Impact of the 2014 NCCN guidelines for genetic testing on an academic gynecologic oncology practice

Hehir, Kristin
IMPACT OF THE 2014 NCCN GUIDELINES FOR GENETIC TESTING ON AN ACADEMIC GYNECOLOGIC ONCOLOGY PRACTICE

by

KRISTIN HEHIR

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Approved by

First Reader

Carl Franzblau, Ph.D.
Professor of Biochemistry

Second Reader

Judy E. Garber, M.D., M.P.H.
Director, Center for Cancer Genetics and Prevention
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
IMPACT OF THE 2014 NCCN GUIDELINES FOR GENETIC TESTING ON AN ACADEMIC GYNECOLOGIC ONCOLOGY PRACTICE

KRISTIN HEHIR

ABSTRACT

Objective: To determine the impact the change in NCCN guidelines for genetic counseling had on an academic Gynecologic Oncology practice. Further, to evaluate the patients being referred and the effectiveness of the genetic counseling referral process for ovarian cancer patients.

Design: A retrospective medical chart review was conducted of new ovarian cancer patients seen prior to (n=144) and following (n=173) the change in guidelines. Data such as cancer diagnosis, age at diagnosis, cancer family history, referral for genetic counseling, genetic counseling date, and genetic testing type was collected. Data was coded and analyzed using descriptive statistics and SPSS to determine if there was a statistically significant change before and after the guidelines publication.

Results: The referral rate for genetic counseling from January-March 2013 was determined to be 52% and in 2014 was 83.3%. This showed a 31.3% increase in
genetic counseling referrals (p=.019). However, there were still patients not being referred and some patients did not have complete genetic testing.

**Discussion:** The change in NCCN guidelines did have an impact on patient care in this academic gynecologic oncology clinic. An effective referral system needs to be set up not only for new patients, but also for established patients who never had genetic testing or had incomplete testing.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td>i</td>
</tr>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>iv</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>ix</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>METHODS</td>
<td>25</td>
</tr>
<tr>
<td>RESULTS</td>
<td>28</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>36</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>40</td>
</tr>
<tr>
<td>CURRICULUM VITAE</td>
<td>48</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baseline Characteristics of Patients Seen in the Gynecologic Oncology Clinic</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>Genetic Counseling Referral Rate Based on Age at Diagnosis</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>Genetic Counseling Referral Rate Based on Family History of Cancer.</td>
<td>34</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Top Ten Cancer Incidence and Death Rates by Gender</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>The Fanconi Anemia &amp; BRCA Pathway</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Genetic Test Results from BRCA Testing only and Panel Testing</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Flow chart of medical record review for January-March 2013</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Flow chart of medical record review for January-March 2014.</td>
<td>31</td>
</tr>
</tbody>
</table>
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Ataxia telangiectasia mutated</td>
</tr>
<tr>
<td>AT</td>
<td>Ataxia telangiectasia</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Breast Cancer Gene 1</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Breast Cancer Gene 2</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>Breast Cancer Genes 1 and 2</td>
</tr>
<tr>
<td>BRIP1</td>
<td>BRCA1-Interacting Protein 1</td>
</tr>
<tr>
<td>Ca-125</td>
<td>Cancer Antigen 125</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Checkpoint Kinase 2</td>
</tr>
<tr>
<td>DFCI</td>
<td>Dana Farber Cancer Institute</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DSBs</td>
<td>Double Strand Breaks</td>
</tr>
<tr>
<td>HBOC</td>
<td>Hereditary Breast-Ovarian Cancer Syndrome</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>LMR</td>
<td>Longitudinal Medical Record</td>
</tr>
<tr>
<td>MAP</td>
<td>MUTYH-associated Polyposis</td>
</tr>
<tr>
<td>MLH1</td>
<td>MutL homolog 1</td>
</tr>
</tbody>
</table>
MSH2 ......................................................................................... MutS protein homolog 2
MSH6 ......................................................................................... MutS protein homolog 6
MUTYH ...................................................................................... mutY Homolog
NCCN .................................................................................. National Comprehensive Cancer Network
PALB2 ...................................................................................... Partner And Localizer of BRCA2
PTEN .................................................................................. Phosphatase and tensin homolog
RAD51C ...................................................................................... RAD51 homolog C
RAD51D ...................................................................................... RAD51 homolog D
TP53 ................................................................................... Tumor Protein p53
INTRODUCTION

Epithelial ovarian cancer accounts for about 224,000 new cases of cancer per year and causes over 14,000 deaths per year. It is the tenth most common female cancer and the fifth in mortality rate (Figure 1) (Siegel et al., 2013). This demonstrates that ovarian cancer is a common and deadly cancer, which poses a public health issue that needs to be addressed. The high death rate is partially due to the cancer being diagnosed in late stages. Not only are there not adequate screening methods, but the symptoms of ovarian cancer can easily go un-noticed or be mistaken for other medical issues. The most common symptoms of ovarian cancer are bloating, abdominal pain, menstrual cycle changes, and urinary symptoms. While these symptoms can be identified, they are not unique to ovarian cancer and therefore make it difficult to diagnosis early. Typically by the time symptoms are noticed, the cancer has already spread (Jayson et al., 2014).
Figure 1. Top Ten Cancer Incidence and Death Rates by Gender.

