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Assessing Identification of Newly Diagnosed Breast Cancer Patients for Referral to Genetic Counseling

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Assessing Identification of Newly Diagnosed Breast Cancer Patients for Referral to Genetic Counseling

by

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ABSTRACT

Since 1998, the National Comprehensive Cancer Network (NCCN) guidelines have specified clinical indications for genetic testing for breast cancer susceptibility genes, but retrospective studies have shown that, despite meeting the NCCN criteria, patients are not always advised of the option of genetic testing. Further compounding this issue, studies have shown that cancer family history intake and documented family history can be incomplete even when taken by oncology providers. At this study site and other cancer centers in the country, patients with a new diagnosis of breast cancer are referred for genetic counseling by their cancer care team if they are deemed to meet NCCN criteria for genetic testing. For this study, the authors sought to explore if a family history, as gathered by a genetic counselor, will find additional patients who meet these criteria. Patients with a new diagnosis of breast cancer who were not referred for genetic counseling and testing were contacted and randomized to have their personal and family history collected via telephone or online questionnaire. Of the 64 patients contacted, 40 provided complete information about their personal and family history. The response rate was higher for the patients offered a pedigree assessment via phone (65.6%, n=21) compared to those offered the questionnaire (59.4%, n=19). In total, 11 (27.5%) individuals were found to meet NCCN criteria after the additional assessment—seven were detected by pedigree and four by online questionnaire. Of note, three of these patients were referred by their oncologist after consultation but prior to notification from the study team, meaning they were ultimately identified by the current system. Furthermore, two of the 11 patients did not meet

criteria after first contact with the genetic counseling team but met criteria after new information was obtained from discussions with relatives. The most common cancers in a family history that were overlooked by previous provider intake were pancreatic cancer (n=4) and prostate cancer (n=3). Since these two cancer types have been added to guidelines more recently, this indicates a need for better provider education following guideline updates. Adding a family history assessment tool to assist with identification of these patients is another avenue for exploration. However, when considering method of assessing patients, it is important to consider patients likelihood to respond. Further studies can build upon the data from this study to assess success of interventions and impact on patient care.

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CHAPTER 1

BACKGROUND AND LITERATURE REVIEW

1.1 Hereditary Breast Cancer

Most cancers are considered sporadic in origin, but approximately 5-10% of cancers are caused by an inherited susceptibility (Garber & Offit, 2005; Lynch et al., 1995). Hereditary cancer syndromes consist of an increased risk for certain types of cancer and are caused by mutations in specific genes. For example, inherited mutations in the *BRCA1* and *BRCA2* genes are associated with Hereditary Breast and Ovarian Cancer syndrome (HBOC), which is characterized by an increased lifetime risk for breast and ovarian cancer as well as prostate and pancreatic cancer. Because these genetic syndromes have known cancer risks, changes in medical management are recommended to either reduce the risk of cancer or increase early detection.

Mutations in *BRCA1* and *BRCA2* make up about 30% of hereditary breast cancer (Couch et al., 2017). The general population risk for breast cancer is roughly 12%, but mutations in *BRCA1* and *BRCA2* can increase the lifetime breast cancer risk to 69-72% (Anglian Breast Cancer Study Group, 2000; Antoniou et al., 2003; Chen & Parmigiani, 2007; Ford, 1994; Hu et al. 2020; King et al., 2003; Kuchenbaecker et al, 2017; Mavaddat et al., 2013; Risch et al., 2006; Van den Broek et al, 2016). In addition to female breast cancer, risks associated with mutations in *BRCA1* and *BRCA2* include a 10% lifetime risk for male breast cancer, a 16.5-40% ovarian cancer risk, a prostate cancer risk of 8.6-20%, a 5-10% risk for pancreatic cancer, and an increased chance of developing melanoma with a mutation in *BRCA2* (Petrucelli et al, 2016).

The *BRCA1* and *BRCA2* genes code for proteins that are part of the Fanconi anemia/BRCA (FA-BRCA) pathway which is involved in homologous recombination repair of DNA double-strand breaks. Mutations in the *BRCA1* and *BRCA2* genes result in

a defect in the repair mechanism leading to an accumulation of somatic cancer-causing mutations (Royfman et al., 2021).

While the *BRCA1* and *BRCA2* genes are among the most well-characterized breast cancer genes, over 20 genes have been associated with an increased lifetime risk for breast cancer including *CDH1, PALB2, PTEN,* and *TP53*. A mutation in *CDH1* increases the risk for diffuse gastric cancer as well as lobular breast cancer (Shenoy, 2019). Mutations in the *PALB2* gene, which is also part of the FA-BRCA pathway, result in an increased lifetime risk for breast cancer to 41-60%, ovarian cancer to 3-5%, and pancreatic cancer to 5-10% (Nepomuceno et al., 2021). *PTEN,* another tumor suppressor gene, is involved in cell cycle regulation, cell growth, and proliferation (Hopkins et al., 2014). Mutations in *PTEN* can increase the lifetime risk for breast cancer to 85% in females, as well as an increased lifetime risk for thyroid cancer (21-35%), renal cell cancer (15-35%), uterine cancer (19-28%), colon cancer (9-16%), and melanoma (5%). Finally, *TP53* is a tumor suppressor gene involved in controlling the cell cycle and apoptosis (Schneider et al., 2019). An inherited mutation in *TP53* results in an overall increase in an individual's lifetime risk for cancer, with the risk for cancer in men being at least 70% and at least 90% in women. The five cancers that are most commonly observed in individuals with *TP53* mutations are breast, brain, adrenocortical carcinomas, leukemia and sarcomas.

