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UNIVERSITY OF CALIFORNIA,
IRVINE

Identification of Cancer Risk During Prenatal Genetic Counseling Sessions:
Evaluation of Frequency and Current Practice Protocols

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Genetic Counseling

by

Jennifer Nell Cech

Thesis Committee:
Professor Maureen Bocian, MS, MD, Chair
Associate Clinical Professor Kathryn Singh, MPH, MS, LCGC
Clinical Professor Kathryn Steinhaus French, MS, LCGC

2018

DEDICATION

To

My family and my husband

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ABSTRACT OF THE THESIS

Identification of Cancer Risk During Prenatal Genetic Counseling Sessions:
Evaluation of Frequency and Current Practice Protocols

By

Jennifer Nell Cech

Master of Science in Genetic Counseling

University of California, Irvine, 2018

Professor Maureen Bocian, MS, MD, Chair

This study determined how often cancer is reported in prenatal three-generation family histories at our center. It also examined if there was a change between the years 2010 and 2016, given changes noted in cancer awareness over the last 10 years. Using a retrospective chart review, we found that 59% of 437 prenatal pedigrees from 2016 reported cancer, a 19% increase from 2010. Using a generalized cancer scoring system, there was a 48% increase in maternal high-risk, 175% increase in maternal intermediate-risk, 16% increase in maternal low-risk, and a 43% increase in paternal low-risk cancer families between 2010 and 2016. This study also assessed current practice protocols of prenatal genetic counselors to identify if there is uniformity in how they evaluate and respond to families with reported cancer history. A survey of 104 prenatal genetic counselors revealed that the majority ask about age at diagnosis when cancer is discussed, but only 53% address cancer every time they take a three-generation family history. When given sample pedigrees, prenatal counselors responded differently to maternal vs. paternal lineage high cancer risk; 24% elected to refer to cancer genetic counseling for a paternal high-risk family compared to 62% for a maternal high-risk family. Taken together, the results of this study support the importance of obtaining comprehensive three-generation pedigrees that

include cancer in the prenatal setting and developing institutional protocols for prenatal

counselors to evaluate, respond, and relay information regarding cancer genetic risk assessment

to prenatal patients.

I. INTRODUCTION

1.1 Background and significance of the research

1.1.1 Hereditary cancer predisposition syndromes

Most cases of cancer are sporadic; however, approximately 5-15% of cancer cases are caused by germline mutations in cancer predisposition genes (CPGs), depending on the cancer type (Garber & Offit 2005, Riley *et al*. 2012, Lynch *et al*. 2013, Stoffel *et al*. 2015, Schneider third edition, Counseling about Cancer). There are at least 64 known hereditary cancer predisposition syndromes and at least 114 cancer predisposition genes (CPGs), in which a genetic mutation in one or both alleles of a gene increases an individual's risk of cancer beyond that of the general population (Lindor *et al*. 2008, Weitzel *et al*. 2011, Rahman *et al*. 2014). Identification of individuals with hereditary cancer predisposition is recommended because screening or surgical management may begin at an earlier age than for the general public. For example, individuals with Hereditary Breast and Ovarian Cancer Syndrome (HBOC) have mutations in the *BRCA1/2* genes. Standard screening guidelines for HBOC established by the National Comprehensive Cancer Network (NCCN) (Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2018) recommend annual breast MRI starting at age 25-29, discussion of risk-reducing bilateral mastectomy and prophylactic oophorectomy at the end of child-bearing age for those who carry mutations. In comparison, screening guidelines for women in the general population consist of annual mammography screenings starting at 40 years of age. Another example is for individuals with Lynch Syndrome, which increases the risk for colorectal

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cancer and several other types of cancer and is caused by mutations in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes. Affected individuals are advised to have colonoscopies every 1-2 years starting at age 20-25, or 2-5 years prior to earliest known cancer in the family (Genetic/Familial High-Risk Assessment: Colorectal. Version 3.2017). In comparison, recommendations for colorectal cancer surveillance in the general population consist of colonoscopies every 5-10 years starting at age 50.

1.1.2 Importance of a three-generation family history

Given that one out of every three people in the United States will be affected with cancer at some point in their lifetime (Noone *et al*. SEER Cancer Statistics Review 2015), it is expected that many family histories will include cancer. The importance of a three-generation family history is that it can help bring to light patterns of cancer, ages at diagnosis, and other factors that may suggest hereditary cancer predisposition. A standard three-generation family history includes, but is not limited to, documentation about general health, congenital anomalies, intellectual disabilities or developmental delay, chronic illness, early deaths, cancer, and ethnicity in a person's extended family, including first-, second-, and third-degree[1] relatives on both the maternal and paternal sides of the family (Bennett *et al*. 1995). The clinical importance and value of a three-generation family history for the identification of genetic risk factors to both individuals and families has been well established (American College of Obstetricians and Gynecologists ACOG Committee Opinion 478 2011, Frezzo *et al*. 2003, Guttmacher *et al*. 2004,

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[1] First (full siblings, children, parents); Second (grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings); Third (first-cousins, great-grandparents or great grandchildren).

Rich *et al.* 2004, Bennett RL 2010). Early identification of these risk factors can lead to better prevention, surveillance, treatment, and reduction in disease (Guttmacher *et al.* 2004, Eichmeyer *et al.* 2014). For example, documentation of three generations of breast cancer in a family may lead to an as-yet unaffected woman having a mammogram prior to age 40. Documentation of a relative with a known genetic syndrome, such as cystic fibrosis, may lead to other family members electing preconceptional or prenatal genetic screening to determine their own reproductive risks. Lastly, documentation of a strong family history of heart disease may lead to other family members pursuing early cardiac care and lifestyle changes to reduce their own risk of heart disease.

1.1.3 What are the barriers to non- geneticist physicians taking three-generation family histories?

While any physician may take three-generation family histories and may also understand their value, a complete and thorough family history can be time consuming and may not be able to be completed during an average physician appointment. The annual 2017 Physician Compensation Report surveyed 19,270 physicians in the United States and found that 59% of physicians spend between 13-24 minutes in face-to-face patient interaction; 22% of the participants were either practicing family medicine or internal medicine (https://www.medscape.com/slideshow/compensation-2017-overview-6008547#42). In a 2016 study, observations of 57 United States physicians across 4 states and 4 specialties (including family medicine, internal medicine, cardiology, and orthopedics) concluded that physicians only spend 27% of their work hours in face-to-face patient contact (Sinsky *et al.* 2016). A similar trend is seen for housestaff trainees, with one study showing that internal medicine interns spend

less than 20 minutes per new patient hospital admission (Block *et al.* 2013). While the reason

behind the decreasing amount of time spent face-to-face with patients can be debated, some

speculate that the use of the electronic medical records, or even the increase in insured patients

after the Affordable Care Act in 2010, may contribute to this reduction in face-to-face time

(Anderson 2014, Sinsky *et al.* 2016, ASCO report 2017, Carroll, A.E. Nov 2016. "A Doctor

Shortage? Let's Take a Closer Look." The Upshot, nytimes.com). Regardless of the reason, it is

clear that this limited amount of time is now a mainstream concept, even chronicled in places

like the New York Times (Chen, P.W. May, 2013. "For New Doctors, 8 Minutes Per Patient."

Well, nytimes.com).

Given these limitations, it may not be possible for physicians and other providers to take

a detailed three-generation family history during an average patient appointment. A 2000 study

reviewed over 4,500 patient visits across 158 family physician practices and revealed that a

discussion of family history only occurred in 51% of new patient visits. While this study was

limited to the state of Ohio, it did find that the average amount of time spent discussing a family

history was less than 2.5 minutes (Acheson *et al.* 2000). Multiple studies have suggested that the

time it takes to obtain an expanded or three-generation pedigree is, on average, around 20

minutes (Waters *et al.* 1994, Frezzo *et al.* 2003). While there are obvious time limitations, the

benefit of taking a three-generation family history in a primary care setting has been well

documented.

1.1.4 There are established guidelines to help physicians and other providers know when to refer
an individual or family for cancer genetic counseling

If providers are able to take a family history, they must be knowledgeable about when to refer for expert genetics evaluation—for example, to a genetic counselor specializing in cancer risk assessment. There are multiple guidelines created by various national professional organizations regarding when to refer someone, or a family, for cancer genetic risk assessment counseling. The NCCN has established guidelines differentiating between when to refer to genetic counseling versus criteria for genetic testing. However, these detailed guidelines are specific to common cancers like breast, ovarian, prostate, colon, and melanoma (https://www.nccn.org/professionals/physician_gls/default.aspx#detection). The American College of Medical Genetics and Genomics (ACMG) and the National Society of Genetic Counselors (NSGC) jointly published a set of guidelines in 2015 detailing when to refer for cancer genetic counseling based on organ system, cancer type, or other non-cancer findings (Hampel *et al.* 2015). A previous study by the lead author in 2004 included differentiation among high-, moderate-, and low-risk family histories (Hampel *et al.* 2004); however, this distinction was not included in the 2015 ACMG/NSGC guidelines. While it is recommended that primary care physicians use the ACMG/NSGC guidelines to help them evaluate a family history of cancer, the guidelines are very detailed, with almost seven pages of text and additional pages of tables. Other guidelines limited to single-table formats have been established specifically for common cancers, such as breast and colon cancer (Maradiegue *et al.* 2008, Frieder & Berlin 2012, Lu *et al.* 2014). In addition, these guidelines are primarily focused on highly penetrant, high-risk cancer predisposition syndromes. With more moderately penetrant cancer predisposition genes, individuals who do not have a family history suggesting a classical

hereditary cancer predisposition syndrome may not be appropriately referred if these more
limited guidelines are used.

*1.1.5 Accuracy of non-geneticist physicians' family history documentation and family cancer risk
assessment*

Even though taking a comprehensive three-generation family history may not be possible
in many clinical visits, a survey of 860 physicians concluded that while only 33% reported taking
a three-generation family history, 89% routinely assessed a family history of cancer (Vig *et al.*
2009). This is evident by the percentage of cancer genetics referrals made by non-geneticist
providers. While limited in size, a survey of 40 genetics providers, including genetic counselors,
reported that only 10% of patients were self-referred, while 89% were referred by providers,
including 39% by oncologists, 22% by obstetrician-gynecologists, 22% by primary care
physicians, and 18% by surgeons (Rolnick *et al.* 2011). However, multiple studies suggest that
incorrect estimates of cancer genetic risk by primary care physicians and oncologists may lead to
missed referrals for cancer genetic counseling and ultimately missed early prevention;
(Eichmeyer *et al.* 2014, Baldwin *et al.* 2014).

The 2009 study by Vig *et al.* of 860 primary care physicians revealed that 54.6% of those
surveyed took a family history that only included first-degree relatives. Another study, in 2010,
surveyed 867 physicians across family medicine, internal medicine, and gynecology to assess
how they used family history data when assessing cancer risk. This study showed that only 25-
50% of these physicians reported frequently asking about family history of grandparents and
aunts and uncles, and fewer than 40% reported asking about third-degree relatives *(Flynn et al.*

2010). A 2007 study assessed the comprehensiveness of family cancer history assessments in primary care (Murff *et al.* 2007). This study compared information documented by the provider in the electronic medical record regarding family history of a new patient to information collected via a survey sent to the same patient. For the 310 patients who participated, age at cancer diagnosis for first-degree relatives was documented by the provider in 61.7% of cases, compared to 94.7% identified from the patient survey. Age at diagnosis for second-degree relatives was documented by the provider in only 27.2% of cases compared to 76.4% identified from the patient survey. Of the 48 patients categorized as being at "increased risk" (defined by American Gastroenterology Association guidelines) based on the patient survey, only 19 had documentation of this risk in their medical record.

Appropriate referrals to cancer genetics specialists are dependent on the accuracy of referring providers' assessments of patient and family histories. The accuracy of a cancer risk assessment can depend on data from second- and third-degree relatives, including specifics such as age at time of diagnosis. This suggests that some families with increased cancer risk may not be referred for cancer genetic risk assessment counseling simply because they are not being adequately assessed.

Even within specialties associated with cancer, the accuracy of cancer risk assessment is not 100%. A study of 387 patients with colorectal cancer compared the accuracy of patients' self-reported family cancer histories on a questionnaire to that obtained in person at their first physician appointment. They found that oncologists only reported 184 out of the 311 patients who documented a family history of cancer (Grover *et al.* 2004). Importantly, one third of the

patient-reported cancers missed by physician assessment occurred in first-degree relatives, and 68% of the missed endometrial and colon cancers were in first- or second-degree relatives. A study in 2010 from a cancer center reviewed 3,765 charts of women diagnosed with ovarian cancer. While only 12% of individuals whom the researchers identified to be at substantial risk to have a hereditary cancer syndrome (defined by the ACOG 2009 consensus guidelines as individuals with more than 20–25% risk for having a *BRCA1* or *BRCA2* mutation) were referred for genetic counseling in 1999, 48% were referred in 2007, showing great improvement. However, this still indicates that over 50% of those who should have been referred were not. The study did not examine whether patients were at risk for other hereditary cancer risk cancer syndromes associated with ovarian cancer, such as Lynch syndrome, PTEN hamartoma tumor syndrome, or Peutz-Jeghers syndrome (Meyer *et al.* 2010). A much larger study, led by the American Society of Cancer Oncologists (ASCO), reviewed 10,466 cancer patients' charts across 212 practices in 2011 (Wood *et al.* 2014) and revealed that 77.4% and 61.5% of cases had documentation of first- or second-degree relatives, respectively. Additionally, of the patients who were considered to be at increased risk (defined by consensus criteria extracted from available guidelines published by ASCO, NCCN, and the United States Preventative Services Task Force) for a hereditary cancer predisposition syndrome, only 43% were either referred for genetic counseling or offered genetic testing (Wood *et al.* 2014). While large efforts have been made to increase the training of oncologists to recognize a family history suggestive of a hereditary condition (Lu *et al.* 2014), it is possible that time limitations may not always make this feasible in oncology clinics with high patient volume. Therefore, Lu *et al.* in 2014 recommended a minimum adequate family history that includes first- and second-degree relatives. But is this really adequate?

The American College of Obstetricians and Gynecologists (ACOG) has established practice bulletins recommending that cancer risk assessment for hereditary cancer predisposition syndromes be part of routine obstetrics-gynecology care (ACOG bulletin No. 634, 2015). Obstetrician-gynecologists are considered to be more accurate than other providers in their assessments for breast and ovarian cancer; the study by Vig *et al*. (2009) showed that 77% of obstetrician-gynecologists surveyed make referrals for cancer genetic counseling, compared to 39% of internal medicine physicians and 47% of family medicine doctors. A study in 2014 used a 12-page questionnaire sent to 1,555 physicians including family physicians, general internists, and obstetrician-gynecologists. While these clinicians were able to accurately assess a family history of colon cancer 62% of the time and of ovarian cancer 57% of the time, they also found that the same clinicians both over- and underestimated cancer risks. Of the patients with an increased risk for ovarian cancer, 65% of the physicians underestimated their risks. Of the individuals with a general population risk for ovarian cancer, 27% of the physicians overestimated their risk. For patients with general population risk, obstetrician-gynecologists were less likely to overestimate risk than were other physicians. However, for patients with an increased risk of ovarian cancer, obstetrician-gynecologists were more likely than others to underestimate their risk (Baldwin *et al.* 2014). While underestimating cancer risk can lead to missed referrals and missed early screening, overestimating risk can also lead to inappropriate use of screening, anxiety, and increased burden on already busy cancer genetic counseling clinics. A 2011 survey of cancer genetics service providers estimated that only 22% of cancer genetic counseling referrals come through obstetrician-gynecologists (Rolnick *et al.* 2011). While obstetrician-gynecologists are trained to assess for certain cancer risk factors, it is still

uncertain how many of their patients with any identifiable cancer risk are referred to see a cancer genetic counselor. Lastly, there are at least 55 other cancer predisposition syndromes that may present with other types of cancer for which obstetrician-gynecologists may not be screening.

1.1.6 Accuracy of patient-reported family history of cancer

While many physicians do ask limited questions regarding family history, the data they collect is reliant on correct information provided by the patient. There are additional barriers to cancer risk assessment using a family history that are not due to counselor or physician error or to incomplete data collection. Accuracy of a family history can depend on patient-family dynamics, how recently family members were diagnosed, geographical location of relatives, patient recollection during the appointment, adoption, estrangements, or even loss of medical records (Murff *et al.* 2004; Schneider third edition, Counseling about Cancer).

A meta-analysis in 2004 reviewed published studies between 1985 and 2004 that evaluated the accuracy of patient reporting. The authors concluded that cancer history reporting is most accurate for breast and ovarian cancer in first-degree relatives and that reporting for more distant relatives and for other cancers may not be as accurate. Factors that may lead to patient misinformation include confusion between benign vs metastatic tumors and confusion between primary vs. metastatic cancer site (Murff *et al.* 2004). Other studies have shown that the accuracy of reporting also depends on the cancer type (Fiederling *et al.* 2016, Schneider third edition, Counseling about Cancer). A 2007 study comparing 39,662 patient questionnaires with the same patients' results found in a tumor registry showed that the sensitivity of reporting a

personal history of breast cancer was around 92%, with false negative rates for both uterine and colorectal cancer as high as approximately 38% (Dominguez *et al.* 2007).