Figure taken from Cancer Statistics in CA: A Cancer Journal for Clinicians.

Ovarian cancer is the tenth most common cancer and the fifth most common cause of death due to cancer among women.

The death rate of ovarian cancer has not significantly declined over the last 30 years despite the fact that there has been development of new therapies.
In comparison, the death rate of breast cancer has dropped 34% over the past 20 years (DeSantis et al., 2014). This decrease could be attributed to increased screening by mammograms resulting in early diagnosis and improved survival or the development of more effective therapies.

Diagnosing cancer at early stages is critical to overall survival. The five-year survival rate for stage one ovarian cancer is 90%; however only 15% of ovarian cancers are diagnosed at stage one. The majority of ovarian cancers are diagnosed at stage three and the five-year survival is only 50% (American Cancer Society, 2014). In comparison, the majority (61%) of breast cancers are diagnosed at stage one for which the five year survival rate is 98.5% (National Cancer Institute, 2011). Not only are more breast cancers diagnosed at earlier stages than ovarian cancer, but the survival rate at each stage is also superior.

Currently the only screening methods for ovarian cancer are pelvic exams, transvaginal ultrasounds, and measuring the tumor marker CA-125 in the blood (National Cancer Institute, 2014). CA-125 is a plasma protein that can be measured in the blood and can be used as a tumor marker for ovarian cancer. In many women with ovarian cancer CA-125 will be high and if their treatment is effective then there will be a drop in this tumor marker. However, not every woman with ovarian cancer has a high Ca-125 and sometimes healthy women
will have a high CA-125 (American Cancer Society, 2015). This makes it difficult to use CA-125 to detect ovarian cancer. In one study, it found that screening healthy women with CA-125 and transvaginal ultrasound leads to increased testing and surgeries, but did not have an impact on decreasing deaths from ovarian cancer (Fung et al., 2004). Therefore, it has been debated if these methods are valuable tools to recommend to patients. At the present time these screening methods are not used in the general population.

On the other hand, screening for breast cancer by mammography is used widely. For women without family history, mammograms are recommended on a personal basis for ages 40-49 and every two years for ages 50-74 (Nelson et al., 2009). This is recommended because there is a phase in breast cancer in which one is asymptomatic, but mammograms can typically detect the cancer (Harris et al., 2011). It has been found that for women ages 39-49 screening by mammograms will reduce a woman’s mortality by breast cancer by 15% (Nelson et al., 2009). However, there are negatives to mammograms such as false positives, pain during the procedure, radiation exposure, and anxiety or stress. Nonetheless, preventing breast cancer outweighs the negatives of mammograms for most women and the majority of women over the age of 40 decide to have annual mammograms (Pace et al., 2013). This demonstrates that in order to
decrease the mortality due to ovarian cancer, a more effective screening method needs to be developed.

Ovarian cancer is indisputably a difficult disease to treat, especially at late stages. There is a need for improved screening and prevention; however this has clearly been a challenging task to accomplish. The survival from ovarian cancer is especially poor once recurrence has occurred and about 71% will relapse at some point (National Cancer Institute, 2014). The median progression free-survival from ovarian cancer is about 18 months, which is not a desirable prognosis (Jayson et al., 2014). Clearly, there is a need to determine how to prevent and detect ovarian cancer in order to make progress with this difficult health issue.

**Risk Factors for Ovarian Cancer**

Risk factors for ovarian cancer include early menarche, late menopause, nullparity, obesity, personal history of breast cancer, and family history (Hunn & Rodriguez, 2012). Family history of ovarian cancer is the most influential risk factor in predicting if an individual will develop ovarian cancer in her lifetime. If someone has a first degree relative with ovarian cancer then her lifetime risk increases from 1.4% to 5%. That risk will then increase to 7% if there are 2 or more first degree relatives (Weissman et al., 2012). Accurate intake of family
history is especially crucial in ovarian cancer patients to help determine if there could be a hereditary factor that is related to their cancer.

One of the reasons family history is such an influential risk factor for ovarian cancer is the fact that there could be an underlying genetic mutation that increases one’s risk for ovarian cancer. It used to be thought that about 1 in every 10 women with ovarian cancer has a hereditary mutation. Over time that number has increased and currently data shows that about 1 in every 4-5 women with ovarian cancer carries a hereditary mutation (Weissman et al., 2012). This is compared to only 5-7% or 1 in every 14-20 women with breast cancer is found to have a hereditary mutation (Gage et al., 2012). In a short period of time the number of genes linked to ovarian cancer has grown. Presently, there are at least 16 genes that have been shown to confer an increased risk of hereditary ovarian cancer (Pennington et al., 2012).

Identifying genetic mutations in women with ovarian cancer is crucial since it has been proposed that greater than 30% of women with inherited mutations have no family history of breast or ovarian cancer (Walsh et al., 2011). Without finding these mutations in the affected individual there would be no reason to believe that these families are at high risk for ovarian cancer. The lack of family history in families with inherited mutations can partially be explained
by small families, lack of information, male dominated families, or inheritance from unaffected fathers.

