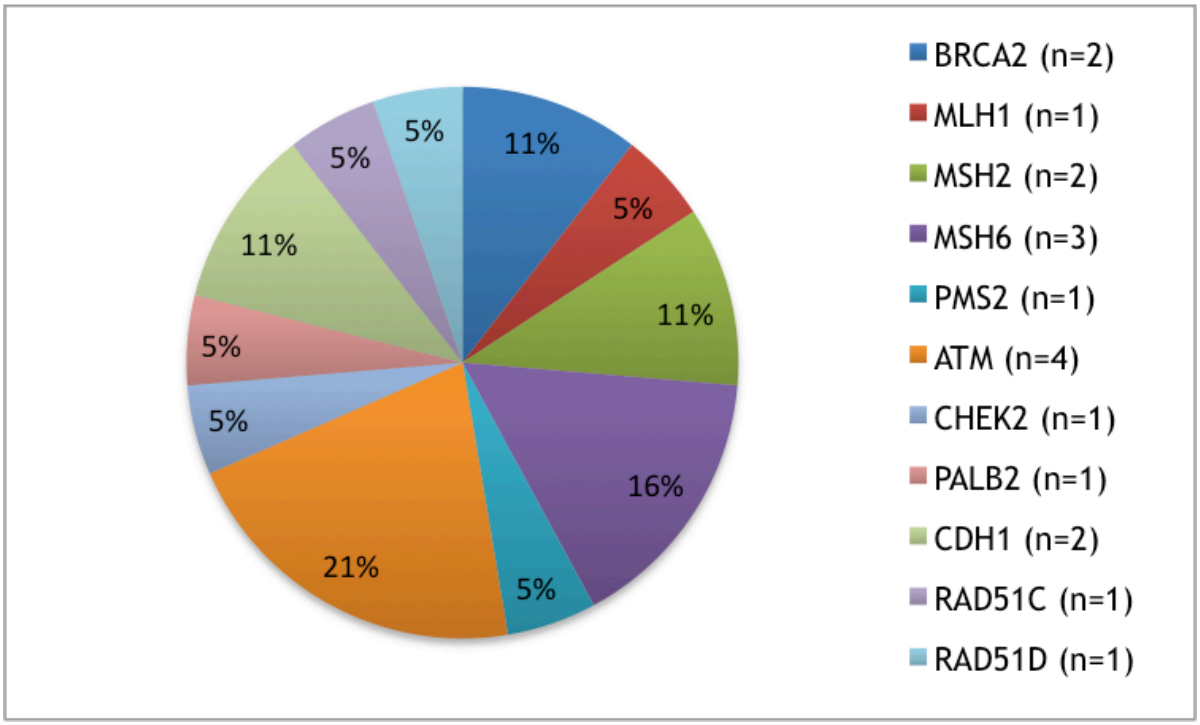
Figure 11. Test Results for N=6 Patients Scheduled in Cancer Genetics at UC Irvine: Genes Identified with Pathogenic Mutations and/or Likely Pathogenic Variants (VLP)



*** Total number of pathogenic mutations/VLP's is greater than 6 because each patient may have had a pathogenic mutation/VLP identified in one or more genes.*

Of the patients in the study sample who were referred to cancer genetics, scheduled in the cancer genetics clinic at UC Irvine, chose to undergo genetic testing and had a variant of unknown significance identified, 11% (2/19) had a VUS identified in *BRCA1*, 5% (1/19) in *MLH1*, 11% (2/19) in *MSH2*, 16% (3/19) in *MSH6*, 5% (1/19) in *PMS2*, 21% (4/19) in *ATM*, 5% (1/19) in *CHEK2*, 5% (1/19) in *PALB2*, 11% (2/19) in *CDH1*, 5% (1/19) in *RAD51C*, and 5% (1/19) in *RAD51D* (Figure 12).