Because of these challenges, non-geneticist providers often rely on genetic counselors for a more extensive evaluation of a possible high-risk family. Genetic counselors are trained to use patient medical records to confirm a reported cancer diagnosis, obtain other pertinent family members' medical records when possible, take *at least* a detailed three-generation family history, and ask questions about non-cancer findings that can also be associated with specific cancer syndromes (Trepanier *et al.* 2004, Riley *et al.* 2012, Schneider third edition, Counseling about Cancer). All of these factors aid in increasing the accuracy of risk assessment during a cancer genetic counseling session.

1.1.7 Genetic counselors are uniquely qualified to take three-generation family histories that may identify risks outside of their clinical specialty

While cancer genetic counselors are equipped to make such risk assessments and to offer cancer genetic testing, most patients require a referral to see a cancer genetic counselor and rely on their physician to identify those for whom referral is indicated. Genetic counselors who specialize in areas other than cancer predisposition, however, are also trained to identity and refer these potentially high-risk cancer families to cancer genetic counselors for additional risk assessment and testing.

All genetic counselors are trained to take detailed family histories of at least three generations. While genetic counselors often work in one specific specialty, such as prenatal,

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cancer, adult, or pediatric genetics, they are trained across all specialties and can identify a family at risk for a disorder other than the one for which they were referred. For example, prenatal, pediatric, and adult genetic counselors are all able to identify families with increased risk for a hereditary cancer predisposition syndrome. Conversely, genetic counselors specializing in cancer genetic risk assessment can also identify individuals with reproductive risks unrelated to cancer, such as the identification of a cancer patient's risk for disorders like cystic fibrosis or muscular dystrophy in future or current pregnancies, or consanguineous couples at risk for autosomal recessive disorders.

It has been shown that many additional risk factors outside of traditional prenatal-related conditions (i.e., birth defects, chromosomal abnormalities, Mendelian disorders, teratogenic exposures, and recurrent miscarriage) can be identified during a prenatal genetic counseling session. A 1992 study reviewed prenatal clinical charts of 800 women seen between 1986-1990 who were referred for a positive maternal serum alpha-fetoprotein (MS-AFP) screen that was done to detect certain fetal anomalies. They then assessed how often additional risk factors were identified in the family history (Larabell *et al.* 1992). Among other findings, eight cases (1%) were identified with a non-gynecological cancer risk suggestive of a possible hereditary etiology. A study assessing family history data for 700 women seen in a prenatal clinic between 2003 and 2006 looked to identify how often additional risk factors outside of the prenatal specialty were documented. This study showed that 28% of women seen during this period had additional risk factors that warranted a genetics evaluation, including 9% where the additional risk factor was breast cancer (Hafen *et al.* 2009). Another study in 2010 re-addressed the identification of additional risk factors in women under 35 years of age who were seen in the prenatal genetic

counseling setting due to a positive screen result through the California Prenatal Screening

Program for certain birth defects or chromosome abnormalities in the year 2007 (Hoang 2010)

and revealed that 43% of the women had additional risk factors that alone would have warranted

a genetic counseling referral, including 13% with a family history of cancer. A 2014 study

evaluated 1,300 patient charts at three Italian clinical genetics services from the year 2010 to

quantify additional risk factors identified during a prenatal genetic counseling session for

advanced maternal age (AMA) (Pompilii *et al.* 2014). In contrast to the previous studies, the

authors reported that only 6.4% of the women seen during this time had previously unidentified

genetic risk factors. While this number is lower than in previous studies, it still remains that 1 in

15 women with a prenatal referral for genetic counseling due to AMA had additional genetic risk

factors, including some with a family history of cancer.

1.1.8 Prenatal genetic counselors may identify cancer risks that other health care providers may have missed

Any pregnant woman may be offered prenatal genetic counseling if she is over the age of

35 (AMA), had a screening test that is positive for Trisomy 21 (Down syndrome), Trisomy 13,

Trisomy 18, neural tube defects, or certain other disorders, has abnormal fetal ultrasound

findings, had possible teratogenic exposures, or is at risk to have offspring with a genetic

disorder based on family history or genetic screening. Since a genetic counselor usually takes at

least a three-generation family history, there frequently are instances in which additional risks,

such as cancer, that may have been missed by other providers are identified during a prenatal

genetic counseling session.

In addition, the State of California provides maternity insurance options for all pregnant women. If a woman does not have insurance through an employer, the California health insurance marketplace (Covered California), or Medi-Cal (the California Medicaid equivalent), she is eligible for the Medi-Cal Access Program (MCAP), or pregnancy-related Medi-Cal, which provides healthcare access to individuals who do not have citizenship or immigration status (http://www.dhcs.ca.gov/services/medi-cal/Documents/Pregnancy_Fact_Sheet_Chart.pdf). Any pregnant woman in the state of California is also eligible for the California Prenatal Screening Program, which provides equal access to prenatal screening services for certain chromosomal disorders, neural tube defects such as spina bifida and anencephaly, and certain other disorders. For women who may not have had insurance prior to pregnancy, their prenatal genetic counseling may be the first time they have had a family history taken, let alone an extensive one. Therefore, prenatal genetic counseling sessions may result in the initial identification of family histories from the mother and/or the father of the pregnancy that indicate increased risk for hereditary cancer syndromes, especially given that many of these individuals are at the age when genetic cancer predisposition syndromes may manifest.

1.1.9 Increasing complexity of prenatal sessions means genetic counselors must efficiently determine if families should be referred for cancer genetic counseling

In the last decade, there has been significant growth in the number of genetic tests available to pregnant women. These include screening and diagnostic tests for several chromosomal disorders and other screening tests including parental expanded carrier screening for over 170 different conditions. This means that during an average genetic counseling session, there are many more complex topics to discuss and obtain consent for, in addition to addressing

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the primary reason for referral. For example, in an initial one-hour prenatal consultation, a genetic counselor must cover prenatal screening options including standard maternal serum screening and cell-free fetal DNA screening, fetal ultrasound, invasive diagnostic testing options (chorionic villus sampling and/or amniocentesis), laboratory analysis (karyotype, chromosomal microarray), carrier screening, and sometimes specific molecular or other testing in addition to taking a three-generation family history. While prenatal counselors ask about cancer when obtaining a family history, they may not have time to obtain a fully integrated cancer-specific family history in the same way that a cancer genetic counselor would. Because the patient's initial evaluation is for the pregnancy, counselors must find a way to extract critical information regarding other important factors, such as the cancer history, often in a limited amount of time.

Furthermore, because the primary reason for prenatal genetic counseling is to address pregnancy-related concerns, counselors are often conscientious about not overwhelming the patient and her family with additional risks that may not be immediately relevant. Therefore, it is important to know when a family history of cancer warrants an immediate referral for genetic counseling or whether an extensive cancer genetic counseling visit can be deferred until after the birth of the baby. Because of time constraints, a prenatal genetic counselor may not be able to fully differentiate between a cancer risk that is considered intermediate and non-emergent versus a high risk requiring a more immediate referral. Another key dilemma is that the prenatal genetic counselor usually will not see the family again after the birth of the child. A counselor may mention in the clinic note to the referring physician that cancer genetic counseling is recommended, but the referring physician is usually an obstetrician, who is unlikely to provide long-term general medical care for the patient after delivery (although the routine post-partum

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visit could present that opportunity). For patients identified with an intermediate cancer risk that can be addressed following the birth of their child, what is the likelihood that they actually will have that appointment?

1.1.10 Changes to the genetics/genomics field in the last ten years

Genetic testing and societal views on genetics have changed dramatically in the last ten years. After Angelina Jolie announced the results of her testing of two major breast cancer predisposition genes—*BRCA1* and *BRCA2* in 2013, there was an approximately 2.5-fold increase in the number of women referred for cancer genetic risk assessment (Evans *et al*. 2014, Raphael *et al*. 2016). A 2013 survey of 2,572 adults in the United States revealed that while fewer than 10% of those surveyed correctly understood *BRCA1/2*-related cancer risk *vs* the risk in the general population, nearly 9% of those surveyed indicated that after hearing about Angelina Jolie, they would consider genetic testing for themselves or a family member (Borzekowski *et al.* 2014).

The Surgeon General Family History Initiative began in 2004. It also was intended to increase awareness about the importance of knowing one's family history and understanding how this information can change one's medical management. It is still ongoing today with the availability of an online family history tool (My Family Health Portrait Tool, https://familyhistory.hhs.gov/FHH/html/index.html). This has led to the Precision Medicine Initiative, which started in 2015 and aims to increase awareness about the future of tailoring medical treatment based on a person's genetic, environment, and lifestyle factors. Genetic counselors are also likely to have changed the way they ask about cancer history during this

period due to dramatic improvements in genetic testing. With recent advances in gene

sequencing technology, we have learned that beyond *BRCA1/2*, there are many more genetic

variants that can increase one's risk for cancer (Weitzel *et a*l. 2011, Rahman *et al*. 2014). Since

the *BRCA1/2* genes were identified in the early 1990's, more than 114 genes associated with

hereditary cancer predisposition syndromes have been identified, leading to the implementation

of cancer genetic testing panels (LaDuca *et al*. 2014). The first commercial, clinically available

multi-gene cancer panel became available in 2012 (Ambry Genetics) and led to an increased use

of genetic testing in cases in which the family history of cancer is not suggestive of an obvious

specific hereditary cancer predisposition syndrome. All of these changes to the field of genetics

have increased both the public's awareness about the importance of knowing one's family's

medical history and the way in which genetic counselors ascertain and educate patients about

their cancer risks in a non-cancer-related genetic counseling session.

1.1.11 Importance of differentiating among high-, intermediate-, and low- risk cancer family

histories

While there are guidelines available that provide information intended to help physicians

determine whether a family is at risk for a highly penetrant cancer predisposition syndrome, we

are now learning that there are many more moderately-penetrant genes that also can increase a

person's risk for cancer. These moderately-penetrant and moderate-risk gene mutations may still

be inherited in a family but may not result in as obvious a history as would a classical high-risk

cancer syndrome (Stanislaw *et al*. 2016). One might ask if all families with ANY cancer history

should be referred for cancer genetic counseling? Given that one in three individuals in the

United States will be affected by cancer within their lifetime, it is easy to assume that many to

most families will have someone affected by cancer. Referring everyone will not only overwhelm already busy cancer genetic clinics but may also lead to unnecessary anxiety or screening in those families. This is especially true when discussing cancer risk in a prenatal setting. Families preparing for the birth of a child will have several months and many other pregnancy-related items to focus on prior to and after the birth of the child. It is critical that genetic counselors can recognize when a cancer risk is high enough to warrant prompt cancer genetic counseling referral versus when the evaluation can be postponed and can ensure that the referral does not get lost in the complexities of the healthcare system.

1.1.12 Gaps

No study in the United States has been published in recent years to determine whether there has been a change in how often prenatal genetic counselors identify a family history of cancer during a prenatal genetic counseling session.

In addition, while prenatal genetic counselors can identify cancer risk in a family history, they often do not have time to take a detailed cancer-specific family history as a cancer genetic counselor would. While there are suggested guidelines for quick and efficient assessment for HBOC and Lynch syndrome, there are no guidelines to quickly assess for other hereditary cancer preposition syndromes. Lastly, when a family with intermediate or high cancer risk is identified in a prenatal session, there are currently no protocols for how prenatal genetic counselors should inform patients of this risk or follow up with cancer genetic counseling referrals.

1.2 Purpose of study and specific aims

Using a retrospective chart review of prenatal genetic counseling sessions from 2010 and from 2016, this study aims to determine whether there was a significant change in the number of families with a history of cancer identified in a prenatal setting in 2016 versus in 2010. By establishing a generalized scoring system for cancer risk, this study also will identify if there was an increase in the number of families determined to have an increased risk for cancer (including high-, intermediate-, and low-risk). I hypothesize that there will have been more prenatal patients with a family history of cancer identified in 2016 than in 2010. Increased ascertainment is likely to be due to patients' increased awareness of cancer risk and knowledge of cancer in their families, to our willingness to ask about it, and to the increasing availability and accessibility of more broad-based testing (panels) for families that do not fit a classical profile for single-gene testing. I also hypothesize that there will not be any significant increase in the number of high-risk family histories ascertained but that there will be an increase in the number of intermediate- and low-risk family histories.

Using an online survey of prenatal genetic counselors, this study will also examine the current practice protocols of prenatal genetic counselors when they identify a high-, intermediate-, or low-risk cancer family history during a prenatal genetic counseling session. The survey will also assess current genetic counselors' views on how often families with cancer risk are identified compared to reports of practice protocols from genetic counselors who practiced in 2010. The study also aims to assess the current practice behaviors of prenatal genetic counselors with the hope of establishing a standard protocol regarding cancer genetic counseling referrals arising from prenatal genetic counseling visits.

II. METHODS

2.1 IRB approval

This study was approved by the University of California, Irvine (UCI) Institutional Review Board (IRB) under study HS#: 2017-4010.

2.2 Retrospective Chart Review

Prenatal clinical genetic counseling charts, including the three-generation family history (pedigree), from both the year 2010 and the year 2016 were reviewed by the lead author. These two years were used because they provide relatively recent data and span events in genetics history that may reflect differences in patient recall of family history information. The year 2017 was excluded because the lead author participated in some of the prenatal sessions during that year. Charts from 2010 had been scanned previously as electronic files and uploaded into a secure folder, where they were accessible only by secure password-protected log-in. Charts from 2016 had been scanned previously as electronic files and uploaded into a secure electronic database (FileMaker).

Charts reviewed from both 2010 and 2016 included those of patients seen at two separate UCI Prenatal Diagnostic Centers (PDCs). Three-generation family histories were taken by either a prenatal genetic counselor or by one of five or more different genetic counseling graduate students under the direct supervision of a faculty genetic counselor.

A list of all patient charts from the 2010 and 2016 cohorts was generated, and each chart was given a unique non-identifying number. In total, 498 patient records had been scanned and were available to review from 2010. This number does not reflect all patients seen in 2010 because not all charts were scanned and available to review, but those that had been scanned were randomly selected for scanning and thus would not be expected to have biased the results in any way. In total, 528 patient records from 2016 were reviewed; however, this does not reflect all available charts from 2016. For the year 2010, 437 of the 498 charts met criteria for inclusion (criteria detailed below). Therefore, charts from 2016 were randomly selected using a random number generator until 437 charts meeting inclusion criteria had been reviewed.

Any patient under 18 years of age was excluded from this study because pre-symptomatic cancer genetic testing is generally not recommended for individuals younger than 18 years of age. Because we were assessing if there was a change in patient knowledge of family history between 2010 and 2016, patient records were also excluded if the mother of the pregnancy, father of the pregnancy, or either of their parents was adopted. Lastly, patients were excluded if the patient had been previously seen for prenatal genetic counseling in any prior year, because pedigrees were updated at every visit rather than collected new each time. A total of 61 charts reviewed from 2010 and 91 charts reviewed from 2016 were excluded on the basis of these criteria.

Demographic information including age of the mother of the pregnancy, insurance type, and reason for referral was collected for each of the total 437 charts reviewed from each year (Table 1). Private insurance type "HPO" included HMO, PPO, or other private insurance.

Insurance type "State" included any state-funded insurance, including Medi-Cal (of any form) or anyone seen through the California Prenatal Screening Program with no other insurance documented. A patient was only documented as having "California Prenatal Screening Program only" insurance if they had no other insurance listed. If the patient had any other insurance listed, the other insurance was documented as their primary insurance. Referral indication "AMA" included individuals referred for advanced maternal age (age $\geq$35). Referral indication "other" included referral for positive California Prenatal Screening Program result, other positive screen results, ultrasound findings, family history, or possible teratogen exposure.

A data collection sheet was generated to review each chart, and only this data collection sheet was used for subsequent analyses. No Protected Health Information (PHI) was documented on the data collection sheet. For each pedigree, any cancer in the family was documented, as was the age at diagnosis, if known. If the age at diagnosis was not known, the age at death was used as a proxy. If the cancer type was not known, it was documented as CA-NOS (cancer - not otherwise specified). If neither the individual's age nor age at death was known, the age was documented as "unknown." If there was cancer in any individual in the family, on either the maternal or paternal side or both, the pedigree was given a score of one for "any cancer reported." If there was any cancer reported on the maternal side of the family, the pedigree was also given a score of one for "any cancer-Mat." Similarly, for any cancer reported on the paternal side, the pedigree was given a score of one for "any cancer-Pat." All pedigrees with a score for "any cancer reported" would also have either a positive score for any cancer-Mat, any cancer-Pat, or both. Similar scoring was performed for any maternal or paternal first-

degree, second-degree, and third-degree relative (Mat 1st/Pat 1st, Mat 2nd/Pat 2nd, Mat 3rd/Pat 3rd) (Table 2).