The phenotype of hereditary breast and ovarian cancer syndrome (HBOC) includes young age at diagnosis, individuals with multiple primaries, bilateral breast cancer, male breast cancer and first or second degree relatives with these same cancers. HBOC is due to an inherited mutation that is passed on in an autosomal dominant pattern. This means that the mutation is not sex linked and the individual only needs one copy of the gene to be at increased risk (Powers & Stopfer, 2014). If a parent is heterozygous for a mutated copy of one of these genes then his or her children each has a 50% chance of inheriting that mutation. The only way to identify an inherited mutation is by genetic testing to analyze one’s DNA to determine if there is a pathogenic mutation in a particular gene.

Identifying genetic mutations is important because there is then the ability to take action to reduce one’s risk of cancer. Patients are encouraged to increase screening, use chemo-preventative measures, and have prophylactic surgeries. For example, patients with a BRCA 1 or BRCA2 mutation are recommended to have a prophylactic mastectomy and salpingo-oophorectomy. It is predicted that women undergoing both of these surgeries will have life expectancy gain of 3.3-11.7 years (Salhab et al., 2010). This demonstrates that identifying these
mutations early can allow action to be made in order to decrease the risk for cancer.

**BRCA1 and BRCA2**

The BRCA1 gene codes for a tumor suppressor protein that was discovered in 1990 and later cloned in 1994. BRCA1 is situated on the long q arm of chromosome 17 and translates into a predicted protein consisting of 1863 amino acids. The protein contains a zinc finger (Miki et al., 1994). The BRCA1 gene is expressed in breast, ovarian, and other related tissues. BRCA1 is responsible for maintaining chromosomal stability, sensing cell damage, and is involved in cell cycle checkpoints (Venkitaraman, 2002). In particular, BRCA1 is involved with repairing DNA double strand breaks through homologous recombination (Gudmundsdottir & Ashworth, 2006). Homologous recombination is an accurate method of DNA repair and essential to ensuring DNA stability. It was shown that mice deficient in BRCA1 were unable to repair DSBs by homologous recombination (Moynahan et al., 1999). The many roles of the BRCA1 protein are critical in preventing a cell from developing into a cancerous cell by assisting with DNA stability. The loss of a tumor suppressor protein such as BRCA1 will accelerate the development of cancer.
BRCA2 is also a tumor suppressor protein that is located on the q arm of chromosome 13 and encodes for a protein consisting of 3418 amino acids (Wooster et al., 1995). The gene was first discovered in 1994 a few years after BRCA1. BRCA2 is mostly expressed in breast and ovarian tissue, but is found in other tissues. BRCA2 plays an important role in repairing DNA double strand breaks and specifically acts through RAD51 (Gudmundsdottir & Ashworth, 2006). BRCA2 binds directly to RAD51 and this interaction is critical to identify DSBs (Davies et al., 2001). BRCA1/2 play important roles in the interaction with the Fanconi Anemia pathway, which controls the cell’s response to DNA damage (Figure 2) (D’Andrea & Grompe, 2003). Similar to BRCA1, the loss of BRCA2 will lead to DNA instability and accelerate the transformation of a cell from normal to cancerous.
Figure 2. The Fanconi Anemia & BRCA Pathway.

Figure taken from D’Andrea & Grompe (2003). The Fanconi Anemia pathway is activated upon DNA damage and interacts with BRCA1/2 in vivo.

Individuals will inherit one copy of each of the BRCA genes from their parents. Carriers of BRCA1 mutations are thought to have a lifetime breast cancer risk of 55-65% and ovarian cancer risk of 39-49%. Similarly, BRCA2 mutations will have a lifetime risk of breast cancer between 45-47% and ovarian cancer risk of 11-18% (Girolimetti et al., 2014). The BRCA1/2 genes are of high
penetrance (Chen & Parmigiani, 2007). BRCA1/2 are thought to account for the majority (about 50-80%) of hereditary breast and ovarian cancer families. It is estimated that BRCA1/2 mutations occur in about 1 in 400 individuals in the population, but this number depends on ethnicity (Petrucelli et al., 2013). In general, BRCA1/2 mutations are rare in the general population, but more common in families with compelling breast and ovarian cancer history.

**Lynch Syndrome**

Lynch syndrome is caused by mutations in germline mismatch repair genes such as MLH1, MSH2, MSH6, or PMS2. Mutations in these genes are inherited in an autosomal dominant pattern (Cohen & Leininger, 2014). Mismatch repair is a process that occurs in cells to help preserve DNA. If incorrect nucleotides are connected they can be identified and fixed by mismatch repair proteins. This process requires the coordination of many proteins. If one of those proteins is not functional then it leads to the inability to correct these changes and eventually unstable DNA (Zhang et al., 2015).

Lynch syndrome is also called Hereditary Nonpolyposis Colorectal Cancer. Individuals with Lynch syndrome are at a high risk for colon cancer, endometrial cancer, ovarian cancer, and stomach cancer. There is an 80% risk of developing colon cancer and the majority of these occur in the proximal colon.
The lifetime risk of ovarian cancer is anywhere from 4-11% (Weissman et al., 2012). It is believed that about 2-4% of ovarian cancer is due to inherited mutations in mismatch repair genes (Malander et al., 2006). If a family has colon and ovarian cancer history then Lynch Syndrome definitely needs to be considered.