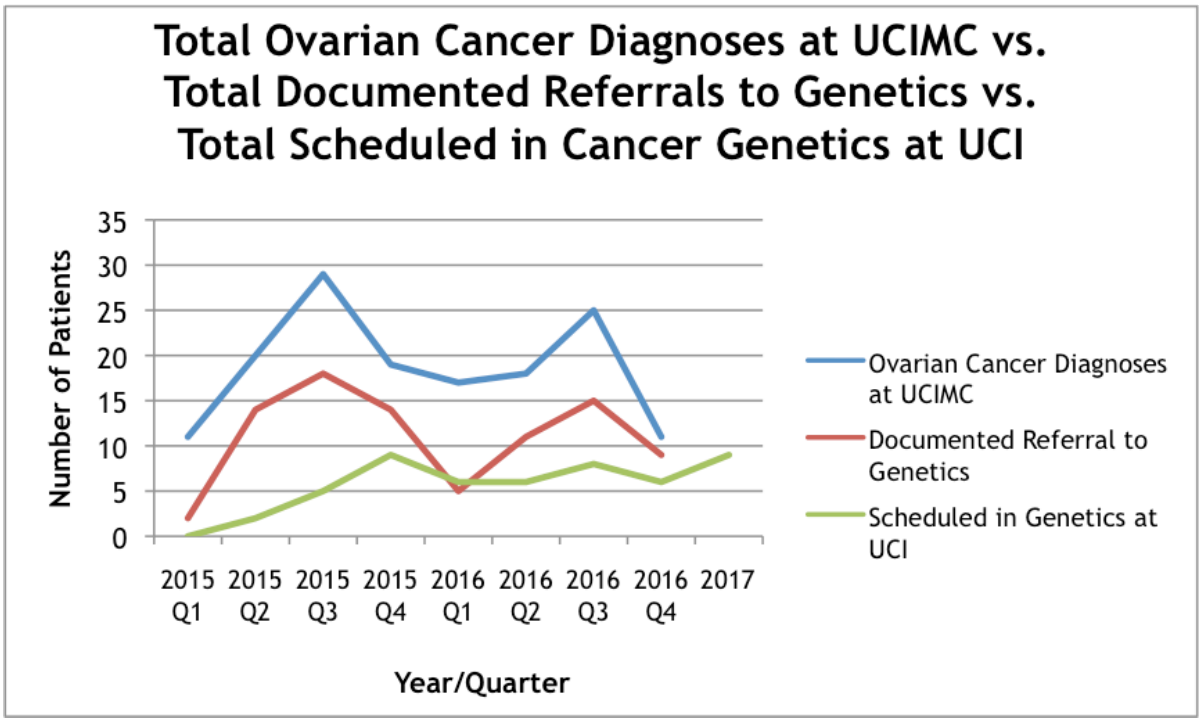
Figure 12. Test Results for N=14 Patients Scheduled in Cancer Genetics at UC Irvine: Genes Identified with Variants of Unknown Significance (VUS)



*** Total number of VUS's is greater than 14 because each patient may have had a VUS identified in one or more genes.*

The total number of ovarian cancer diagnoses made at UCIMC (January 1, 2015-January 1, 2017), total documented referrals to genetics (January 1, 2015-January 1, 2017) and total scheduled in the cancer genetics clinic at UC Irvine (January 1, 2015-onward) were examined over time for any observed differences (Figure 13). A peak in "Ovarian Cancer Diagnoses at UCIMC" and "Documented Referral to Genetics" was seen in the third quarter of both 2015 and 2016, followed by a peak in "Scheduled in Genetics at UCI" in the fourth quarter. Both the numbers of "Ovarian Cancer Diagnoses at UCIMC" and "Documented Referral to Genetics" appear to have decreased from 2015 to 2016. The number of patients "Scheduled in Genetics at UCI" appears to have increased from 2015 to 2017.

Figure 13. Total Ovarian Cancer Diagnoses at UC Irvine Medical Center vs. Total Documented Referrals to Genetics vs. Total Scheduled in Cancer Genetics at UC Irvine



4 DISCUSSION

As scientific and technological advances continue to revolutionize the field of clinical cancer genetics, an understanding of the unique value that genetic risk assessment and testing can add to medical management in the realms of prevention, targeted treatment, and pre-symptomatic screening strategies is imperative to optimizing the outcomes of patient care. Referral to cancer genetics in the context of personal and/or family history of cancer thus becomes increasingly important, as does the need to gather information regarding the decision-making of providers in the referral process of their patients for genetics consultation and evaluation.