Using the data collection sheet, each pedigree was given a final maternal and paternal cancer "risk score" based on the reported family history of cancer. Using guidelines published by the NCCN, ACMG/NSGC (Hampel *et al.* 2015) and other published guidelines (Maradiegue *et al.* 2008, Frieder & Berlin 2012, Lu *et al.* 2014), a condensed scoring chart was created giving different ages of diagnosis and different cancer types a variety of points (Appendix A). The total score was then summed for the family histories of both the mother and father of the pregnancy to give a final maternal and paternal "risk score." Final cancer risk scores <8 points were classified as "low-risk." Scores ≥8 but <15 were classified as "intermediate-risk," and any score ≥15 was classified as a "high-risk" family.

Using the scoring system, nine de-identified pedigrees representing eight high-risk, five intermediate-risk, and five low-risk cancer histories were provided to six practicing cancer genetic counselors for preliminary validation. The cancer genetic counselors were asked to indicate for the maternal and paternal sides of each family whether they would characterize the family history as high-, intermediate-, or low-risk for a hereditary cancer predisposition syndrome. These cancer genetic counselors were informed that the patients in question were prenatal patients who had been referred for a variety of reasons. They were not given the scoring chart, but were informed that a high-risk cancer family history would warrant an immediate referral to cancer genetic counseling for someone in the family, an intermediate cancer risk

family would be given the option of cancer genetic counseling, and a low-risk family would be informed that the history is not suggestive of a hereditary cancer predisposition syndrome.

The error rate of collected data was determined by randomly selecting 10% of the reviewed charts for re-analysis. A total of 88 charts (44 from each year) were re-analyzed for all variables including age, insurance type, reason for referral, any cancer reported, cancer reported by first-, second-, and third-degree relatives, maternal numerical score, paternal numerical score, and maternal and paternal cancer risk category (high, intermediate, or low). Initially analyzed chart data were compared to re-analyzed data to determine the data collection error rate.

2.3 Anonymous Online Survey of Genetic Counselors

An anonymous online survey was conducted using the publicly available survey software, SurveyMonkey®. The survey was available from a unique weblink through surveymonkey.com. Participants were recruited through the National Society of Genetic Counselors (NSGC) email listserv and the NSGC prenatal genetic counseling special interest group listserv. The NSGC listserv reaches practicing genetic counselors and genetic counseling graduate students who are active NGSC members and who have chosen to subscribe, and the prenatal special interest group is a subset of NSGC members who practice in the prenatal setting and have chosen to participate in the group. Consent was asked prior to the start of the survey and was implied by voluntary completion.

Any board-certified or board-eligible prenatal genetic counselor who worked in the United States was eligible for this study. The survey was open from January 29 through February

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29, 2018. If participants indicated that they were not currently prenatal genetic counselors or were genetic counseling students, they were excluded from the study. The survey included a total of 17 questions; participants were able to skip any question, with the exception of the question regarding their current status as a prenatal genetic counselor. A total of 132 participants responded, with an 83% participation rate for the majority of questions, giving a total of approximately 104 complete responses and 6 partial responses.

The survey (Appendix B) consisted of six demographic questions and six questions relating to current or previous practice protocols regarding three-generation family histories and cancer genetic risk assessment. Participants were asked to indicate in what setting they currently practice.

Lastly, participants were given four hypothetical pedigrees depicting family histories with cancer risk categorized (according to the scoring chart previously described in Appendix A) as maternal high-risk, paternal high-risk, maternal intermediate-risk, and maternal low-risk. Cancer risk categorization (high, intermediate, or low) was not provided to the survey participants. Participants were asked to indicate what next steps they would take in each of these situations, given their current practice protocols. They could select one of five responses, including an option for open-ended responses. The first response option was "Strong suggestion that patient OR ANY relative depicted on the image should seek cancer genetic counseling as soon as possible. Give patients information how to do so, or provide immediate formal referral if applicable." The second and third response options both were "inform patient that cancer genetic counseling is an option for some family members, no immediate referral or directions for cancer

GC." The second response included to "mention in report to referring physician to discuss," and the third response included to "not mention in report to referring physician." During data analysis, these two responses were combined. The fourth response option was "no discussion with patient during appointment, but write in report to referring physician to discuss cancer family history." The fifth response option was "inform patient that history is not suggestive of hereditary cancer syndrome, or do not discuss with patient at all."

2.4 Data Analysis: Retrospective Chart Review

Data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics version 25 (IBM SPSS Statistics for Windows, Armonk, N.Y., USA. IBM Corp.) and SAS software version 8.2 (SAS Institute Inc., Cary, N.C., USA). Patient characteristics and outcomes of interest were summarized using means and standard deviations for continuous variables and using counts and percentages for categorical variables. Frequency and chi-square values were calculated using SPSS or SAS descriptive analysis tools. P-values <0.05 were considered statistically significant.

Additional analysis including a logistic regression model was provided by Marija Pejcinovska (senior statistician) at the UCI Center for Statistical Consulting. Methods below reflect this analysis.

Patient characteristics and outcomes of interest were summarized using means and standard deviations for continuous variables and using counts and percentages for categorical variables. Additionally, estimates of univariate associations were provided based on mean

differences for continuous variables and odds ratios (OR) for categorical variables along with corresponding 95% confidence intervals (CI).

A logistic regression model was used to quantify the strength of the association between each outcome of interest and the independent variate of year seen (either 2010 or 2016) after adjusting for the age and insurance type of the mother of the pregnancy.

For each outcome, the odds ratio for the main comparison of interest (year seen) was reported along with a 95% confidence interval and corresponding p-value. The odds ratio was considered to be statistically significant if the confidence interval excluded the value 1, or equivalently if $p<0.05$.

To account for the multiple testing, adjusted p-values obtained via the Holm method were calculated. This multiple testing correction was applied to the set of p-values for estimated odds ratios.

2.5 Data Analysis: Survey

Survey data were analyzed using SAS software version 8.2 (SAS Institute Inc., Cary, N.C., USA). Fisher's exact values were calculated using SAS (Figures 3, 4, and 5 and Table 5). If open-ended question responses fell into a category similar to one of the available responses, the response was changed from "other" to the best fit category. All p-values are 2-sided, and $p<0.05$ was considered significant.

III. RESULTS

3.1 Retrospective Chart Review

A retrospective chart review of three-generation family histories was conducted to quantify if there was a change in the number of prenatal genetic counseling patients who reported a family history of cancer in the year 2016 as compared to 2010.

Equal numbers of charts were reviewed from both 2010 and 2016. The demographic characteristics of patients analyzed were very similar across years (Table 1). Mean age for patients seen in 2010 and 2016 was 34.6 and 34.7, respectively. For both 2010 and 2016, 69% of patients were age 35 or older. Additionally, there was a similar distribution of reason for referral between 2010 and 2016. The only substantial difference between 2010 and 2016 concerned the number of patients who had private insurance (HPO) (46.9% of patients had private insurance in 2010 vs. 55.6% in 2016) ($p=0.01$).

Table 1. Demographic features of retrospective chart review

Characteristic	2010 (N=437) N (%)	2016 (N=437) N (%)	P-value
Age (Mean/SD)	34.60 /5.74	34.74 /5.28	*0.713
Age (categories)			0.339
18–20	13 (3.0)	8 (1.8)	
21–25	33 (7.6)	25 (5.7)	
26–30	41 (9.4)	52 (11.9)	
31–35	103 (23.6)	117 (26.8)	
36–40	202 (46.2)	197 (45.1)	
> 40	45 (10.3)	38 (8.7)	
Advanced maternal age			0.884
Yes (≥35)	302 (69.1)	300 (68.6)	
No (<35)	135 (30.9)	137 (31.4)	
Insurance Type			0.010
HPO (private)	205 (46.9)	243 (55.6)	
State	232 (53.1)	194 (44.4)	
Reason for referral			0.375
Advanced Age ≥35	253 (57.9)	240 (54.9)	
Other	184 (42.1)	197 (45.1)	

Summaries of quantitative and selected dichotomous variables based on complete cases. Percentages reflect the number of complete. HPO: HMO, PPO, Tricare. State: Medi-Cal, California screening program only. Other: abnormal ultrasound, positive screen, possible teratogen exposure, family history. Percentages rounded to nearest tenth. P-values from chi-square analysis, * P-value from two-tailed t-test.

Pedigrees were assessed to see if any cancer was reported in any family member on either side of the family, and, more specifically, if cancer was reported on the maternal "any cancer-Mat" or paternal "any cancer-Pat" side of the family. There was a statistically significant difference between 2010 and 2016 in the total number of pedigrees with any family history of cancer reported; 58.6% of pedigrees reviewed in 2016 had any cancer reported compared to 49.4% in 2010 (p=0.007, Table 2). There was a statistically significant difference between 2010 and 2016 in the total number of families with any maternal family history of cancer; 47.4% of family histories reviewed in 2016 had any maternal family cancer reported, compared to 36.4% in 2010 (p=0.001, Table 2). There was also a statistically significant difference between 2010 and 2016 in the total number of families with any paternal family history of cancer; 32.3% of

family histories reviewed in 2016 had any paternal family cancer history reported, compared to 24.3% in 2010 (p=0.009, Table 2).

Table 2. Prenatal pedigrees with reported cancer by year

Characteristic	2010 N=437 N (%)	2016 N=437 N (%)	P-value
Any cancer reported	216 (49.4)	256 (58.6)	0.007
Any cancer-Mat	159 (36.4)	207 (47.4)	0.001
Any cancer-Pat	106 (24.3)	141 (32.3)	0.009
Mother of pregnancy cancer	6 (1.4)	3 (0.7)	✣
Mat 1st cancer reported	64 (14.7)	79 (18.1)	0.17
Mat 2nd cancer reported	116 (26.5)	164 (37.5)	0.001
Mat 3rd cancer reported	13 (3.0)	26 (6.0)	0.033
Father of pregnancy cancer	1 (0.2)	4 (0.9)	✣
Pat 1st cancer reported	64 (14.7)	73 (16.7)	0.402
Pat 2nd cancer reported	53 (12.1)	94 (21.5)	<0.001
Pat 3rd cancer reported	8 (1.8)	7 (1.6)	0.795
Score High-Mat	31 (7.1)	46 (10.5)	0.073
Score High-Pat	25 (5.7)	24 (5.5)	0.883
Score Intermediate-Mat	8 (1.8)	22 (5.0)	0.009
Score Intermediate-Pat	5 (1.1)	8 (1.8)	0.402
Score Low-Mat	120 (27.5)	139 (31.8)	0.159
Score Low-Pat	76(17.4)	109 (24.9)	0.006
Score High (All)	56 (25.9)	70 (27.3)	✣
Score Intermediate & High (All)	69 (31.9)	100 (39.1)	✣

Mat: maternal. Pat: paternal. 1st, 2nd, and 3rd: degree relative. P-values from chi-square analysis. ✣ p-value could not be calculated.

Pedigrees were also assessed for differences in any cancer reported in maternal and paternal first-, second-, and third-degree relatives (Mat/Pat 1st, Mat/Pat 2nd, Mat/Pat 3rd, respectively, see Table 2). There was no significant difference in the number of maternal or paternal first-degree relatives or paternal third-degree relatives with reported cancer between 2010 and 2016. There was, however, a significant increase in the number of maternal second-, maternal third-, and paternal second-degree relatives with reported cancer between 2010 and 2016. There were 48 more maternal second-degree relatives with reported cancer in 2016, a 41.4% increase from 2010 (p=0.001, Table 2). There were 13 more maternal third-degree

relatives with reported cancer in 2016 (a 100% increase) (p=0.033), and 41 more paternal

second-degree relatives with reported cancer in 2016 (a 77.4% increase) (p<0.001, Table 2).

Pedigrees were also scored for cancer risk. Pedigrees with any reported cancer on the

maternal side were given a maternal score of high, intermediate, or low cancer risk. Pedigrees

with any reported cancer on the paternal side were given a paternal score of high, intermediate,

or low cancer risk. While not statistically significant, there were 15 more maternal high-risk

families identified in 2016, a 48.3% increase from 2010 (Table 2). The number of maternal

intermediate-risk families more than doubled from 2010 to 2016; 8 were identified in 2010

compared to 22 in 2016 (p=0.009, Table 2). There were 19 more maternal low-risk families

identified in 2016, a 15.8% increase from 2010, and there were 33 more paternal low-risk

families identified in 2010, a 43.4% increase from 2010 (Table 2). High-risk cancer histories

were identified in 25.9% of 2010 prenatal pedigrees with reported cancer and 27.3% of 2016

prenatal pedigrees with reported cancer. When combining both high and intermediate cancer risk

families, the numbers increase to 31.9% in 2010 and 39.1% in 2016. There was no significant

difference in the number of paternal high or intermediate cancer risk families reported in 2010

vs. 2016 (Table 2).

Due to the 18.5% increase in patients in 2016 with private insurance (HPO) compared to

2010 (Table 1), further analysis was performed to characterize how often patients with private

insurance reported a family history of cancer in 2016 and in 2010 (Figure 1). Of the 205 patients

with private insurance in 2010, 139 (67.8%) reported cancer in their families. Similarly, of the

243 families with private insurance in 2016, 170 (69.9%) reported cancer in their families. While

overall there were fewer individuals with state-funded insurance in 2016 compared to 2010 (44.4% vs. 53.1%), of those with state-funded insurance, 44.3% reported a family history of cancer in 2016 compared to 33.3% in 2010 (Figure 1, note the lower percentages for state-funded insurance regardless of year). Analysis to characterize how many patients aged 35 and older reported a family history of cancer in 2010 vs. 2016 was also performed (Figure 1). In total, there were more patients 35 and older than under 35 in both years. Of the 302 patients 35 and older in 2010, 160 (53.0%) reported any cancer, and of the 300 patients 35 and older in 2016, 192 (64.0%) reported any cancer (Figure 1).
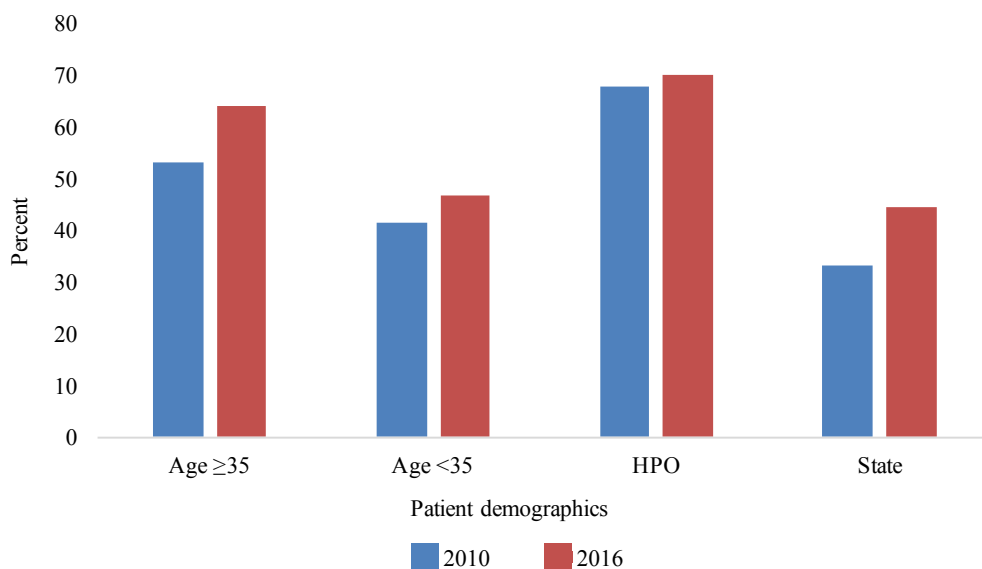
Figure 1: Cancer is reported more often in pedigrees of patients who are over 35 or who have private insurance. Percentages reflect percent of patients within each demographic category who reported any family history of cancer. Age and insurance information reflects mother of pregnancy only. Private insurance: HMO, PPO, Tricare. State Insurance: Medi-Cal, California screening program only. Statistical analysis between demographic groups not performed.

Using a logistic regression model adjusted for age and insurance type, the odds ratio (OR) for any cancer being reported in a family in 2016 vs. 2010 was 1.34 (CI 1.01-1.78, p=0.206, Table 3). The OR for any reported maternal family history of cancer was 1.47 (CI 1.11-1.95, p=0.058). The OR for a patient to have reported a maternal second-degree relative with

cancer in 2016 vs. 2010 was 1.55 (CI 1.15-2.09, p=0.043) and for a maternal third-degree relative was 1.98 (CI 0.99-3.97 p=0.217).

Table 3. Odds ratios for reported cancer in 2016 compared to 2010. 2016 survey results were compared to 2010 based on odd ratio (OR) for dichotomous variates of interest. 95% confidence intervals were calculated for the population value.