**TP53**

TP53 is located on the short arm of chromosome 17 and encodes for the transcription factor protein p53 (Isobe et al., 1986). P53 is a key tumor suppressor protein that is involved in regulation of the cell cycle, DNA repair, apoptosis, and cellular senescence. P53 is normally activated under cell stress and p53 function is lost in the majority of cancers (Sorrell et al., 2013). P53 plays a key role in preventing uncontrolled cell growth; therefore germline TP53 mutations put individuals at high risk for many cancers. Germline mutations in TP53 are associated with Li-Fraumeni syndrome (Malkin et al., 1990). Penetrance is nearly 100% by the age of 70 (Mai et al., 2012).

Typically Li-Fraumeni syndrome is associated with bone or soft tissue sarcomas, adrenal cortical carcinomas, premenopausal breast cancers, and brain tumors. It is less frequently associated with ovarian cancer; however it is seen in individuals with TP53 mutations (Gonzalez et al., 2009).
**Moderate Penetrance Genes**

**PALB2**

PALB2 was named that because it stands for “partner and localizer of BRCA2”. The main role of PALB2 is to be the binding protein for BRCA2. It is believed that about 50% of PALB2 interacts with BRCA2 and vice versa (Xia et al., 2006). This indicates that a large portion of PALB2 is needed for the adequate function of BRCA2 DNA repair.

If one is heterozygous for a PALB2 mutation then it is thought that they are at increased risk for cancer. It has been estimated that a female with a mutation in PALB2 has a lifetime risk of breast cancer of about 35% (Antoniou et al., 2014). Families with PALB2 mutations tend to look like families with BRCA2 mutations.

**CHEK2**

CHEK2 is located on the long arm of chromosome 22 and is a protein kinase. CHEK2 is activated when damaged DNA is identified and then will stop a cell from going through mitosis (Cybulski et al., 2004). CHEK2 acts through the ATM gene. In addition, CHEK2 interacts with BRCA1, BRCA2, and TP53 in vivo and helps to ensure DNA stability.
CHEK2 is expressed in many tissues and has been associated with increased risk for cancer. In particular, CHEK2 has been estimated to increase one’s breast cancer risk by 2 fold (Walsh et al., 2006). CHEK2 mutations have also been associated with ovarian cancer, but the exact risk is not known (Walsh et al., 2011).

PTEN

PTEN is located on the q arm of chromosome 10 and encodes for a tumor suppressor protein (Steck et al., 1997). PTEN is expressed throughout various tissues in the body and acts through its phosphatase product to control the cell cycle (Chu & Tarnawski, 2004). Mutations in PTEN result in Cowden’s Syndrome, which is autosomal dominant. Cowden’s syndrome is typically associated with benign characteristics such as macrocephaly, uterine fibroids, or fibrocystic breasts (Eng, 2000). PTEN is commonly mutated in cancer and people with germline mutations have an elevated risk for breast, endometrial, colorectal, thyroid, and kidney cancers (Tan et al., 2012). Cases of individuals with PTEN mutations and ovarian cancer have been reported (Walsh et al., 2011).

ATM

ATM is located on the q arm of chromosome 11 and encodes for a protein that is 3056 amino acids long (Shiloh, 2003). The main function of the ATM
protein is to control cell division and assists with repairing double strand DNA breaks (Ellis & Offit, 2012). Homozygous germline mutations are associated with Ataxia-teangiesctasia (AT), which presents during childhood. AT results in progressive neurodegeneration, immune defects, and increased risk for cancer (McKinnon, 2004). Individuals who are heterozygous for ATM mutations are at risk for breast and pancreatic cancer (Geoffroy-Perez et al., 2001). ATM mutations have been reported in cases of ovarian cancer; however the exact risk is not known.

Other Genes

RAD51C

The RAD51 gene is thought to be involved in DNA repair by homologous recombination. In one study they found a RAD51C mutation in 1.3% of families with both breast and ovarian cancer (Meindl et al., 2010). Another study looking at probands with ovarian cancer found a RAD51C mutation in 2/360 participants (Walsh, 2011). Currently the exact cancer risk associated with RAD51C is not defined, but it is thought to elevate one’s risk for breast and ovarian cancer.
**RAD51D**

RAD51D is also involved in the Fanconi Anemia pathway and is involved with DNA repair. Mutations in RAD51D have been seen in highly penetrant breast and ovarian families (Pennington et al., 2012).

**MUTYH**

MUTYH is located on the short arm of chromosome 1 and is involved in base excision repair. Base excision repair is a process that fixes damaged DNA from reactive oxygen species. MUTYH is one of the many proteins involved in this pathway and helps to initiate this process (Cheadle & Sampson, 2003). MUTYH is important in ensuring stable DNA is maintained.