This study aimed to determine whether specific demographic variables (age at diagnosis, ethnicity, stage of cancer, and insurance type) distinguished a population of patients referred for genetics consultation upon receiving a diagnosis of ovarian cancer from those who were not referred. By obtaining and reviewing data from the California Cancer Registry, electronic medical records, and the Cancer Genetics Clinic database at UC Irvine for the 150 patients who were diagnosed with ovarian cancer at UC Irvine Medical Center between January 1, 2015 and January 1, 2017, we were able to explore these potential predictors of genetics referral across a two-year time frame following the NCCN guideline update in 2014, which recommended genetics consultation and evaluation for all women with ovarian cancer.

Perhaps the most important conclusion to be drawn from this research is that women with ovarian cancer continue to be under-referred for cancer genetic counseling. Our study found that only 59% (95% CI +/- 8%) of the study sample had documentation of

referral to cancer genetics following their diagnosis. In other words, based on our study sample, the referral rate has a 95% probability of ranging between 51-67%, while the recommendation is that *all* ovarian cancer patients be referred.

This lack of referral to cancer genetics could have adverse effects on health outcomes -- for the patient herself if the underlying genetic etiology for her ovarian cancer is due to a genetic change that also predisposes her to additional types of cancer, as well as for her family members who may be currently unaffected but also share the same genetic change. Genetic testing also acts as an important tool in assisting in optimal choice of treatment. Many treatments that have been developed over the recent years are specific to tumor genetics, meaning that they are more effective for patients who are carriers of specific mutations. Thus, the choice of the best treatment for a patient renders genetic testing a critical component of their cancer care. Additionally, the genetics evaluation of the 40% of the ovarian cancer patients with no documentation of referral to cancer genetics could provide an opportunity to learn more about the possible genetic etiologies of ovarian cancer through genetic testing and thus aid in furthering our understanding of the underlying causes of the disease. Assuming that this analysis can be generalized to the referral practices of other large medical centers, the missed opportunity could be consequential both for the patients and their families and for the field of cancer genetics on a broader scale.

The distribution of ages at diagnosis in the study sample was observed to be 18.1% aged 20-44, 44.3% aged 45-64, and 37.6% aged 65 or older. In comparison to the expected distribution of age at diagnosis for ovarian cancer patients in all of California as reported by the CCR (17.2% aged 20-44, 42.9% aged 45-64, and 39.9% aged 65 or older), our data

appeared consistent (California Cancer Registry, California Department of Public Health 2013). While referral rates were seen to be lower for younger women and higher for older women, there was no trend with increasing age. It does not appear that age differences are responsible for the differences seen in referral rate.

The ethnic distribution in the study sample was observed to be 54.7% White/Non-Hispanic, 20.7% Hispanic, 1.3% Black, and 23.3% Asian (Table 1). This distribution was consistent with the expected ethnic distribution for ovarian cancer patients in all of California as reported by the CCR: 62.5% White/Non-Hispanic, 20.9% Hispanic, 4.9% Black, and 10.8% Asian (California Cancer Registry, California Department of Public Health 2013). The fact that UCIMC is located in Orange County, where there is a larger Asian population than in most other areas of the state, likely explains the higher proportion of Asian ovarian cancer patients observed compared to expected.

Data from the study sample for distribution of stage at diagnosis was also compared to data reported by the CCR for ovarian cancer patients in all of California. In the study sample, 12.7% patients had Stage 1 ovarian cancer, 11.3% had Stage 2 ovarian cancer, 31.3% had Stage 3 ovarian cancer, 12.0% had Stage 4 ovarian cancer, and 32.7% had Other/Unknown stage ovarian cancer (Table 1). The CCR reported a distribution of 24.0% for Stage 1, 6.1% for Stage 2, 27.9% for Stage 3, 21.0% for Stage 4, and 21.1% for Unknown stage (California Cancer Registry, California Department of Public Health 2013). The percentage of patients with unknown stage at diagnosis in our study sample was higher than that reported by the CCR overall, though similar to that reported by Yang et al. 2016 for ovarian cancer patients in case-control studies participating in the Ovarian Cancer Association Consortium.