	OR Est. (95% CI)	p-value	df	Adjusted p-value
Any cancer reported	1.34 (1.01-1.78)	0.041	874	0.206
Any cancer-Mat	1.47 (1.11-1.95)	0.007	874	0.058
Score High-Mat	1.51 (0.93-2.45)	0.095	874	0.284
Score Int-Mat	2.69 (1.19-6.07)	0.017	874	0.121
Score Low-Mat	1.13 (0.84-1.53)	0.435	874	0.772
Mother of pregnancy cancer	0.49 (0.12-1.96)	0.311	874	0.514
Mat 1st cancer reported	1.24 (0.86-1.78)	0.257	874	0.514
Mat 2nd cancer reported	1.55 (1.15-2.09)	0.004	874	0.043
Mat 3nd cancer reported	1.98 (0.99-3.97)	0.054	874	0.217

Associations based on logistic regression models for dichotomous outcomes. Adjustments were based on age and insurance type (private or state). P-values adjusted for multiple comparisons using Holm's method. df: degrees of freedom. Mat: maternal. Pat: paternal. Int: intermediate. 1st, 2nd, and 3rd: degree relative.

For preliminary scoring chart validation, six practicing cancer genetic counselors gave a high, intermediate, or low cancer risk score for both the maternal and paternal sides of nine de-identified pedigrees. The nine de-identified pedigrees each had cancer reported on both the maternal and paternal sides. In total, the cancer genetic counselors analyzed eight high-risk, five intermediate-risk, and five low-risk cancer family histories (as defined by the scoring chart in Appendix A). The cancer genetic counselors correctly reported the high-risk pedigrees as high-risk 62.5% of the time; all discordant responses were scored as intermediate-risk. The cancer genetic counselors correctly reported the intermediate-risk pedigrees as intermediate-risk 66.7% of the time; 60% of discordant responses were scored as low-risk, and 40% were scored as high-risk. The cancer genetic counselors correctly reported the low-risk pedigrees as low-risk 96.7% of the time; the single discordant response was scored as intermediate-risk (data not shown).

Each patient chart was reviewed by the lead author. Ten percent of charts were analyzed a second time to calculate the collection and risk assessment error rate; data collected included: year, PDC, age, referral indication, insurance type, any cancer reported, any cancer-Mat, any cancer-Pat, cancer reported in maternal and paternal first-, second-, and third-degree relatives, numerical cancer score for each side of the family, and cancer risk categorization. The functional error rate (errors that would result in a change in categorization of high-, intermediate-, or low-risk family histories, or mis-documentation of an individual with cancer) was approximately 2% (52 errors out of 2,728 data points). An assumption of this study is that such errors were randomly distributed among the different groups, so they are unlikely to account for the differences observed between 2010 and 2016 (see Discussion).

3.2 Anonymous Online Survey of Genetic Counselors

The observed increased reporting of family history of cancer could have resulted from changes in protocols used by genetic counselors to assess cancer risk. Additionally, it is unknown how current prenatal counselors handle evaluating and discussing cancer risk during prenatal counseling sessions. To help evaluate the extent of any such changes in protocols, and to determine if there are discrepancies among current practice protocols, an anonymous online survey of practicing prenatal genetic counselors was conducted. The survey aimed to analyze current and prior practice protocols regarding cancer risk assessment and to review current practice protocols regarding cancer risk discussions with prenatal patients.

Demographic data on survey participants can be found in Table 4. A total of 132 participants responded, with an 83% participation rate for the majority of questions. This resulted

in a total of approximately 104 complete responses and 6 partial responses. The overwhelming majority (94.6%) of participants were female. While 53.2% of respondents had been practicing genetic counselors for 0-5 years, 27.9% percent had been practicing for at least 10 years. Respondents worked in a variety of settings, including private obstetrics and gynecology or fertility clinics (10.8%), academic medical centers (43.2%), managed care organizations (3.6%), private/community/government hospitals (30.6%), Maternal Fetal Medicine (MFM) practices (8.1%), or other (3.6%). Respondents also had a variety of previous genetic counseling clinical practice areas, including pediatric (21.8%), adult (11.8%), cancer (29.1%), and other (7.3%). Of note, 55.5% of respondents had only practiced prenatal genetic counseling. Respondents were asked how many prenatal patients they see per week; 5.4% saw 0-5 patients per week, 29.7% saw 5-10 patients per week, 55.9% saw 10-20 patients per week, and 9.0% saw >20 patients per week.

Table 4. Survey demographic information

Characteristic	N (Total responded)	Percent
Total participants	132	
Total practicing prenatal genetic counselors	129 (132)	97.7
Male	6 (111)	5.4
Female	105 (111)	94.6
Current age		
20-25	15 (111)	13.5
26-35	64 (111)	57.7
36-50	23 (111)	20.7
51+	9 (111)	8.1
Total years practicing		
0-5	59 (111)	53.2
5-10	21 (111)	18.9
10-20	20 (111)	18.0
>20	11 (111)	9.9
Current work location		
Private OB or fertility clinic	12 (111)	10.8
Academic medical center	48 (111)	43.2
Managed care organization	4 (111)	3.6
Private/community/government hospital	34 (111)	30.6
MFM	9 (111)	8.1
Other	4 (111)	3.6
Other specialties ever practiced		
Pediatric	24 (110)	21.8
Adult	13 (110)	11.8
Cancer	32 (110)	29.1
None, only prenatal	61 (110)	55.5
Other	8 (110)	7.3
Number of prenatal patients seen per week		
0-5	6 (111)	5.4
5-10	33 (111)	29.7
10-20	62 (111)	55.9
>20	10 (111)	9.0

OB: obstetrician-gynecologists. Managed care: e.g Kaiser, GroupHealth. MFM: Maternal Fetal Medicine

Participants were given four hypothetical pedigrees depicting family histories with cancer risk categorized as: maternal high-risk (question 16), paternal high-risk (question 14), maternal intermediate-risk (question 17), and low-risk (question 15) (Appendix B). Participants were not given information to indicate the risk categorization of each pedigree. These data are presented in Table 5 and Figure 2. Of the 104 participants who responded to the question associated with the paternal high-risk pedigree, 24.0% selected "suggest cancer GC with referral if possible" and

70.2% selected the "option of cancer GC." This is in contrast to the maternal high-risk pedigree; of the 105 participants who responded, 61.9% selected "suggest cancer GC with referral if possible," and 36.2% selected the "option of cancer GC." The majority of respondents (70.5%) selected the "option of cancer GC" for the maternal intermediate-risk, while only 16.2% elected to "suggest cancer GC with referral if possible." While 59.0% of participants selected the "option of cancer GC" for the low-risk pedigree, 31.4% responded that the pedigree was "likely not hereditary." There was no significant difference in responses by participants with prior cancer genetic counseling experience compared to those with only prenatal genetic counseling experience (Table 5). However, counselors with prior cancer genetic counseling experience elected that the low-risk family was "likely not hereditary" more often than those with only prenatal genetic counseling experience (46.7% vs. 29.8%) (Table 5 and Figure 2).

Table 5. Prenatal genetic counselor pedigree responses to hypothetical high-, intermediate-, and low-cancer risk pedigrees. Responses by prior cancer counseling experience and prenatal only experience provided.

Pedigree cancer risk	Total N (%)	Prior cancer experience N (%)	Prenatal only experience N (%)	p-value
Paternal High-Risk	104 (100.0)	29 (100.0)	57 (100.0)	0.957
Suggest cancer GC with referral if possible	25 (24.0)	7 (24.1)	11 (19.3)	
Option of cancer GC	73 (70.2)	21 (72.4)	42 (73.7)	
No discussion with patient, PCP to discuss	1 (1.0)	0	1 (1.8)	
Likely not hereditary, no discussion	3 (2.9)	1 (3.4)	2 (3.5)	
Other	2 (1.9)	0	1 (1.8)	
Maternal High-Risk	105 (100.0)	30 (100.0)	57 (100.0)	0.922
Suggest cancer GC with referral if possible	65 (61.9)	20 (66.7)	35 (61.4)	
Option of cancer GC	38 (36.2)	10 (33.3)	20 (35.1)	
No discussion with patient, PCP to discuss	1 (1.0)	0	1(1.8)	
Likely not hereditary, no discussion	0	0	0	
Other	1 (1.0)	0	1 (1.8)	
Maternal Intermediate-Risk	105 (100.0)	30 (100.0)	57(100.0)	0.288
Suggest cancer GC with referral if possible	17 (16.2)	4 (13.3)	8 (14.0)	
Option of cancer GC	74 (70.5)	22 (73.3)	40 (70.2)	
No discussion with patient, PCP to discuss	1 (1.0)	0	1 (1.8)	
Likely not hereditary, no discussion	11 (10.5)	2 (6.7)	8 (14.0)	
Other	2 (1.9)	2 (6.7)	0	
Maternal Low-Risk	105 (100.0)	30 (100.0)	57 (100.0)	0.436
Suggest cancer GC with referral if possible	3 (2.9)	1 (3.3)	1 (1.8)	
Option of cancer GC	62 (59.0)	13 (43.3)	35 (61.4)	
No discussion with patient, PCP to discuss	4 (3.8)	1 (3.3)	3 (5.3)	
Likely not hereditary, no discussion	33 (31.4)	14 (46.7)	17 (29.8)	
Other	3 (2.9)	1 (3.3)	1 (1.8)	

GC: genetic counseling. Prior cancer experience reflects current prenatal genetic counselors who have ever been a practicing cancer genetic counselor. Prenatal only experience reflects current prenatal genetic counselors who have only practiced in prenatal genetic counseling. Percentages rounded to nearest tenth. P-values from Fisher's exact test.
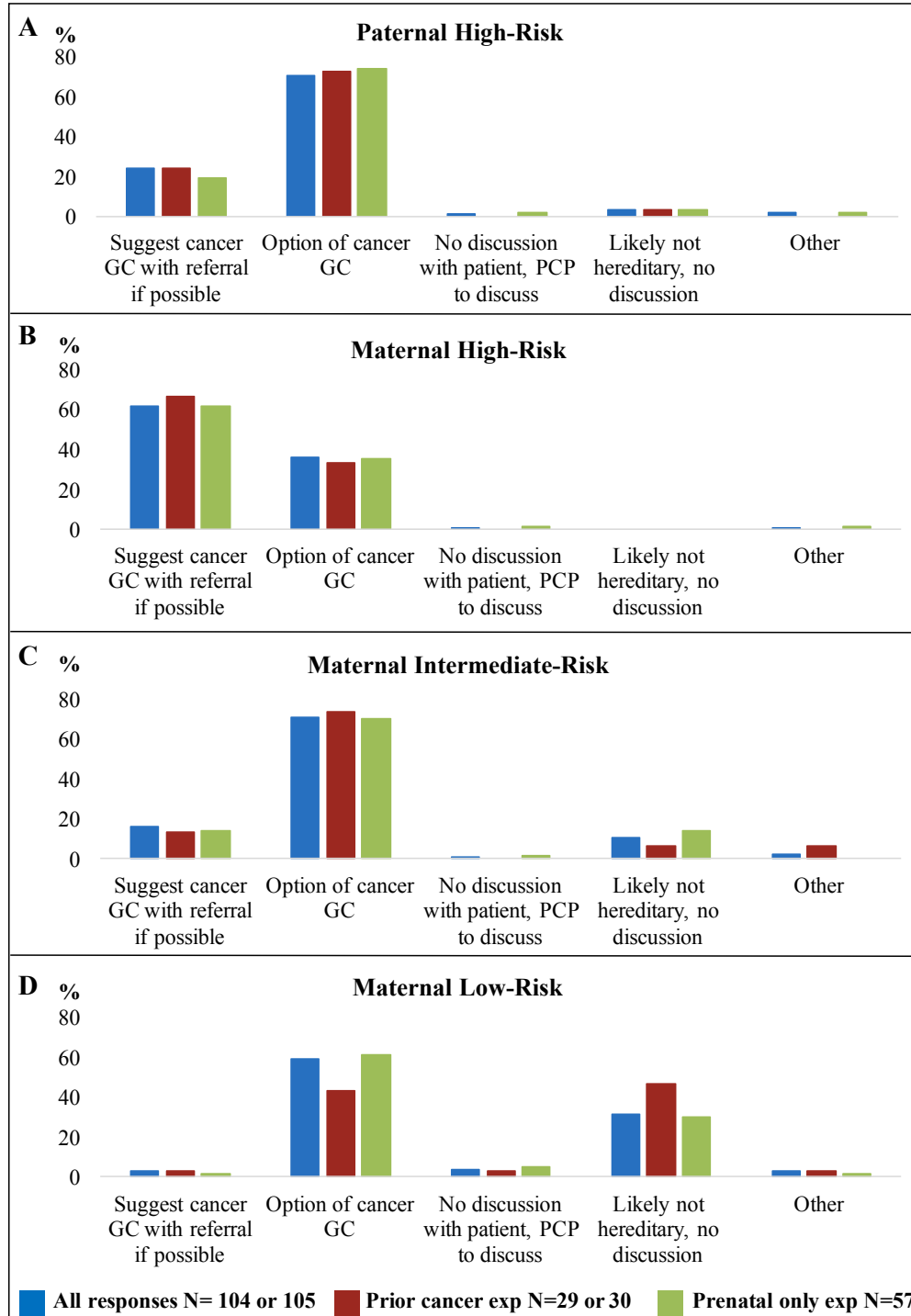
Figure 2. Prenatal genetic counselors responded differently to high-risk pedigrees depending on whether the history was in maternal vs paternal relatives. Responses of prenatal genetic counselors to low-risk pedigrees differ by prior genetic counseling experience. Prenatal genetic counseling responses to pedigrees scored as: A) maternal high-risk, B) paternal high-risk, C) maternal intermediate-risk, or D) maternal low-risk for a hereditary cancer syndrome. GC: genetic counseling. PCP: primary care physician. Within A, B, C, and D, there was no significant difference between answer choice by type of respondent (all, those with prior cancer exp (experience), and those with only prenatal exp (experience)) (p-values shown in Table 5).

Fisher's exact analysis was performed to determine if location of current practice or number of prenatal patients seen per week influences how often a three-generation family history that includes cancer is taken. Overall, 52.7% of participants currently take a three-generation family history that includes cancer every time they take a family history, and 11.8% use a questionnaire that includes cancer (Figure 3), but 22.7% only document cancer history if the patient brings it up. For respondents who practice in obstetrics/gynecology or fertility clinics, 75.0% inquire about cancer every time a family history is taken, compared to 64.6% of those who work in an academic medical center, 66.7% who work in MFM offices, 30.3% who work in a hospital setting, and 25% who work at a managed care organization (Figure 3). Overall, there were no significant differences in how often a three-generation family history that includes cancer is taken depending on practice location or number of prenatal patient seen per week (Figure 3).
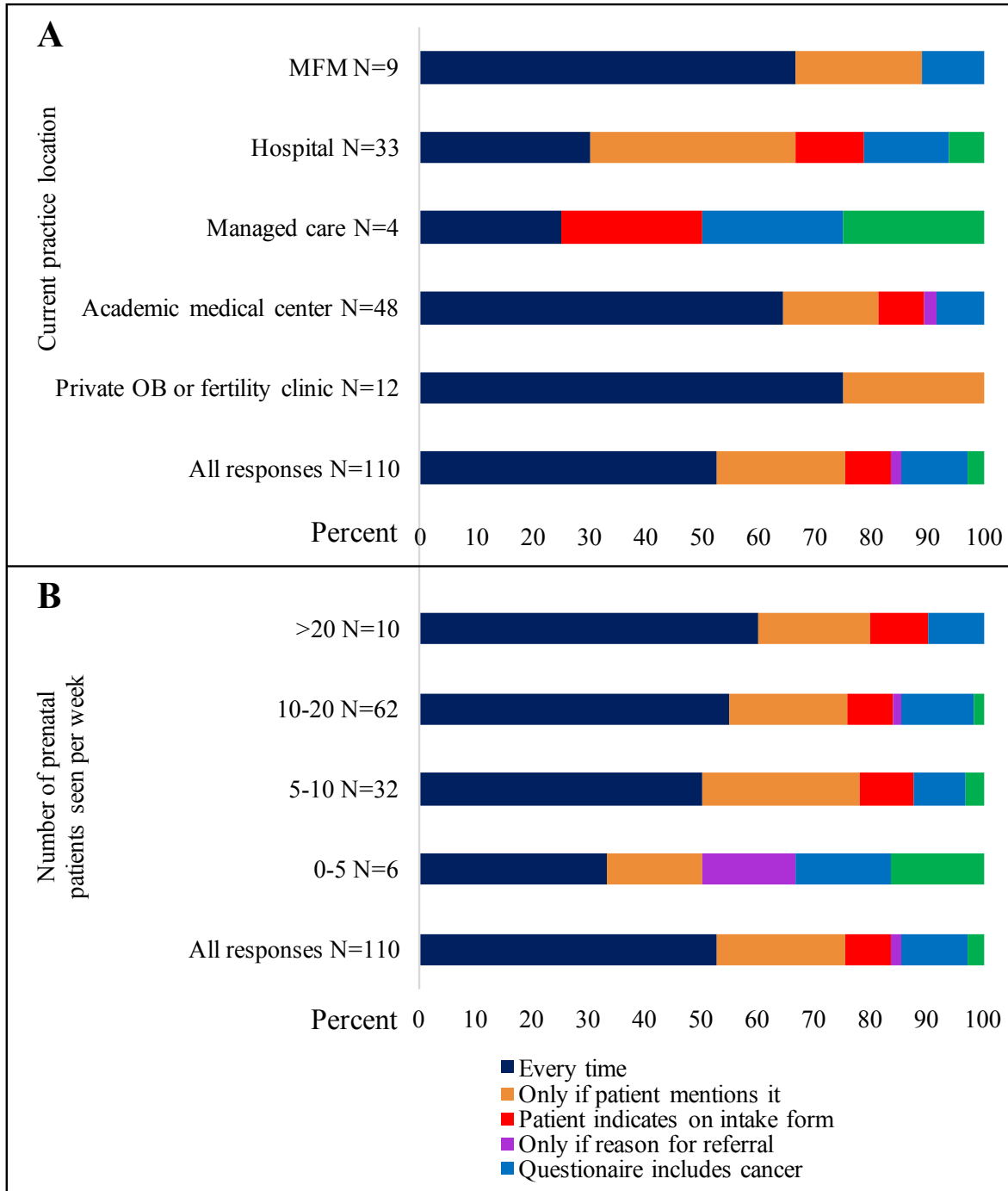
Figure 3. How often cancer is addressed during a prenatal three-generation family history. No major difference in how often prenatal genetic counselors address cancer when taking a three-generation family history by A) current practice location or B) how many prenatal patients the counselor sees per week. OB: obstetrician-gynecologists. Managed care: e.g Kaiser, GroupHealth. MFM: Maternal Fetal Medicine. There was no significant difference (Fisher's exact) in how often a three-generation family history that includes cancer is taken depending on practice location ($p = 0.054$) or number of prenatal patient seen per week ($p = 0.696$).