Individuals who are homozygous for the MUTYH mutation have MUTYH-associated polyposis (MAP). Individuals with MAP are at an 80% chance of developing colorectal cancer (Jenkins et al., 2006). If one is heterozygous for the MUTYH mutation then they are thought to have an increased risk of breast, stomach, and endometrial cancer (Rennert et al., 2012) (Win et al., 2011). MUTYH mutations have been reported in families with ovarian cancer, but the exact risk is not known (Walsh et al., 2011).
BRIP1

BRIP1 is located on chromosome 17 and encodes for a tumor suppressor protein (Walsh et al., 2010). BRIP1 is involved in the Fanconi Anemia pathway and interacts with BRCA1 in vivo to help with DNA repair. BRIP1 mutations have been seen in individuals with breast and ovarian cancer, but further studies need to be done in order to investigate the risk association (Seal et al., 2006).

Genetic Counseling

Genetic counseling is a time intensive process in which detailed family history is taken, patients are counseled on the meaning of mutations, the various test types available are discussed, and genetic testing is coordinated if desired. A typical genetic counseling visit will require at least one hour with a genetic counselor or genetics trained professional.

Family History Intake

The most important task of the genetic counselor is to obtain an accurate and thorough family history with a focus on cancer. It is suggested that the genetic counselor obtain at least three generations on both the maternal and paternal side of the family. This is typically recorded as a pedigree, which can help identify patterns that indicate an inherited cancer syndrome (Powers &
Stopfer, 2014). This is a time intensive process that most physicians do not have the time to coordinate.

Some families have striking family histories that are easily identifiable; however other families are not so obvious. This could be due to lack of accurate information, male dominated families, small family size, adoption, or interventions that reduce cancer risk (Stopfer, 2000). These factors are all things that genetic professionals are used to identifying, but a professional not exposed to genetics could easily overlook.

**Genetics Education**

After the family history intake, the genetic counselor’s role is to provide the patient with general genetics information such as pattern of inheritance, the implications of an inherited mutation for your family, penetrance of mutations, associated risk of various genes, type of testing available, and the various classification of results. Currently there are five classifications of results: definitely pathogenic, likely pathogenic, uncertain significance, likely not pathogenic, not pathogenic or negative (Plon et al., 2008). Patients need to be made aware of the various results they could receive before they decide to initiate testing. For some individuals, a variant of uncertain significance could be
difficult to deal with since it is unclear and they need to be prepared for the possibility.

Most patients have not been exposed to genetics before their visit and education is important, in order for them to be able to make an informed decision about testing. Ensuring that a patient has a thorough background of the implications is crucial before initiating testing because the results could not only have medical implications for themselves, but also their family members (DeMarco et al., 2007). Patients need to be informed on the meaning and limitations of test results before testing occurs (Ballinger, 2012).

**Genetic Testing**

Myraïd Genetics was the first lab to offer BRCA testing in the 1990’s. Until 2013 Myraïd Genetics held a patent for BRCA1/2 due to a supreme court ruling the patent was removed. Since then there have been an increase in clinical labs offering this testing. Most recently, a new technology called Next Generation Sequencing has been developed to allow for faster and more cost effective testing (Rainville & Rana, 2014). Next generation sequencing is a technology in which many sequences of a gene can be looked at in one reaction, which significantly decreases the amount of time and labor needed for analyzing one’s genes (Hilbers et al., 2013). Due to this development many cancer genetic clinics have
been offering panel tests in which genetic testing for multiple genes is ordered in one test. This allows patients the option to have 5-43 genes tested at once. The panels of genes are normally grouped by cancer syndrome. This type of testing allows for more complete testing, but also can be difficult due to the high rate of variants of uncertain significance and the lack of clinical information of some genes (Figure 3) (Hilbers et al., 2013). Panel testing has made counseling more difficult since there is a great need for more clinical information on these genes; however it has been helpful for some families in identifying a reason for one’s family history of cancer.

Figure 3. Genetic Test Results from BRCA Testing only and Panel Testing.

Figure taken from Hilbers et al (2013). If one has a panel tests versus only BRCA1/2 then there is a much higher chance that a variant of uncertain significance will be identified.
Disclosure of Test Results

The genetic counselor also has a critical role in post-test counseling. Their job is to disclose the results, explain implications of results, review recommendations, and give psychosocial support. If the result is negative then the patient must be told that that result is not completely informative. There could be other genes not yet identified that could confer increased risk of ovarian cancer and they should be encouraged to re-contact the genetic counselor as time goes on. This is especially important if there is a change in family history (Riley et al., 2012). With the rapid growth of genetic testing it is expected that testing and information about genes will be significantly changing in the next decade.

If the patient has a positive result then they should be advised to come back in to clinic for recommendations on screening and prevention. They also need to be encouraged to share this information with their family members and encourage their family to come in for testing (Riley et al., 2012). This is when the psychosocial evaluation is crucial in order to ensure the patient is getting the care they need.

If the individual has a variant of uncertain significance then surveillance should be based on family history and family members would not be
recommended for testing unless the variant is reclassified to pathogenic. The majority of variants of uncertain significance will be reclassified to negative.

The role of the genetic counselor is crucial in cancer genetics, since counseling is a time and labor intensive process. One study found that genetic counselors spent almost 50% of their time on patient related activities and only 25% of their time with direct patient contact (McPherson et al., 2008). It is clear that the hour the genetic counselor spends with the patient is only a fraction of the time that is needed per patient.