Of the four demographic characteristics studied, ethnicity, insurance type and age at diagnosis were not found to be statistically significantly associated with genetics referral. When analyzing stage at diagnosis, however, patients with "other/unknown" stage of cancer were found to have a significantly lower percentage of documented referral to cancer genetics than patients with early and late stage cancer. Comparison between patients with unknown stage at diagnosis and those with known stage illustrated this statistical significance ($p<0.0005$).

The high proportion of patients with "other/unknown" stage ovarian cancer led us to conduct further analyses to determine whether a patient in this category is more likely to be within a certain subgroup of ethnicity, insurance type, and/or age at diagnosis. No statistically significant associations were seen between these variables for either the referred group or the group with no documentation of referral to genetics. Therefore, there does not appear to be any association between unknown stage at diagnosis and a particular subgroup of age at diagnosis, ethnicity, insurance type, or histology. With the data we had available, we could not explain the lower referral rates in women with unknown stage at diagnosis.

Ovarian cancer comprises several distinct histology groups that confer a range of prognoses. Given the high proportion of "other/unknown" stage cancers in the dataset, we examined the tumor histology data to determine whether there appeared to be a statistically significant association between histology and documented referral rate to cancer genetics. There were no differences seen in referral rates by histology, suggesting that the tumor histology and its anticipated prognosis in each case did not affect the likelihood of a patient having a documented referral to cancer genetics. Furthermore, when

compared to population-based data in the literature for the distribution of cases by tumor histology (Wentzensen et al. 2016, Yang et al. 2012), the observed distribution within our study sample remained largely consistent with the expected distribution (Table 13). In the Yang et al. study specifically, ovarian cancer diagnoses and tumor histology were ascertained through the crosschecking of cancer registries across the United States, thus allowing a suitable comparison for the observed distribution in our study. If our study sample had a higher percentage of patients with unknown stage at diagnosis than expected, this might have contributed to the lower referral rates seen for those patients (i.e. incomplete data). However, given that the percentage of patients with unknown stage is similar to what has been seen in other studies, there must be some other explanation for the lower referral rates for this group. Our data were unable to identify what patient characteristic was responsible for the lower referral rates among ovarian cancer patients with unknown stage at diagnosis.

Table 13. Histology Distribution in Study Sample Compared to Expected Distribution

Histology	Study Sample		Expected
	N	%	%
Clear Cell	9	6.0	3-6
Endometrioid	17	11.3	9-13
Serous	79	52.7	53-74
Mucinous	4	2.7	5-7
Sex-Chord Stromal	2	1.3	
Germ Cell	1	0.7	
Other/NOS/Unknown	38	25.3	30
Total	*150*	*100.0*	

Table 13. Data on expected distribution of histology obtained from Wentzensen et al. 2016 and Yang et al. 2012.

The number of patients with known vs. unknown histology was also compared to those with known vs. unknown stage at diagnosis to determine whether there could be overlap in the missing information across these two variables; the subsets of patients making up the two groups in each variable were not found to be the same. This left the lower referral rates observed for patients in the study sample with unknown stage at diagnosis still unexplained; it is possible that these patients received an inadequate clinical evaluation, which could explain the lower referral rate. It is also possible that their staging data were merely incomplete and not entered into the CCR database, however this is unlikely to explain the lower referral rate. However, given the current dataset, this reasoning cannot be substantiated.

Descriptive data for the patients in the study sample who were referred to cancer genetics and scheduled in the cancer genetics clinic at UC Irvine were categorized according to type of genetic test ordered and the genetic test results. Twelve percent of these patients were found to carry a pathogenic mutation or likely pathogenic variant, which is consistent with data in the literature suggesting that approximately 15-23% of ovarian cancer cases result from contributions of cancer-predisposition genes (Gayther 2010, Walsh et al. 2011). Additionally, 28% of the tested patients were found to have one or more variants of unknown significance; these variants may be re-classified later as more information is gathered regarding their pathogenecity or lack thereof.