Fisher's exact analysis was also performed to determine if location of current practice or number of patients seen per week influences how often the age at cancer diagnosis is addressed. Overall, 91.7% of participants always ask about the age at cancer diagnosis, while 8.3% only sometimes address age at diagnosis. Only 75.0% of those working in an obstetrics/gynecology or fertility clinic or a managed care setting always ask about age at diagnosis, compared to >90% for those working in academic, hospital, or MFM settings. However, overall there were no significant differences in how often age at cancer diagnosis is obtained based on practice location or number of patients seen per week (Figure 4).
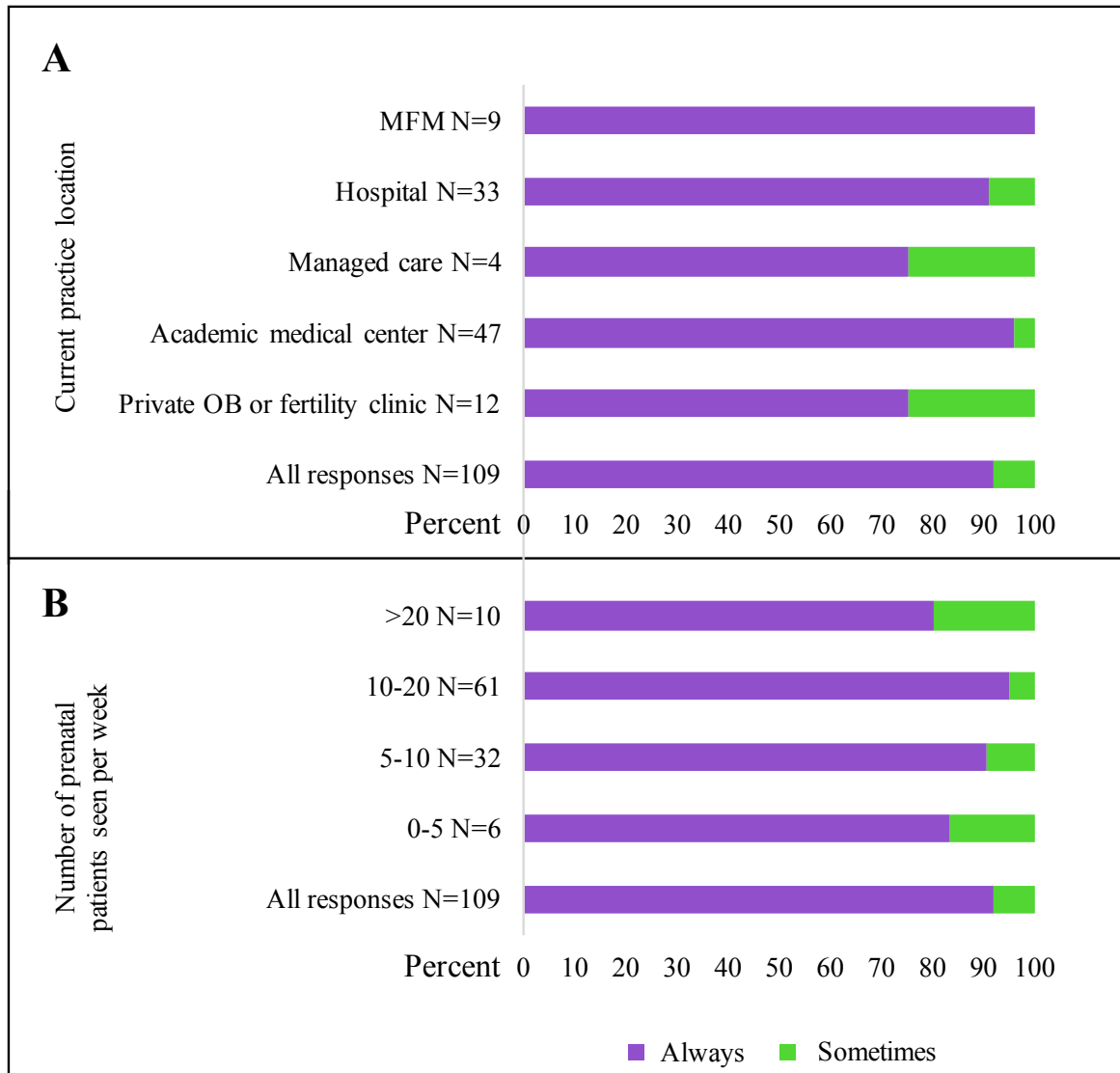
Figure 4. How often age at cancer diagnosis is addressed when cancer is reported during a prenatal three-generation family history. There was no major difference (Fisher's exact) in how often prenatal genetic counselors address age at cancer diagnosis by A) current practice location (p=0.108) or B) how many prenatal patients are seen per week (p=0.193). OB: obstetrician-gynecologists. Managed care: e.g Kaiser, GroupHealth. MFM: Maternal Fetal Medicine.

There were no significant differences in how often a three-generation family history that includes cancer was taken or age at cancer diagnosis was assessed for participant responses in 2010 ("2010 experience, 2010 practice response") compared to those same genetic counselors' current practice response ("2010 experience, current practice response") to how often a three-generation family history that includes cancer is currently taken or age at cancer diagnosis is

currently assessed (Figure 5). There was also no significant difference in how often a three-generation family history that includes cancer was taken or age at cancer diagnosis was assessed for participant practice responses in 2010 compared to current practice responses for participants who did not practice in 2010 ("no 2010 experience, current practice response") (Figure 5).
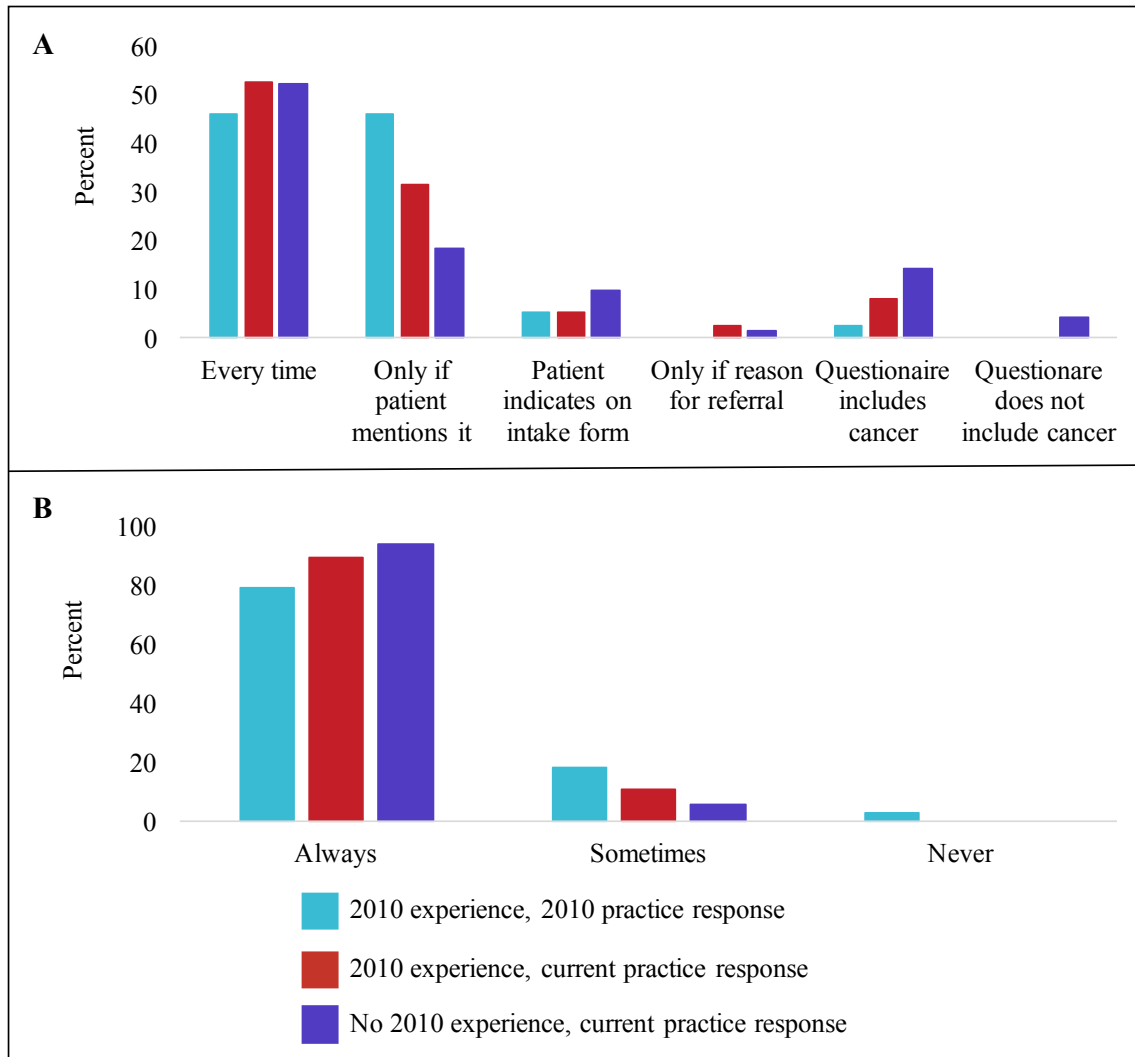
Figure 5. Prenatal genetic counseling practices are changing over time. Paired responses between 2010 responses of counselors who practiced in 2010 (2010 experience, 2010 practice response) compared to how they would currently respond (2010 experience, current practice response) to A) how often cancer is addressed during a prenatal genetic counseling three-generation family history and B) if age at cancer diagnosis is addressed. Current practice responses also shown for counselors who did not practice in 2010 (no 2010 experience, current practice response). Fisher's exact analysis between "2010 experience, current practice response" and "No 2010 experience, current practice response" for A) p=0.399, and B) p=0.362

IV. DISCUSSION

This study aimed to determine if there was a change over time in how often prenatal genetic counselors identify a family history of cancer during prenatal genetic counseling sessions. The study also aimed to assess the current practice protocols of prenatal genetic counselors to understand if there is uniformity or discrepancy in how they evaluate and respond to families with reported cancer history. While the underlying reason is yet to be identified, this study found that there was an increase in the number of patients who reported a family history of cancer in 2016 as compared to 2010. Additionally, there was also an increase in the number of maternal high-, maternal intermediate-, and both maternal and paternal low-risk cancer histories identified in 2016 vs. 2010. There was no significant difference in the number of paternal high- or intermediate-risk families reported in 2016 vs. 2010. Overall, prenatal genetic counselors uniformly bring up the topic of cancer genetic counseling with high or intermediate cancer-risk families. However, there are clear differences in how they respond to paternal vs. maternal high-risk cancer family histories in terms of either an immediate referral or only discussing the option of cancer genetic counseling. This report highlights the need for a standard practice protocol to guide prenatal genetic counselors on how to respond and relay information regarding cancer genetic risk assessment and when to strongly suggest or refer a family member to cancer genetic counseling vs. discuss the option of cancer genetic counseling after completion of the pregnancy.

4.1 Retrospective Chart Review

The goal of the retrospective chart review was to determine whether there was a significant change in the number of families with a history of cancer identified in a prenatal

setting in 2016 versus in 2010. It also aimed to establish a proposed generalized scoring system for cancer risk to be used in the prenatal clinical setting.

The main observation from the analysis concerned the frequency with which cancer was reported in family histories. There was a significant increase in how often any cancer was reported and how often both maternal and paternal family histories with cancer were reported in 2016 compared to 2010. While there was also an increase in the number of maternal second-, maternal third-, and paternal second-degree relatives with cancer, the overall number of third-degree relatives reported with cancer was substantially smaller, suggesting knowledge of extended relatives' cancer history is still much lower than for closer relatives. Lastly, in both years, there were more maternal than paternal family histories with any cancer reported (Table 2).

Cancer incidence *per se* should not change much in the general population in a six-year period, so the change in reported cancer in this study is likely due to other circumstances. Factors influencing the differences reported above might include, but are not limited to, changes in patient recollection, differential reporting of maternal vs. paternal cancer histories, family communication, counselor practice protocols, access to insurance, and availability of cancer genetic counselors. For example, the NSGC professional surveys from 2010 and 2016 indicate that only 27% of practicing genetic counselors worked in cancer as a primary specialty in 2010 as compared to 48% in 2016.

Pedigrees were also scored for cancer risk and given both a maternal and a paternal score of high-, intermediate-, or low-risk. While not statistically significant, there was a 48.4% increase in maternal high-risk cancer families reported in 2016 compared to 2010; 46 maternal high-risk family histories were reported in 2016 compared to 31 in 2010. There was a significant increase (175.0%) in maternal intermediate-risk families reported in 2016 vs. 2010; however, this large percentage increase is based on a small number of families (22 maternal intermediate-risk families reported in 2016 compared to 8 in 2010). There was also a 15.8% increase in maternal and 43.2% increase in paternal low-risk families identified in 2016 compared to 2010. There were no statistically significant differences in the numbers of paternal high- or intermediate-risk families reported in 2016 vs. in 2010 (Table 2); this may be due to a lack of paternal family history awareness if the father of the pregnancy was not present during the appointment (this variable was not collected, although in hindsight, it would have been an important variable to capture). Of note, there were still a total of 24 high-risk paternal family histories reported in 2016, which is significant when considering the potential risk for cancer in all of the individuals in these families. Overall, there was in increase in cancers reported in first-, second-, and third-degree maternal relatives from 2010 to 2016. There was also an increase in the number of maternal high-, intermediate-, and low-risk pedigrees in 2016 compared to 2010. While there was only an increase in the number of paternal low-risk families and not in paternal high- or intermediate-risk families, the number of paternal first- and second-degree relatives who were reported to have cancer did increase from 2016 to 2010.

Previously published studies of prenatal clinical chart reviews reported incidental cancer risk that would warrant further cancer genetic counseling approximating 1.0%, 9.0%, and 13.0%

in the years 1985-1990, 2003-2006, and 2007, respectively (Larabell *et al.* 1992, Hafen *et al.* 2009, Hoang 2010). The current study identified incidental high-risk cancer histories in 25.9% of 2010 cases and in 27.3% of 2016 cases. When combining both high and intermediate cancer risk families, the numbers increase to 31.9% in 2010 and 39.1% in 2016. Thus, the results of the current study support previous research indicating a continued increase in identification of incidental high-risk cancer family histories in the prenatal setting over time.

Due to an 18.5% percent increase in patients with private insurance (HPO) in 2016 compared to 2010, further analysis was performed to characterize how many individuals with private insurance reported cancer in their families in 2016 vs. in 2010 (Figure 1). There were notable differences in how often cancer was reported in 2016 vs. 2010 as a function of both age and type of insurance. The logistic regression was only performed for maternal outcomes because age and insurance type were only documented for the mother of the pregnancy. The analysis suggests that patient age or insurance type may influence how often patients report a family history of cancer, but the reason behind this is not entirely clear. While the age and insurance type of the mother of the pregnancy may not directly influence cancer reporting, the results of the regression analysis support the idea that other variables besides year may play a role in the increase in the total number of families who reported a history of cancer in 2016 compared to 2010. Other variables that might influence patient reporting were not documented but might include ethnicity, religion, native language, communication between family members, how many prior children the family has, and size and location of extended family.

Six cancer genetic counselors were asked to determine cancer risk in nine de-identified pedigrees to assess how well the scoring system created in this analysis classified cancer risk.