**NCCN Guidelines**

The National Comprehensive Cancer Network (NCCN) is a group of various cancer centers across the world that work together to establish guidelines for physicians (NCCN Guidelines, 2015). They work to make evidence based recommendations in order to improve cancer care. In January 2014, the guidelines for patients with ovarian, fallopian tube, or primary peritoneal cancer changed from the guidelines published in February 2013. They were updated to recommend that all of these patients be referred for genetic testing regardless of family history (Minion et al., 2015). However, it is noted that treatment should not be delayed due to lack of genetic counseling referral.
The reason for this change was the increasing amount of inherited mutations identified in these patients who had no family history (Walsh et al., 2011). Missing an inherited mutation in a family could lead to the lost opportunity for cancer risk-reducing interventions. The guidelines do not indicate what type of testing should be offered to the patient and that decision should be left to the genetic professional. Many patients with ovarian cancer were diagnosed years ago and have only had limited BRCA1/2 molecular analysis, so there is the possibility that patients with certain family histories would need to be re-referred to a genetic consultation due to the availability of new testing.

**Specific Aims**

The purpose of this research study is to determine if the changes in the NCCN guidelines from January 2014 had any impact on the Gynecologic Oncology Clinic at DFCI. In particular, this study is going to investigate whether patients with new diagnoses of ovarian, primary peritoneal, or fallopian tube cancer are being referred to obtain genetic testing. The amount of time from diagnosis to getting testing will be quantified to see if there is a need for a more effective referral process. The type of testing that the patient underwent will also be examined. The results of this study will quantify the impact of the NCCN
guidelines on clinical practice and the effectiveness of the referral process for genetic testing.
METHODS

Study Design

This study is a retrospective medical chart review of approximately 317 consult adult patients from the gynecologic oncology clinic at Dana Farber Cancer Institute (DFCI). This project was reviewed and approved by the Institutional Review Board (IRB) at Dana Farber/HCC.

Data Collection

The records from all consult patients seen in the gynecologic oncology clinic at DFCI between 01/02/2013 - 03/29/2013 and between 01/02/2014 - 03/28/2014 were reviewed in order to determine the correct patient population. Data was collected from the Partner’s Health Care Longitudinal Medical Record Database (LMR). LMR is the electronic medical record and provides general patient information, current and past diagnosis and treatment, diagnosis dates, healthcare provider, and all medical notes from providers within the Partner’s system.

Data was also confirmed using the DFCI Center for Cancer Genetics and Prevention Progeny Database. The Progeny Database is clinical software for capturing family history in pedigree format and genetic testing information for
patients seen in the Center for Cancer Genetics and Prevention. The database tracks general patient information, cancer history, family history, ethnicity, genetic testing information, and genetic counselor. Both LMR and the Progeny Database are secure and can only be accessed by staff with access codes.

Patients were eligible for inclusion if (1) they were new patients to the gynecologic clinic, (2) had been newly diagnosed with ovarian, primary peritoneal, or fallopian tube cancer, and (3) were seen either from January to March 2013 or from January to March 2014. This retrospective chart review screened a total of 317 consult patients seen in the Gynecologic Oncology Clinic at DFCI. It was found that there were 144 consult patients in 2013 and 173 consult patients in 2014. During January to March 2013, 50 consult patients were diagnosed with ovarian, fallopian tube, or primary peritoneal cancer. Similarly during January to March 2014, 57 patients had one of these three diagnoses.

Data was collected on these individuals to determine the date of their diagnosis, age at diagnosis, race, cancer type, if they were referred to genetic testing, cancer family history, if they had genetic testing, the date of genetic testing, and the type of genetic testing. Their diagnosis was confirmed by pathology report and genetic test type was confirmed by original copy. Referral to genetic testing was specified if it was documented in the medical record. Out
of all the patients whom had documented referral to genetic testing, zero declined the appointment as documented in the medical record.

**Data Analysis**

Data was collected and summarized using standard descriptive statistics. Analysis was done using Microsoft Excel 2007 for Windows and statistical software IBM SPSS statistics 2014. Univariate analyses were performed using chi square tests and independent t tests. A P value of <.05 was considered statistically significant.
RESULTS

Medical records from a total of 144 Gynecologic oncology patients with a new diagnosis of ovarian cancer were reviewed from January 2013-March 2013. Of those 144 patients 33 or 22.9% were second opinions who did not establish their care at DFCI. 50 or 45% of the patients who established their care at DFCI were diagnosed with ovarian, fallopian tube, or primary peritoneal cancer.

Similarly for 2014, a total of 173 consult patient charts were reviewed from January 2014-March 2014. Of those 173 patients 61 or 35.2% were seeking second opinions and did not establish their care at DFCI. Of the patients who established care at DFCI, 57 or 50.9% were diagnosed with ovarian, fallopian tube, or primary peritoneal cancer.

The baseline characteristics of the patients diagnosed with ovarian, fallopian tube, or primary peritoneal cancer were summarized and the characteristics are listed in Table 1. The mean age at diagnosis for 2013 was 59.98 and the median age for 2014 was 60.50. The range of age at diagnosis for 2013 was 61 and the standard deviation was 12.479. Likewise the mean age at diagnosis for 2014 was 58.63, the median was 59. The standard deviation was 10.964. The age at diagnosis for 2013 and 2014 were found to be similar. The majority of
patients (82%) in 2013 were diagnosed with ovarian cancer and similarly for 2014 the majority (89.5%) were diagnosed with ovarian cancer.