Finally, the total number of ovarian cancer diagnoses made at UC Irvine Medical Center between January 1, 2015 and January 1, 2017 were compared to the number of referrals made to cancer genetics and to the number of patients who were referred to cancer genetics and scheduled in the cancer genetics at UC Irvine. Interestingly, a slight

peak was seen in the number of patients diagnosed with ovarian cancer at UCIMC in the third quarter of both 2015 and 2016. This peak was also seen in the number of referrals made to cancer genetics and in the number of patients who were referred to cancer genetics and scheduled to be seen in the cancer genetics clinic at UC Irvine. The later peak likely reflects the lag time between a referral to cancer genetics being made and an appointment being scheduled for the patient to be seen. Recent data on the seasonality of various conditions has described seasonal variation for ovarian cancer. Specifically, ovarian cancer was found to be among a cluster of conditions that exhibit "a pronounced and prolonged increase in [hospital] utilizations during the summer" (Haimovich et al. 2017). This identification of temporal variation is suggestive of a possible underlying seasonal factor that may explain the peaks in ovarian cancer diagnoses demonstrated by our study sample. The time of year during which a diagnosis of ovarian cancer is made was not found to have any significant influence on the prognosis of the disease (Liu et al. 2014).

Our data do not suggest any statistically significant association between the potential demographic predictors studied and referral rate. Therefore, specific subgroups that might have particularly low referral rates, with the exception of patients with unknown stage at diagnosis, could not be identified from this study sample.

The relatively small size of the study sample used in this research study is a limiting factor for the data analyses. It is possible that with a larger sample size, some differences (such as the lower referral rates for early stage vs. late stage) might have reached statistical significance. The relatively small size of this study confers limited power; with 75 patients per subgroup, we would have 80% power to detect a difference in referral rate of 20% using a two-tailed chi-square test with significance level 0.05. In general, the subgroups in

this study are smaller and have smaller differences, thus the study is underpowered to detect the observed differences.

It is also important to consider the influence of other essential factors that could not be addressed in this study. Among these are incomplete data from the CCR (i.e. unknown stage, insurance type), which may have resulted from variable information being known but not entered into the Registry. It is also possible that staging may have been listed prior to surgery based on biopsy and that the re-staging after surgery was not updated into the Registry, especially if the surgery was done at another hospital following diagnosis at UCIMC. Another alternative is that staging at diagnosis may not have been determined for some patients in the study sample.

An additional factor that may have affected the outcomes of this study is erroneous or incomplete documentation within the electronic medical records. In other words, lack of documentation of referral to cancer genetics may not accurately reflect the referral status of a given patient in the study sample if documentation practices are not properly followed. Furthermore, patients may have already had relevant genetic testing (i.e. based on family history, prior to personal diagnosis) that was not documented in their records; providers may have ordered genetic testing themselves that was not well-documented in the patient records (and thus would not have been identified in our reviewing of the EMR) without referring the patient for genetics consultation; and/or patients may have decided to seek cancer care (and/or genetics referral) elsewhere after diagnosis, in which case their EMR would not reflect any subsequent care at another facility.

Finally, the influence, or lack thereof, of data that we could not collect for this study must be considered. The role of possible provider influence on patient referral (i.e.

examining which physicians were and were not referring their patients to cancer genetics), as well as patients' family histories of cancer, which may have influenced their providers' decisions to refer versus not, were not able to be included in this study. Future studies should seek to clarify the potential effects of these factors and determine the significance of the influence they may have on a patient's referral status for genetics consultation that is indicated based on their personal health history.

The results of this investigation show that patients diagnosed with ovarian cancer are being under-referred to cancer genetics. This suggests that there is a general unmet need to further educate providers on the importance of referral for genetics evaluation in the context of ovarian cancer. Awareness of the potential benefits of genetics evaluation for these patients must be enhanced in order for referral rates to increase. While genetic counselors practicing in the cancer specialty are key sources of knowledge and awareness for their colleagues and patient populations, all genetic counselors and genetics professionals can play an important role in expanding awareness in this regard and improving the outcomes of patient care while simultaneously contributing to the growth of the field of cancer genetics. This would ultimately allow for the achievement of cancer risk reduction, early detection, and decreased cancer morbidity and mortality overall.

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