While the cancer genetic counselors' assessments of the five low-risk family histories were in strong agreement with our scoring system, there were some differences between the five intermediate- and eight high-risk family histories. While only 62.8% of cancer genetic counselor classifications agreed with the high-risk classification based on our scoring chart, those that disagreed all documented the histories as intermediate-risk. For example, one maternal high-risk pedigree included a maternal second-degree relative with both breast and ovarian cancer, diagnosed in her 80s and at 96, respectively. While the scoring system gave that individual more points for having ovarian cancer and having two cancers in the same person, the number of unaffected individuals in the family was not taken into consideration. While 66.7% of cancer genetic counselors agreed with the intermediate-risk classification based on our scoring chart, those who disagreed differed in their risk assessments; 20.0% documented the history as high-risk, and 13.3% documented the history as low-risk. This preliminary data suggests that overall, the scoring system accurately assesses low-risk histories but may score more histories as high-risk than intermediate-risk as compared to the risk assessment by cancer genetic counselors. This however, only reflects responses of six practicing cancer genetic counselors and needs further validation.

4.2 Anonymous Online Survey of Genetic Counselors

The goal of the online survey was to assess the current practice protocols of prenatal genetic counselors in order to understand if there is uniformity or discrepancy in how counselors evaluate and respond to families with reported cancer history. If discrepancies are identified, can we use this information to establish a standard protocol regarding making cancer genetic counseling referrals during a prenatal genetic counseling visit?

Participant responses to the four pedigrees depicting family histories with varying degrees of cancer risk are summarized in Table 5. Overall, 94.2% and 98.1% of participants elected either to refer or to discuss the option of cancer genetic counseling for the paternal high-risk and maternal high-risk pedigrees, respectively. However, when broken down by specific action, only 24.0% of respondents elected to refer to cancer genetic counseling for the paternal high-risk pedigree compared to 61.9% for the maternal high-risk pedigree. This result highlights obvious discrepancies between how counselors handle paternal vs. maternal high-risk cancer histories during a prenatal appointment. Open-ended responses to the four pedigrees revealed several interesting concepts (Appendix C). Regarding paternal family histories of cancer, a few respondents mentioned the challenges of counseling or providing referrals for the partner of a patient because during a prenatal session, the counselor's patient is technically the mother of the pregnancy. However, if discussions of pregnancy-related topics such as carrier screening are presented to both parents, it seems that paternal cancer risk should be addressed similarly to maternal cancer risk.

Survey responses also indicate that practice protocols of prenatal genetic counselors change over time. There was a 6.5% increase in how often a three-generation family history that includes cancer was taken by counselors who practiced in 2016 vs. those same counselors' responses for 2010 (Figure 3). Similarly, there was a 10.0% increase in how often age at cancer diagnosis was asked by counselors who practiced in 2016 vs. those same counselors' responses for 2010 (Figure 4). These changes in practice over time may contribute to the increased reporting of cancer between 2010 and 2016 documented in the first part of this study. Other

differences in practice protocols that were not addressed in this study might also play a role, such as the ability to refer to cancer genetic counseling and average length of prenatal appointment.

Other open-ended responses to the four pedigrees highlighted additional important concepts. One respondent mentioned determining cancer risk referrals based on the emotional state of the patient. While a standard scoring method for cancer histories could be established, prenatal counselors must make subjective assessments of each patient's emotional capacity and anxiety in a limited amount of time and then use that assessment to weigh the benefits and disadvantages of discussing cancer risk history during a potentially stressful time. Lastly, multiple respondents also made note of the value of informing families of the importance of cancer screening, especially in low-risk family histories (Appendix C). Although reviewing cancer screening can be time-consuming, many counselors indicated its importance as part of routine cancer assessment when addressed in the prenatal setting.

Survey respondents were asked to provide suggestions for how prenatal genetic counselors can better help relay a recommendation for a cancer genetic counseling referral for the patient or someone in their family after the pregnancy has completed (Appendix D). Many indicated the need for an information sheet provided specifically for prenatal patients, ideally created by the NSGC cancer special interest group, that could be given to prenatal patients when a cancer history is documented. Some even suggested a standard letter patients could provide to their primary care physicians to make sure the cancer family history is addressed at a later time.

4.3 Limitations

A major limitation of this study is that only two years of data were analyzed. While the data suggest an increase in cancer reporting in 2016 compared to 2010, additional years of data are needed to confirm this finding.

Another limitation of this study is that data were collected only once from each prenatal chart and by a single individual. The error rate, which was estimated as 2%, is low enough that it is unlikely to affect any of the major conclusions of this study. However, re-review of all data collected, either for a second time or by an additional individual, would rectify most errors and provide a more accurate analysis.

The accuracy of the assessment of paternal family histories of cancer is difficult to determine because there was no data collected regarding whether or not the father of the pregnancy was present during each prenatal appointment. Therefore, we cannot ascertain whether any changes in the number of paternal cancer family histories with reported cancer may have been due to mis-reporting of the father's family history by the mother of the pregnancy.

The cancer risk scoring system used in this study has not been externally validated. While the scoring system was based on published guidelines (Maradiegue *et al.* 2008, Frieder & Berlin 2012, Lu *et al.* 2014, NCCN, ACMG/NSGC Hampel *et al.* 2015), it was created by the lead author with the aim of being simple and easy to use. Differences in how cancer genetic counselors rated the pedigrees compared to how the scoring system classified these pedigrees

highlight the importance of, and need for, further validation and editing by additional cancer genetic counselors prior to use in a prenatal clinical setting.

The 2018 NSGC Professional Status Survey indicated that there were at least 600 practicing prenatal genetic counselors in the U.S. in 2018. Only 104 prenatal counselors completed the survey, indicating that this study did not document responses from the majority of current prenatal counselors. Further analysis of more individuals is needed to better assess current and previous practice protocols.

4.4 Future Directions

An important next step in the continuation of this project would be the assessment and validation of the cancer scoring system by a large group of cancer genetic counselors. The group of six cancer genetic counselors used in this study was selected based on personal relationships, and given that several were from the same clinical practice, it is likely that these six are not representative of the total cohort of cancer genetic counselors. Until this can happen, prenatal genetic counselors should still use previously published guidelines, such as Hampel et al (2015), to assess cancer family histories. Once the scoring system is validated, prenatal charts would have to be reviewed and scored again by multiple individuals for further validation of results.

While it may seem safe to err on the side of caution and discuss the option of cancer genetic counseling with most families that have a history of cancer, prenatal counselors must be aware of the potential disadvantages of this approach. This study shows an increase over time in the number of people who reported a family history of cancer. It is critical for prenatal

counselors to carefully evaluate histories and use good judgment on when to refer patients to cancer genetic counselors. While there are more cancer genetic counselors than in the past, it is important not to overwhelm cancer genetic counselors with unnecessary referrals, or, more importantly, not to alarm pregnant couples unnecessarily during a time when they may be trying to control stress.

The discrepancies observed between how prenatal counselors respond to a paternal vs. a maternal high cancer risk pedigree suggest that a standard scoring system and protocol would be helpful. As suggested by many survey participants, it would be useful to have a standard protocol established for prenatal counselors to follow when a cancer history is reported. This could be as simple as a stock letter mentioning that a cancer risk was identified, a recommendation for cancer genetic counseling, and how to find a cancer genetic counselor. Additionally, a standard letter patents could bring to their primary care physicians could potentially help them continue the conversation with a physician who sees them on a more regular basis.

Lastly, this study did not document the outcome of each case. It would be very interesting to determine if patients with a high-risk assessment were ever seen by a cancer genetic counselor or if their referring physicians ever discussed the topic with them after the recommendation for cancer genetic counseling was made. Are the patients themselves receptive to our recommendations? Did patients with an intermediate cancer risk who discussed the option of cancer genetic counseling remember the recommendation and follow up on it? If we are identifying families with high or intermediate cancer risk but the downstream cancer genetic counseling is not occurring, what are the barriers?

4.5 Conclusions

The results of this study support previous data suggesting an increase in the identification of incidental cancer risk during prenatal genetic counseling sessions in recent years. This study identified incidental high-risk cancer histories in 25.9% of cases from 2010 and 27.3% of cases from 2016. When combining both high- and intermediate-risk families, the numbers increase to 31.9% in 2010 and 39.1% in 2016. Overall, there was an 18.5% increase in the number of patients who reported any family history of cancer in 2016 compared to 2010. Factors such as patients' age and insurance type, among others, might play a role in this increase in cancer reporting between 2010 and 2016.

The results of the survey indicate discrepancies in how prenatal genetic counselors respond to paternal *vs* maternal high-risk cancer histories. While the majority of prenatal counselors surveyed discussed the topic of cancer genetic counseling, there are large differences between when they actually refer patients for cancer genetic counseling and when they only discuss the option of cancer genetic counseling. There are also differences in how counselors respond to low-risk family histories that depend on whether or not the counselor had prior cancer genetic counseling experience.

Given the overall increase in patients reporting a family history of cancer during prenatal genetic counseling sessions during the study period and discrepancies among current prenatal practice protocols, there is clear importance and need for a standard guideline that prenatal counselors could use when evaluating and discussing cancer risks.

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REFERENCES

Acheson, L.S. *et al.* 2000. Family history-taking in community family practice: implications for genetic screening. *Genetics in Medicine*, 2(3), pp.180–185.

American College of Obstetricians and Gynecologists. 2011. Family history as a risk assessment tool. ACOG Committee Opinion no. 478. *Obstetrics and Gynecology*, 117;747-750

American College of Obstetricians and Gynecologists. 2015. Hereditary cancer syndromes and risk assessment. ACOG Committee Opinion No. 634. *Obstetrics and Gynecology,* 125:1538-43.

Anderson, A. 2014. Report: The Impact of the Affordable Care Act on the Health Care Workforce. The Heritage Foundation. pp.1-29

Baldwin, LM. *et al.* 2014. Accuracy of Ovarian and Colon Cancer Risk Assessments by U.S. Physicians. *Journal of General Internal Medicine*, 29(5), pp.741–749.

Bennett, R.L. *et al.* 1995. Recommendations for standardized human pedigree nomenclature. *Journal of Genetic Counseling*, 4(4), pp.267–279.

Bennett R.L. The practical guide to the genetic family history. 2nd ed. Hoboken (NJ): Wiley-Blackwell; 2010.

Block, L. *et al.* 2013. In the Wake of the 2003 and 2011 Duty Hours Regulations, How Do Internal Medicine Interns Spend Their Time? *Journal of General Internal Medicine*, 28(8), pp.1042–1047.

Borzekowski, D.L.G. *et al.* 2014. The Angelina effect: immediate reach, grasp and impact of going public. *Genetics in Medicine*, 16(7), pp.516–521.

Carroll, A.E. Nov 2016. "A Doctor Shortage? Let's Take a Closer Look." The Upshot, nytimes.com

Chen, P.W. May, 2013. "For New Doctors, 8 Minutes Per Patient." Well, nytimes.com

Dominguez, F.J. *et al*. 2007. Accuracy of Self-Reported Personal History of Cancer in an Outpatient Breast Center. *Journal of Genetic Counseling*, 16(3), pp.341–345.

Eichmeyer, J.N. *et al*. 2014. The Value of a Genetic Counselor: Improving Identification of Cancer Genetic Counseling Patients with Chart Review. *Journal of Genetic Counseling*, 23(3), pp.323–329.

Evans, D.G.R. *et al.* 2014. The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services. *Breast Cancer Research*, 16(5), pp.183–6.

Fiederling, J. *et al.* 2016. Validity of self-reported family history of cancer: A systematic literature review on selected cancers. *International Journal of Cancer*, 139(7), pp.1449–60.

Flynn, B.S. *et al.* 2010. Primary care physicians' use of family history for cancer risk assessment. *BMC Family Practice*, 11(1), pp.388–8.

Frezzo, T.M. *et al*. 2003. The genetic family history as a risk assessment tool in internal medicine. *Genetics in Medicine*, 5(2), pp.84–91.

Frieder, R.P. & Berlin, S.M. 2012. Hereditary Cancer Risk Assessment in Obstetrics and Gynecology: The Evolving Standard of Care. *OBG Management*, 24(11).

Garber, J.E. & Offit, K., 2005. Hereditary Cancer Predisposition Syndromes. *Journal of Clinical Oncology*, 23(2), pp.276–292.

Grover, S. *et al.* 2004. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*, 2(9), pp.813–819.

Guttmacher, A.E. *et al*. 2004. The family history-more important than ever. *The New England journal of medicine*, 351(22), pp.2333–2336.

Hafen, L.B. *et al.* 2009. The Utility of Genetic Counseling Prior to Offering First Trimester Screening Options. *Journal of Genetic Counseling*, 18(4), pp.395–400.

Hampel, H. *et al*. 2004. Referral for cancer genetics consultation: a review and compilation of risk assessment criteria. *Journal of Medical Genetics*, 41(2), pp.81–91.

Hampel, H. *et al.* 2015. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genetics in Medicine*, 17(1), pp.70–87.

Harrell, F.E. (2001). Regression Modeling Strategies with Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer.

Hoang, V.T.T. 2010. UNIVERSITY OF CALIFORNIA, IRVINE. Genetic Counseling Following a Positive X-AFP Result: Identification of Additional Genetic Risk Factors Before Prenatal Diagnosis. pp.1–99.

LaDuca, H. *et al.* 2014. Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. *Genetics in Medicine*, 16(11), pp.830–837.

Larabell, S.K. 1992. UNIVERSITY OF CALIFORNIA, IRVINE. Genetic Counseling Following a Positive High MS-AFP Result: Identification of Additional Risk Factors Prior to Prenatal Diagnosis. pp.1-61.

Lindor, N.M. *et al*. 2008. Concise Handbook of Familial Cancer Susceptibility Syndromes - Second Edition. *JNCI Monographs*, (38), pp.3–93.

Lu, K.H. *et al*. 2014. American Society of Clinical Oncology Expert Statement: Collection and

Use of a Cancer Family History for Oncology Providers. *Journal of Clinical Oncology*, 32(8), pp.833–840.

Lynch, H.T. *et al.* 2013. Hereditary ovarian and breast cancer: what have we learned? *Annals of Oncology*, 24(suppl 8), pp.viii83–viii95.

Maradiegue, A. *et al.*, 2008. Scoping the family history: Assessment of Lynch syndrome (hereditary nonpolyposis colorectal cancer) in primary care settings—A primer for nurse practitioners. *Journal of the American Academy of Nurse Practitioners*, 20(2), pp.76–84.

Meyer, L.A. *et al.* 2010. Evaluating Women With Ovarian Cancer for BRCA1 and BRCA2 Mutations: Missed Opportunities. *Obstet Gynecol,* 115(5), pp. 945–952

Murff, H.J. *et al.* 2004. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. *JAMA*, 292(12), pp.1480–1489.

Murff, H.J. *et al.* 2007. The Comprehensiveness of Family Cancer History Assessments in Primary Care. *Community Genetics*, 10(3), 174–180.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian (Version 1.2018). https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed Ma 13, 2017.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (Version 3.2017). https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed Ma 13, 2017.

Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

Pompilii, E. *et al.*, 2014. Prenatal genetic counseling referrals for advanced maternal age: still room for improvement. *Prenatal Diagnosis*, 34(1), pp.71–74.

Rahman, N. 2014. Realizing the promise of cancer predisposition genes. *Nature*, 505(7483), pp.302–308.

Raphael, J. *et al.* 2016. The Impact of Angelina Jolie (AJ)'s Story on Genetic Referral and Testing at an Academic Cancer Centre in Canada. *Journal of Genetic Counseling*, pp.1–8.

Rich, E.C. *et al.* 2004. Reconsidering the family history in primary care. *Journal of General Internal Medicine*, 19(3), pp.273–280.

Riley, B.D. *et al.* 2012. Essential Elements of Genetic Cancer Risk Assessment, Counseling, and Testing: Updated Recommendations of the National Society of Genetic Counselors. *Journal of Genetic Counseling*, 21(2), pp.151–161.

Rolnick, S.J. *et al.* 2011. Barriers in Identification and Referral to Genetic Counseling for Familial Cancer Risk: The Perspective of Genetic Service Providers. *Journal of Genetic Counseling*, 20(3), pp.314–322.

Sinsky, C. *et al.* 2016. Allocation of Physician Time in Ambulatory Practice: A Time and Motion Study in 4 Specialties. *Annals of Internal Medicine*, 165(11), pp.753–9.

Schneider, K. (2012). Counseling about Cancer. Hoboken, N.J.: Wiley-Blackwell.

Stanislaw, C. *et al.* 2016. Genetic evaluation and testing for hereditary forms of cancer in the era of next-generation sequencing. *Cancer Biology & Medicine*, 13(1), pp.55–67.

Stoffel, E.M. *et al.* 2015. Hereditary Colorectal Cancer Syndromes: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the Familial Risk–Colorectal Cancer: European Society for Medical Oncology Clinical Practice Guidelines. *Journal of Oncology Practice*, 11(3), pp.e437–e441.