Table 1: Baseline Characteristics of Patients Seen in the Gynecologic Oncology Clinic

<table>
<thead>
<tr>
<th>Variables</th>
<th>2013 (N=50)</th>
<th>2014 (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;39</td>
<td>5</td>
<td>10%</td>
</tr>
<tr>
<td>40-49</td>
<td>4</td>
<td>85%</td>
</tr>
<tr>
<td>50-59</td>
<td>13</td>
<td>26%</td>
</tr>
<tr>
<td>60-69</td>
<td>21</td>
<td>42%</td>
</tr>
<tr>
<td>70-79</td>
<td>6</td>
<td>12%</td>
</tr>
<tr>
<td>80-89</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Cancer Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>41</td>
<td>82%</td>
</tr>
<tr>
<td>Fallopian Tube</td>
<td>5</td>
<td>105%</td>
</tr>
<tr>
<td>Primary</td>
<td>4</td>
<td>8%</td>
</tr>
<tr>
<td>Peritoneal</td>
<td></td>
<td></td>
</tr>
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</table>

Figure 4 shows a flow chart of the patients seen in the gynecologic oncology clinic for January through March of 2013 and 2014. Of the patients diagnosed with ovarian, fallopian tube, or primary peritoneal cancer 7 of the patients in 2013 and 15 in 2014 had genetic testing prior to diagnosis and were excluded. For 2013 prior to the change in NCCN guidelines 26 patients (52.0%) were referred to genetic testing and 17 (70.8%) met with a genetic counselor. Of the patients who meet with a genetic counselor 15 (88.2%) had genetic testing indicating that most patients decide to have genetic testing once they have been
referred. One patient declined testing and one patient’s insurance would not cover testing. For 2014, 35 patients (83.3%) were referred to genetic testing and 31 (88.6%) met with a genetic counselor. All 31 patients decided to move forward with genetic testing. For 2014 there was a higher rate of referral, but similar to 2013 once patients were referred, most decided to have testing.

Figure 4: Flow chart of medical record review for January-March 2013.
A Pearson’s chi square test for independence was run to determine if patients diagnosed in 2014 were more likely to be referred for genetic counseling due to the change in guidelines when compared to 2013. The p-value was found to be .019 and therefore is less than .05 and is statistically significant. It can be concluded that there was a statistically significant difference in referrals for genetic counseling during 2013 and 2014.

Then we sought to determine whether there was difference in the amount of time it took from date of diagnosis to having the patient seen for genetic counseling.

Figure 5: Flow chart of medical record review for January-March 2014.
counseling. For 2013, the mean time from date of diagnosis to date of genetic counseling appointment was 120.41 days with a standard deviation of 145.704. The minimum amount of time was zero days and the maximum was 483 days. For 2014, the mean time from date of diagnosis to date of genetic counseling appointment decreased to 67.32 days with a standard deviation of 68.93. The minimum amount of time was 6 days and the maximum was 335 days. An independent t-test was run to determine if there was a statistically significant difference between the 2013 and 2014 mean time to obtain genetic counseling. It was found that p=.172, which is greater than .05 and therefore the difference in the means is not statistically significant. This could be due to the fact that there was a small sample size.

Characteristics such as age at diagnosis and family history could affect the probability that patients would be referred to genetic counseling. First, the data was split up into groupings based on age at diagnosis. The data was grouped into age brackets as follows: <49, 50-69, and >70. The results are summarized in table 2. For 2013, it was found that the age group <49 and >70 both had a referral rate of 71% while the age group 50-69 had a referral rate of 55%. For 2014, the age group with the highest referral rate was <49 at 100%. Following that the group of
50-69 had an 84% referral rate and >70 had a 67% referral rate. There doesn’t seem to be a difference in referral rate based on age at diagnosis.

Table 2. Genetic Counseling Referral Rate Based on Age at Diagnosis.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>2013 Referred (N=26)</th>
<th>2013 Not Referred (N=17)</th>
<th>2014 Referred (N=35)</th>
<th>2014 Not Referred (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>%</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td>&gt;49</td>
<td>5</td>
<td>71%</td>
<td>2</td>
<td>29%</td>
</tr>
<tr>
<td>50-69</td>
<td>16</td>
<td>55%</td>
<td>13</td>
<td>45%</td>
</tr>
<tr>
<td>&lt;70</td>
<td>5</td>
<td>71%</td>
<td>2</td>
<td>29%</td>
</tr>
</tbody>
</table>

A chi square test of independence was run to determine if there was an association between age at diagnosis and referral rate. For 2013, the p value=.593 which indicates that the difference is not statistically significant, therefore there is not an association between referral rate and age at diagnosis. A chi square test was run for 2014 and the p value=.110 and therefore there is also not an association between referral rate and age at diagnosis.