Trepanier, A. *et al.* 2004. Genetic cancer risk assessment and counseling: recommendations of the national society of genetic counselors. *Journal of Genetic Counseling*, 13(2), pp.83–114.

Vig, H.S. *et al.* 2009. Cancer genetic risk assessment and referral patterns in primary care. *Genetic testing and molecular biomarkers*, 13(6), pp.735–741.

Waters, I., *et al.* 1994. Genograms. Practical tools for family physicians. *Canadian family physician Medecin de famille canadien*, 40, pp.282–287.

Weitzel, J.N. *et al.* 2011. Genetics, genomics, and cancer risk assessment. *CA: A Cancer Journal for Clinicians*, 28(11 suppl), pp.n/a–n/a.

Wood, M.E. *et al.* 2014. Quality of Cancer Family History and Referral for Genetic Counseling and Testing Among Oncology Practices: A Pilot Test of Quality Measures As Part of the American Society of Clinical Oncology Quality Oncology Practice Initiative. *Journal of Clinical Oncology*, 32(8), pp.824–829.

APPENDIX A

Appendix A. Cancer scoring chart

	Points		Points
Personal cancer <50 *	15	Cancer with environmental cause	
1st degree cancer ≤45 *	15	Lung/esoph cancer: smoker/alcohol	1
2nd degree cancer ≤45 *	15	Skin cancer: sun exposure	1
3rd degree cancer ≤45 *	8	Liver cancer: alcohol, hepatitis	1
4th or more diagnosed <45 *	2	Stomach cancer: diet, H. pylori	1
1st degree cancer ≤50 *	10	Any relative cancer ≤45 or 50*	
2nd degree cancer ≤50 *	5	Thyroid <50	2
3rd degree cancer ≤50 *	5	< 3 melanoma under 50	5
1st degree cancer 51-60	4	Testicular cancer <45	2
2nd degree cancer 51-60	2	Leukemia <18	5
3rd degree cancer 51-60	2	Leukemia >18	2
1st degree cancer >61	1	Hodgkin Lymphoma 18-40	1
2nd degree cancer >61	1	Non Hodgkin Lymphoma >50	1
3rd degree cancer >61	1	Brain cancer / tumors:	
1st degree ovarian cancer	15	2 brain cancer/tumor, one dx <45	10
2nd degree ovarian cancer	10	3 brain cancer/tumor one dx <45	15
3rd degree ovarian cancer	8	2 brain cancer/tumor one dx <18	15
Cancer NOS, age dx unknown	1	1 brain cancer / tumor + 1 LFS associated cancer (1 dx <45): sarcoma, brain, breast, adrenocortical, leukemia, colorectal, bronchiolar	15
>4 people in FHx with any cancer on same side	10	1 brain cancer / tumor + 2 LS associated cancer: colorectal, uterine, stomach, ovarian, brain, pancreatic	15
Cervical cancer	1	3 generations cancer one side	10
Skin cancer (>3)	5	Any relative male breast ca	10
Skin cancer (<3)	1	TOTAL 0-7	LOW
3 cancers one person	10	TOTAL 8-14	INT
2 cancers one person	5	TOTAL ≥15	HIGH

CA (cancer), NOS (non-specific), FHx (family history), dx (diagnosis). LFS (Li-Fraumeni), LS (Lynch syndrome)

APPENDIX B

1. Study Information Sheet

Thank you for participating in this survey. Answers will be used to better understand current practice protocols regarding cancer risk assessment in prenatal genetic counseling sessions.

Thesis Title: Identification of cancer risk during prenatal genetic counseling sessions: evaluation of frequency and current practice protocols

Lead Researcher
Jennifer Cech, PhD, Genetic Counseling student
University of California, Irvine
Department of Pediatrics
jcech@uci.edu

Faculty Sponsors
Maureen Bocian, MD and Kathryn Steinhaus French, MS
University of California, Irvine
Department of Pediatrics

· We are asking you to take part in a study conducted by Jennifer Cech, PhD, at the University of California, Irvine. Participating in this study is optional.

· If you choose to be in the study, you will be requested to complete a survey. You will be asked demographic questions along with questions to establish your prenatal genetic counseling practice protocols based on current and previous experience. This survey will help us learn more about how practice protocols have changed in the last 7 years, as well as to better understand the differences among genetic counselors. The survey will take about 15 minutes to complete.

· You can skip questions that you do not want to answer or stop the survey at any time. The survey is anonymous, and no one will be able to link your answers back to you. Please do not include your name or other information that could be used to identify you in the survey responses.

· As this survey is anonymous, the study team may not be able to extract or delete any specific data provided, should you choose to withdraw from the study.

· As part of the completion of this survey, you are agreeing to the "Terms of Use" for SurveyMonkey, the entity administering the survey. The data you provide may be collected and used by this entity as per its privacy agreement. While the research team will make every effort to keep your personal information confidential, it is possible that an unauthorized person might see it. We cannot guarantee total privacy.

· If you have any comments, concerns, or questions regarding the conduct of this research please contact the researchers listed at the top of this form.

· If you have questions or concerns about your rights as a research participant, you can contact the UCI Institutional Review Board by phone, (949) 824-0665, by e-mail at IRB@research.uci.edu or at 141 Innovation, Suite 250, Irvine, CA 92697.

What is an IRB? An Institutional Review Board (IRB) is a committee made up of scientists and non-scientists. The IRB's role is to protect the rights and welfare of human subjects involved in research. The IRB also assures that the research complies with applicable regulations, laws, and institutional policies.

· If you would like to participate in this study, please click the [NEXT] button to start the survey.

Identification of cancer risk during prenatal genetic counseling sessions

2.

* 1. Are you currently a genetic counselor practicing in the prenatal setting?

○ YES

○ NO

Identification of cancer risk during prenatal genetic counseling sessions

3.

2. What gender do you identify with?

○ Female

○ Male

○ Transgender

○ Chose not to identify

○ Other

3. What is your current age?

○ 20-25

○ 26-35

○ 36-50

○ 51+

4. How many years have you been a practicing genetic counselor in ANY setting?

○ 0-5

○ 5-10

○ 10-20

○ >20

○ Student

5. Where do you **currently** practice?

○ Private OB practice

○ Fertility clinic

○ Academic medical center

○ Managed care organization (e.g. Kaiser, GroupHealth)

○ Private hospital

○ Community/Government hospital

○ Other (please describe)

[   ]

6. Do you currently, or have you EVER practiced genetic counseling in other specialties? Check all that apply

☐ Pediatric

☐ Adult

☐ Cancer

☐ None, only prenatal

☐ Other (including specialty clinics, please describe)

[   ]

7. How many prenatal (pregnant or preconception) patients do you typically see a week?

○ 0-5

○ 5-10

○ 10-20

○ >20

8. How often do you **currently** take a three-generation family history that includes asking about **cancer** during a prenatal genetic counseling session?

○ Every time I see a patient for any prenatal genetic counseling appointment

○ Only if the patient mentions it

○ Only if the patient indicates a personal or family history on an intake form

○ Only if it is indicated in the reason for referral

○ I use a questionnaire that includes cancer

○ I use a questionnaire that does NOT include cancer

○ Never

9. If cancer is discussed during a prenatal genetic counseling session, how often do you **currently** ask about **age at cancer diagnosis**?

○ Always

○ Sometimes, if I remember or if there is time

○ Never

10. If you practiced prenatal genetic counseling prior to or during **2010**, **based on your practice protocols at that time**, how often did you take a three-generation family history that included asking about cancer?

○ Every time I saw a patient for any prenatal genetic counseling appointment

○ Only if the patient brought it up verbally

○ Only if the patient indicated a personal or family history on an intake form

○ Only if it was indicated in the reason for referral

○ I used a questionnaire that included cancer

○ I used a questionnaire that did NOT include cancer

○ Never

○ I did not practice prenatal genetic counseling prior to or during 2010

11. If you practiced prenatal genetic counseling prior to or during 2010,**based on your practice protocols** at that time, how often did you ask about the **age of cancer diagnosis**?

◯ Always

◯ Sometimes, if I remembered or if there was time

◯ Never

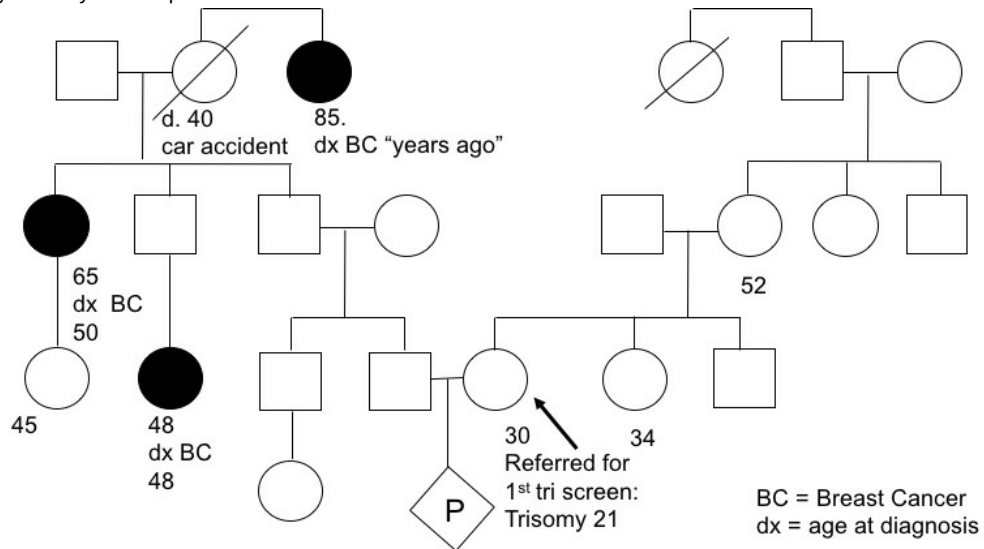◯ I did not practice prenatal genetic counseling prior to or during 2010

12. **Currently**, **please estimate** how often a family history of cancer is discussed in your prenatal genetic counseling sessions?

◯ At least every 1 in 5 patients

◯ Approximately every 1 in 5-20 patients

◯ Approximately every 1 in 20-100 patients

◯ Approximately or less than 1 in 100-200 patients

◯ Never

13. If you practiced prenatal genetic counseling prior to or during 2010,**at or around that time**, **please estimate** how often a family history of cancer was discussed in a prenatal genetic counseling session?
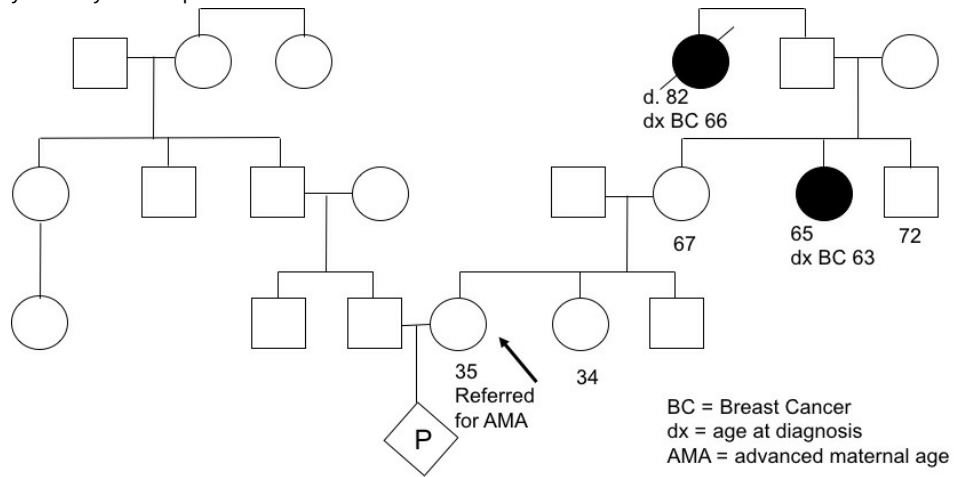
◯ At least every 1 in 5 patients

◯ Approximately every 1 in 5-20 patients

◯ Approximately every1 in 20-100 patients I saw

◯ Approximately or less than 1 in 100-200 patients

◯ Never

◯ I did not practice prenatal genetic counseling prior to or during 2010

14. Based on the following family history and your **current** standard practice guidelines, please indicate your likely next step?

○ Strong suggestion that patient OR ANY relative depicted on the image above should seek cancer genetic counseling as soon as possible. Give patient information on how to do so, or provide immediate formal referral if applicable.

○ Inform patient that cancer genetic counseling is an option for some family members, NO immediate referral or directions for cancer GC, but mention in the report to referring physician that he/she should discuss the topic with the patient.

○ Inform patient that cancer genetic counseling is an option for some family members, NO immediate referral or directions for cancer GC, NO mention in note to referring physician for them to discuss topic with the patient.

○ No discussion with patient during appointment. Write in the report to referring physician to discuss the patient's cancer family history.

○ Inform patient during appointment that history is not suggestive of hereditary cancer syndrome, or do not discuss with patient at all.

○ Other: describe below

15. Based on the following family history and your **current** standard practice guidelines, please indicate your likely next step?

BC = Breast Cancer
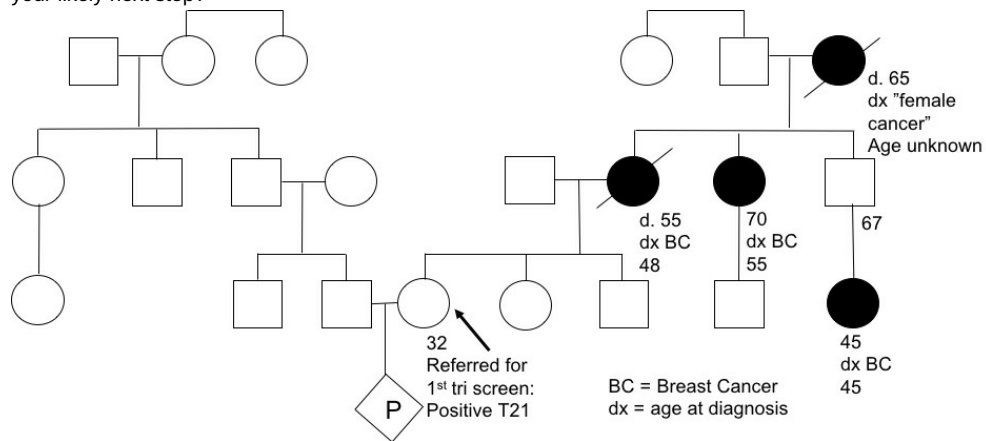dx = age at diagnosis
AMA = advanced maternal age

○ Strong suggestion that patient OR ANY relative depicted on the image above should seek cancer genetic counseling as soon as possible. Give patient information on how to do so, or provide immediate formal referral if applicable.

○ Inform patient that cancer genetic counseling is an option for some family members, NO immediate referral or directions for cancer GC, but mention in the report to referring physician that he/she should discuss the topic with the patient.

○ Inform patient that cancer genetic counseling is an option for some family members, NO immediate referral or directions for cancer GC, NO mention in note to referring physician for them to discuss topic with the patient.

○ No discussion with patient during appointment. Write in the report to referring physician to discuss the patient's cancer family history.

○ Inform patient during appointment that history is not suggestive of hereditary cancer syndrome, or do not discuss with patient at all.

○ Other: describe below

16. Based on the following family history and your **current** standard practice guidelines, please indicate your likely next step?

○ Strong suggestion that patient OR ANY relative depicted on the image above should seek cancer genetic counseling as soon as possible. Give patient information on how to do so, or provide immediate formal referral if applicable.

○ Inform patient that cancer genetic counseling is an option for some family members, NO immediate referral or directions for cancer GC, but mention in the report to referring physician that he/she should discuss the topic with the patient.

○ Inform patient that cancer genetic counseling is an option for some family members, NO immediate referral or directions for cancer GC, NO mention in note to referring physician for them to discuss topic with the patient.

○ No discussion with patient during appointment. Write in the report to referring physician to discuss the patient's cancer family history.

○ Inform patient during appointment that history is not suggestive of hereditary cancer syndrome, or do not discuss with patient at all.
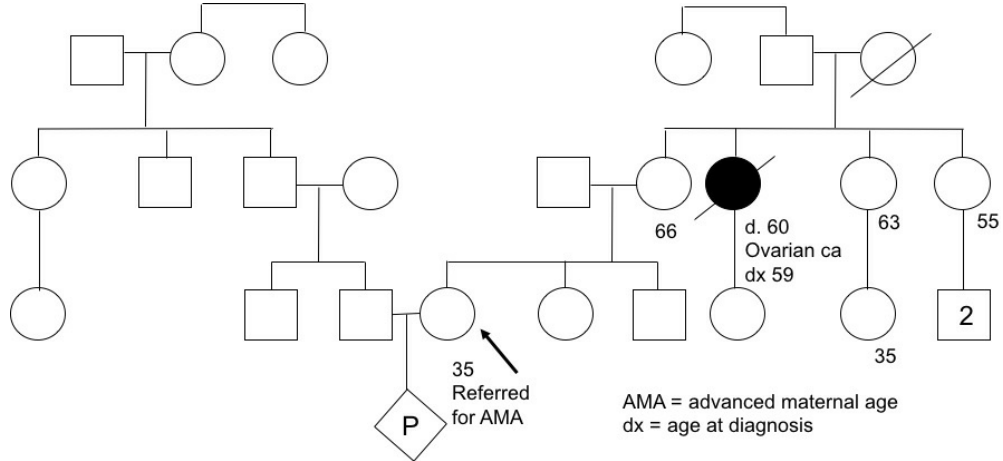
○ Other: describe below

┌───┐
│   │
└───┘

17. Based on the following family history and your**current** standard practice guidelines, please indicate your likely next step?