The data was then divided by the type of family history of cancer the patients had. The categories were breast and ovarian, colon, neither, adopted, or family history not obtained. The results are summarized in Table 3 below. It was found in 2013 that physicians were slightly more apt to refer patients with breast and ovarian family history (76%) than colon family history (71%). Patients with
neither family history were typically not referred (33%). For 2014, all patients with colon family history were referred and there was an increase of 46% of referrals for patients who had neither family history.

Table 3. Genetic Counseling Referral Rate Based on Family History of Cancer.

<table>
<thead>
<tr>
<th>Family History of Cancer</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Referred (N=26)</td>
<td>Not Referred (N=17)</td>
</tr>
<tr>
<td>BR/OV</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td>Colon</td>
<td>16</td>
<td>76%</td>
</tr>
<tr>
<td>Neither</td>
<td>4</td>
<td>33%</td>
</tr>
<tr>
<td>Adopted</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Not Taken</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

A chi square test of independence was run to determine if in 2013 and 2014 patients with family history were more likely to be referred for genetic counseling. The p value=.021 and therefore it was statistically significant since it was less than .05. A chi square test was run to see if there was an association between year of diagnosis and referral rate for patients with no family history. It was found to be statistically significant because the p value=.007 and that is less than .05. As expected there was a statistically significant difference in referral rates for patients without family history diagnosed in 2013 versus 2014.
Finally, the type of genetic testing the patients underwent was studied. The options for testing were either BRCA1/2 genes, Lynch Syndrome genes, or a more comprehensive panel of genes. It was found that in 2013 the majority of patients (75%) had testing for the BRCA1/2 genes and only 25% had a panel. However, in 2014 there was an increase in panel testing. 67.7% of the patients had a panel ordered and only 32.3% of patients had BRCA testing alone. There was a 42.7% increase in panel testing over the course of the year.
DISCUSSION

Mutations in tumor suppressor genes have been linked to ovarian, fallopian tube, and primary peritoneal cancer for some time now; however it was not until January 2014 that the NCCN recommendations suggested that all patients with these diagnoses have genetic counseling regardless of family history. In this project we evaluated if the change in guidelines had an effect on genetic counseling referrals from the gynecologic oncology clinic. For 2013 and 2014 the mean age at diagnosis was very similar (difference of 1.35), regardless it was expected that there would be an increase of referrals in 2014. It was found that the difference in referral rates based on year was statistically significant. There was an increase of 31.3% of patients being offered genetic counseling from 2013 to 2014. It was expected that the younger age at diagnosis would be more likely to be referred; however it was discovered that there was not a statistically significant association between age at diagnosis and referral rate. It was expected that in 2013 patients with family history would be more likely to be referred, but in 2014 there would be the greatest increase in referrals for patients with neither family history. There was an increase in referrals for patients without family history (46%), and it was found that patients without family history were more
likely to be referred in 2014. It was found that overall the change in NCCN guidelines did cause an increase in referrals for genetic counseling especially for the patients without a family history of cancer.

The time from diagnosis to meeting with a genetic counselor decreased from 2013 to 2014 by 53.09 days, but this was not found to be a statistically significant difference. This could be due to a small sample size. There was also a great range of values, which could be due to patient preference. Some patients want to meet with the genetic counselor on the same day as their oncologist to obtain all of the information at once, while others find it overwhelming and want to wait until their treatment is finished.

It was expected that there would be an increase in panel testing since panels were relatively new in 2013 and more widely used in 2014. It was found that there was a 42.7% increase in panel testing in 2014, which is a substantial increase. Panels are chosen because many syndromes can be tested for at once and most patients’ insurance companies will only pay for one genetic test regardless of how many genes were tested. It is expected that as time goes on and more information is learned about the individual genes there will be a great increase in panel testing, which can help identify mutations in families without a clear phenotype.
Limitations

One of the largest limitations in this study was the small sample size. Only three months of time from each year were reviewed and it would be beneficial to study a longer span of time to measure the impact of the guidelines. Since the information was only being pulled from the medical record there could have been data that was missed or was never documented. Also, if a patient had genetic counseling at another institute then that information could have been missed if it was not scanned into the medical record. This could have led to incomplete data abstraction, which potentially could have skewed the data.

Although the number of patient charts that were reviewed was small there were still significant conclusions that could be made. It was clear that the NCCN guidelines made a difference in the practice of this specific academic oncology clinic. It is helpful for these guidelines to be continually updated since they do influence patient care. Further, all the patients who were offered genetic counseling met with a genetic counselor and only one patient decided to decline testing. This shows that most patients would like to know this information for themselves and their families. It is critical that an effective genetic counseling referral system be established in oncology clinics in order to facilitate testing.
Further, oncologists need to be adequately educated on cancer genetics in order to make sure all patients that need to be referred are being offered genetic counseling.
REFERENCES


VITA

KRISTIN HEHIR
BORN: 1991

1091 Boylston St. Boston, MA 02215
Keh2148@bu.edu

Education:

Boston University: Boston, MA  
Masters of Science Candidate, Medical Sciences  
Expected 2015

Columbia University: New York, NY  
Bachelors of Art, Biology  
May 2013

Clinical and Laboratory Experience

Center for Cancer Genetics and Prevention  
Clinical Research Coordinator  
May 2013-present

Biomechanical Engineering Lab  
Research Assistant  
March 2011- 2013