AMA = advanced maternal age
dx = age at diagnosis

○ Strong suggestion that patient OR ANY relative depicted on the image above should seek cancer genetic counseling as soon as possible. Give patient information on how to do so, or provide immediate formal referral if applicable.

○ Inform patient that cancer genetic counseling is an option for some family members, NO immediate referral or directions for cancer GC, but mention in the report to referring physician that he/she should discuss the topic with the patient.

○ Inform patient that cancer genetic counseling is an option for some family members, NO immediate referral or directions for cancer GC, NO mention in note to referring physician for them to discuss topic with the patient.

○ No discussion with patient during appointment. Write in the report to referring physician to discuss the patient's cancer family history.

○ Inform patient during appointment that history is not suggestive of hereditary cancer syndrome, or do not discuss with patient at all.

○ Other: describe below

[   ]

18. If you have suggestions on how prenatal genetic counselors can better help relay a suggestion for a cancer genetic counseling referral for the patient or someone in their family after the pregnancy has completed, please describe below:

[   ]

Identification of cancer risk during prenatal genetic counseling sessions

4.

APPENDIX C

Appendix C: Selected open-ended responses to cancer risk pedigrees

PATERNAL HIGH-RISK

1. "...The family was also encouraged to pursue appropriate cancer screening tests when available due to the family history of cancer. I then provide them with cancer genetic risk assessment clinic business card, if they desire."
2. "Inform patient that cancer GC is option for her partner or his relatives, particularly those affected who are living, and give more info if requested and put info in note; important to note that it is difficult to place formal referrals for partners who are not technically our patients."
3. "Inform patient that cancer genetic counseling is an option for FOR HER PARTNER or some of HIS family members, NO immediate referral, however provide information about cancer GC and document that I did so in the chart. This would NOT be on the referring OB to follow-up on, since the patient's partner is likely not that person's patient."
4. "I would not take this detailed a pedigree for this referral indication--In my opinion, this patient, the 30 yo pregnant woman with a risk for T-21, does NOT have a family history of cancer. Her spouse does, but unless they voice concern about it, I am not likely to refer him for any further eval either. If they voice concern, I will tell them about availability of cancer GC at my center and be done."

MATERNAL HIGH-RISK

1. "It depends on the emotional state of the patient. If she is not very concerned about the high risk for Down syndrome, I may select the 1st option (seek cancer GC as soon as possible). If the patient is very anxious or concerned, I would probably select option 4 (no discussion, write in report)."
2. "...in strong words tell patient her cancer family history is something that needs to be addressed and I will make referral to appropriate person; if she postpones please call me after this prenatal concern has passed and I will make referral then."

MATERNAL INTERMEDIATE-RISK

1. "Ask pt to obtain more information regarding dx (ovarian vs. cervical vs. endometrial) before making assessment."

MATERNAL LOW-RISK

1. "I explain the "clues" for hereditary cancers and that both diagnoses are >60, her mom is healthy at age 67. I'd ask if anyone had genetic testing/counseling, but likely recommend they discuss breast cancer screening with their PCP or genetic counselor if interested."
2. "...The family was also encouraged to pursue appropriate cancer screening tests when available due to the family history of cancer. I then provide them with cancer genetic risk assessment clinic business card, if they desire."
3. "Ask if the patient has talked with her PCP about the family history of breast cancer. Inquire about current screening (i.e., mammogram) - if any. Discuss the age at which screening mammograms are recommended for the general population (~40)."
4. "Would encourage population screening especially for patient and mother. Would mention cancer GC as possibility for more personalized risk assessment, and give specifics if patient is interested. Would mention in note to physician."

Responses are direct quotations.

APPENDIX D

Appendix D: Selected open-ended responses for counselor suggestions on how prenatal genetic counselors can better help relay a suggestion for a cancer genetic counseling referral for the patient or someone in their family after the pregnancy has completed.

1. "Ask the prenatal SIG to develop a FACT SHEET that is specific for prenatal GC's to give to pregnant patients that outlines the concern noted in their family history, the idea to pursue cancer genetic counseling with the possibility of genetic testing, and the potential need for early screening in the patient based on the family history (breast US, mammogram, etc.). May be nice to have a "cheat sheet" on the form where the prenatal GC could check a box after reviewing the family history that indicates what kind of screening should be pursued."

2. "We could hand out an info sheet for the patient to give to her affected family members about hereditary cancers, utility of GC for cancer history, and how to locate a cancer GC."

3. "I do not have time to f/up in future with patients I saw in past. I invite them to contact me in future if they would like me to make a referral at the time."

4. "We are lucky to have several cancer GC's at our institution and include their referral information in the physician letter. If it is most appropriate for the patient to go I do provide her with their referral information on the back of my business card so they can also get in touch with me if they need to. I also direct them to the NSGC website for the "find a genetic counselor" tab when encouraging them to have family members seek services. "

5. "I have business cards with the local cancer GC number on them. I provide that card as well as the information about hereditary vs. sporadic cancer. I then document as stated above."

6. "Indicate the best person in the family to initiate testing. Provide referral for that individual."

7. "It could be a point of discussion in a postpartum care visit."

8. "Make sure the prenatal GCs can communicate the best protocol for a family member to see an oncology GC."

9. "I think this would be difficult, in our clinic we frequently lose contact with patients postpartum. I give the patient paper information about local clinics so they can self-refer or discuss with their primary in the future if they might be interested but don't want an immediate referral."

10. "I think it can be helpful to have a business card or standard printout/flyer to provide to patients so they have something written and concrete to use; formal referrals can also help because it can put them in the work queue for providers who can initiate follow-up."

11. "I work in a medical system which also has a cancer GC department. That team developed a handout for us to give to patients with their information and reasons for referral. It has been a very helpful resource to give to patients and encourage them to follow-up at a time that works for them and it contains the contact information for that department."

12. "We always provide education to patient regarding cancer dx(s) in family. For some we will consider w/u during pregnancy if indicated. For others we will explain importance of possibly seeking testing after pregnancy, if they so desire. Patients are given info for self-referral back to our office."

13. "It's difficult because there is so much we already need to discuss in a prenatal visit, even when the family history of cancer is concerning, there's not time to discuss it as thoroughly as I would like. I don't know if a patient information sheet like this exists, but if there was a handout I could give to patients that explains cancer GC, how to find a cancer GC, etc I think that would supplement what we are able to address in the prenatal setting."

14. "i think it's very hard to ensure that continuity of care. The prenatal consult note will go to the obstetrician typically, not the client's primary physician. Perhaps also sending it to the primary physician will be helpful for increasing the likelihood of follow up on these issues."

15. "For patients with a family history suggestive of a hereditary cancer syndrome, I usually like to "plant the seed." I would inform her that her history requires further evaluation, but not immediately, and that she should consider recontacting our office for cancer GC after she is no longer pregnant."

16. "In a high risk MFM center where patients are already very anxious about the risks to the pregnancy, I have almost always felt that patients are not open to talk in detail about additional risks that have no immediate repercussion for the baby. So I always emphasize reaching out to cancer genetics clinic but do not spend too much time on it. If they seem open then we discuss more and provide them local referral."

17. "Provide specific contact information for local referral site"

18. "Given how rapidly advancements/discoveries are being made within the realm of cancer genetics I no longer believe that it is appropriate for a cancer family history to be explicitly elicited within the prenatal setting unless a provider has specific expertise in that area. Given that hereditary cancer syndromes are outside of my scope as a prenatal genetic counselor, I have not kept abreast of the emerging literature and therefore worry that I will not identify a high-risk family. Not only do I worry that missing a high risk family opens me up to legal liability, but I am concerned that families will get false reassurance from having spoken to a "genetic counselor" about their family history."

19. "If there is a strong family history of cancer I provide contact information for local cancer genetic counselor including business card and brochure. If the family history is NOT strong I mention cancer genetic counseling and just give brochure."

20. "I frequently distribute a brochure for our hospital's cancer genetics clinic and encourage the patient to contact the clinic when they feel ready for an appointment (which may be after their pregnancy is over)"

21. "point out what about her family history raises suspicion or lessens suspicion of hereditary cancer syndrome and suggest that either she or affected family members consider cancer genetic counseling and testing which we provide at our center. emphasize importance of screening guidelines even if no one does have genetic testing."

22. "Simply addressing it in the session is the best way to gauge a patient's understanding and desire for cancer referral. I always mention the option to the patient, but also let the patient know that it is okay to wait until after their pregnancy to pursue the matter any further."

23. "Have genetic counselor provide patient with information regarding how to make an appointment for cancer genetic counseling which the patient can share with family members."

24. "I do cancer genetic counseling as well as prenatal, so if I want the patient or a family member to have genetic counseling, I always give them my card and ask them to call me. If I want the patient herself to consider cancer genetic testing, I usually ask her to call me after she delivers, so as not to add stress to the pregnancy or confuse testing options."

Responses are direct quotations.

APPENDIX E

Dear NSGC member,

My name is Jennifer Cech, and I am a second-year genetic counseling student at the University of California, Irvine. I am looking to recruit prenatal genetic counselors ONLY to participate in an anonymous online survey for my masters thesis: Identification of cancer risk during prenatal genetic counseling sessions: evaluation of frequency and current practice protocols.

This survey is part of a larger research study which includes quantification and evaluation of cancer risk in prenatal genetic counseling sessions. This survey will help us learn more about how practice protocols have changed in the last 7 years, as well as to better understand the differences among current prenatal genetic counselors. Study participation involves a 10-15 minute online survey through SurveyMonkey (multiple choice questions). Participation is voluntary and responses are anonymous. You may skip questions or stop the survey at any time.

Eligible participants must:
CURRENTLY practice PRENATAL genetic counseling
Currently practice prenatal genetic counseling in the United States
Be certified or board eligible
Speak English
If you meet these criteria and would like to participate please click the following link:

https://www.surveymonkey.com/r/CECH2018

 Thank you for your participation!

APPENDIX F

UCI | University of
California, Irvine

November 21, 2017

JENNIFER CECH
PEDIATRICS

RE: UCI IRB HS# 2017-4010   *Identification of cancer risk during prenatal genetic counseling sessions: evaluation of frequency and current practice protocols*

The above-referenced human-subjects research project has been approved by the University of California, Irvine Institutional Review Board (UCI IRB). This approval is limited to the activities described in the approved Protocol Narrative, and extends to the performance of these activities at each respective site identified in the Application for IRB Review. In accordance with this approval, the specific conditions for the conduct of this research are listed below, and informed consent from subjects must be obtained unless otherwise indicated below. Additional conditions for the general conduct of human-subjects research are detailed on the attached sheet.

NOTE: Approval by the Institutional Review Board does not, in and of itself, constitute approval for the implementation of this research. Other institutional clearances and approvals may be required (e.g., EH&S, Radiation Safety, School Dean, other institutional IRBs). Research undertaken in conjunction with outside entities, such as drug or device companies, are typically contractual in nature and require an agreement between the University and the entity. Such agreements must be executed by an institutional official in Sponsored Projects, a division in the UCI Office of Research. The University is not obligated to legally defend or indemnify an employee who individually enters into these agreements and investigators are personally liable for contracts they sign. **Accordingly, the project should not begin until all required approvals have been obtained.**

Questions concerning the approval of this research project may be directed to the Office of Research, 141 Innovation Drive, Suite 250, Irvine, CA 92697-7600; 949-824-6068, 949-824-2125, or 949-824-0665 (biomedical committee) or 949-824-6662 (social-behavioral committee).

Expedited Review: Categories 5 & 7

Cristobal Barrios, MD
Vice Chair, Institutional Review Board

Approval Issued: 11/21/2017
Expiration Date: 11/20/2020
UCI (FWA) 00004071, Approved: January 31, 2003

IRB Determinations as Conditions of Approval:

1.   45 CFR 46.204(d)[1]
2.   Three-Year Extended IRB Approval Granted[2]
3.   Retrospective Review of Records from January 1, 2010 through December 31, 2016

Informed Consent Determinations:
4.   Waiver of Signed Consent Granted
        a.   Study Information Sheet Required
5.   Waiver of Informed Consent Granted
6.   Waiver of UC HIPAA Research Authorization Granted

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[1] *The IRB determined that all of the applicable conditions under Subpart B 45 CFR 46.204(a-j) have been met. **Although there is no direct benefit to the mother or fetus, the risk to the fetus is <u>not greater than minimal</u> and the purpose of the research is the development of biomedical knowledge which cannot be obtained by any other means.***
[2]*Research posing no more than minimal risk to human subjects (Expedited review), is not subject to federal oversight (e.g. federally-supported) and is not subject to UCI COIOC review qualifies for Extended IRB Approval. If during the extended approval period the study becomes ineligible for Extended IRB Approval immediately contact the HRP staff for instructions on how to reset to a one-year (no more than 365 days) approval cycle.*

UNIVERSITY OF CALIFORNIA

APPROVAL CONDITIONS FOR ALL UCI HUMAN RESEARCH PROTOCOLS

UCI RESEARCH POLICIES:
All individuals engaged in human-subjects research are responsible for compliance with all applicable UCI Research Policies.
The Lead Researcher (and Faculty Sponsor, if applicable) of the study is ultimately responsible for assuring all study team
members adhere to applicable policies for the conduct of human-subjects research.

LEAD RESEARCHER RECORDKEEPING RESPONSIBILITIES:
Lead Researchers are responsible for the retention of protocol–related records. The following web pages should be reviewed for
more information about the Lead Researcher's recordkeeping responsibilities for the preparation and maintenance of research
files: Lead Researcher Recordkeeping Responsibilities and Preparation and Maintenance of a Research Audit File.

PROTOCOL EXPIRATION:
The UCI IRB approval letter references the protocol expiration date under the IRB Chair's signature authorization. A courtesy
email will be sent approximately 60 to 90 days prior to expiration reminding the Lead Researcher to apply for continuing review.
For studies granted Extended IRB Approval, a courtesy e-mail will be sent annually to verify eligibility for the continuation of
extended approval. **It is the Lead Researcher's responsibility to apply for continuing review to ensure continuing
approval throughout the conduct of the study.** Lapses in approval must be avoided to protect the safety and welfare of
enrolled subjects.

MODIFICATIONS & AMENDMENTS:
Per federal regulations, once a human research study has received IRB approval, any subsequent changes to the study must be
reviewed and approved by the IRB prior to implementation *except when necessary to avoid an immediate, apparent hazard to a*
subject. **Accordingly, no changes are permissible (*unless to avoid an immediate, apparent hazard to a subject*) to the
approved protocol or the approved, stamped consent form without the prior review and approval of the UCI IRB**. All
changes (e.g., a change in procedure, number of subjects, personnel, study locations, new recruitment materials, study
instruments, etc.) must be prospectively reviewed and approved by the IRB before they are implemented.

APPROVED VERSIONS OF CONSENT DOCUMENTS, INCLUDING STUDY INFORMATION SHEETS:
Unless a waiver of informed consent is granted by the IRB, the consent documents (consent form; study information sheet) with
the UCI IRB approval stamp must be used for consenting all human subjects enrolled in this study. Only the current approved
version of the consent documents may be used to consent subjects. **Approved consent documents are not to be used
beyond the expiration date provided on the IRB approval letter.** Current consent documents are available on the IRB
Document Depot.

UNANTICIPATED PROBLEMS REPORTING:
In accordance with Federal regulations and HRP policies, only internal (where UCI serves as the IRB of record), Unanticipated
Problems must be reported to the UCI IRB. Unanticipated Problems should also be reported to the UCI IRB when UCI is relying
on an external IRB, and the incident occurred at UCI or the incident occurred at an offsite location on a study conducted by a
UCI LR. Unanticipated Problems must be submitted to the IRB via the Unanticipated Problems (UP) Report within 5 business
days upon the Lead Researcher's (LR) knowledge of the event. For additional information visit the updated HPR webpage on
Unanticipated Problems.

CHANGES IN FINANCIAL INTEREST:
Any changes in the financial relationship between the study sponsor and any of the investigators on the study and/or any new
potential conflicts of interest must be reported immediately to the UCI Conflict of Interest Oversight Committee (COIOC). If
these changes affect the conduct of the study or result in a change in the text of the currently-approved informed consent
document, these changes must also be reported to the UCI IRB via a modification request. Research subject to COIOC
oversight is not eligible for Extended IRB Approval.

CLOSING REPORT:
A closing report should be filed with the UCI IRB when the research concludes. Visit the HRP webpage Closing a Protocol for
complete details.