The National Comprehensive Cancer Network (NCCN), a nonprofit network of cancer centers throughout the United States, publishes treatment, screening, and diagnosis guidelines for many types of cancer. These guidelines include criteria for germline genetic testing as well as management and screening recommendations for individuals with a known mutation in a hereditary cancer gene. The NCCN guidelines for Genetic/Familial

High-Risk Assessment: Breast, Ovarian, and Pancreatic suggest genetic testing is clinically indicated for specific individuals with breast cancer (National Comprehensive Cancer Network [NCCN], 2021).The guidelines specifically target *BRCA1, BRCA2, CDH1, PALB2, PTEN*, and *TP53,* a group of high-penetrance breast susceptibility genes. According to these guidelines, additional hereditary cancer genes can be included in a genetic test, but these genes have moderate penetrance. NCCN does not currently endorse for or against the inclusion of these moderate penetrance genes. The 2021 NCCN guidelines for genetic testing of individuals with a personal history of breast cancer are:

Table 1.1 NCCN Testing Criteria of High-Penetrance Breast Cancer Susceptibility Genes (Specifically *BRAC1, BRAC2, CDH1, PALB2, PTEN*, and *TP53*)

Personal history of breast cancer and…
Triple-negative breast cancer
Ashkenazi Jewish ancestry
≤ 45 years
46-50 years and
Unknown or limited family history
Multiple primary breast cancers (synchronous or metachronous)
≥ 1 close blood relative with breast, ovarian, pancreatic or prostate cancer at any age
≥ 51 years and
≥ 1 close blood relative with any:
Breast cancer at age ≤50 year or male breast cancer at any age
Ovarian cancer at any age
Metastatic, intraductal/cribriform histology, or high- or very- high risk group prostate cancer at any age
≥ 3 total diagnoses of breast cancer in patient and/or close blood relatives
≥ 2 close blood relatives with either breast or prostate cancer (any grade) at any age

Because the cancer risk for individuals with mutations in these hereditary cancer genes is higher than the general population risk, the management recommendations for these individuals are also more intensive than the general population recommendations. The goal of increased screenings is to detect cancers earlier so that they are easier to treat. Identification of an individual with a mutation in a hereditary cancer gene can lead not only

to early detection but to personalization of care for the individual and other members in the family (Tischler et al., 2019).

The NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic suggest managing breast cancer risk associated with a *BRCA1* and *BRCA2* mutation by starting annual breast MRI at age 25 and adding annual mammogram at the age of 30 compared to the average risk recommendation of starting annual mammogram at age 40 and having no additional routine imaging. Additionally, these management guidelines include the option of a risk-reducing mastectomy for *BRCA1* and *BRCA2* mutation-carrier women, replacing the need for frequent imaging. To manage the elevated ovarian cancer risk, women are recommended to have a bilateral risk-reducing salpingo-oophorectomy following the completion of childbearing. Guidance for men is also included in these guidelines, and pancreatic screening is recommended for both men and women in the presence of a family history of pancreatic cancer in a first or second degree relative (NCCN, 2021). NCCN provides guidance for the other high-risk genes as well with management recommendations reflecting cancer risks and age when those cancers have been shown to develop.

1.2 NCCN Impact on Care

The NCCN first added genetic testing criteria to their management recommendations in 1998 and the recommendations have changed over time due to advances in genetic testing technology and an increased understanding of hereditary cancer predispositions (Alberty-Oller et al., 2021; Beitsch et al., 2019).

Alberty-Oller et al. (2021) used chart review to assess how many patients meeting NCCN criteria were referred to genetics at the Tisch Cancer Institute at Mount Sinai

Hospital. This retrospective chart review included patients with a diagnosis of invasive breast cancer assessed medical and family history to determine if the patients met NCCN criteria. The researchers found that 21% (45/212) met criteria but were not referred to genetic counseling. For this study, referral to genetic counseling included a conversation about genetics documented by the referring physician and a consultation note by a genetic counselor in the medical record. Of the individuals that were not referred despite meeting criteria, 41 out of 45 had met criteria based on family history, rather than personal factors (Alberty-Oller at al., 2021).

Childers et al. (2017) reviewed the National Health Interview Surveys (NHIS) from 2005, 2010, and 2015. The survey assessed if individuals with a history of breast and/or ovarian cancer had a conversation about genetics with their doctor, were advised to have genetic testing, and/or had genetic testing. Medical and family history from the NHIS were used to see if patients met 2017 NCCN criteria. The researchers found fewer than 1 in every 5 individuals who met NCCN criteria for genetic testing had the testing performed and 81% had never discussed genetic testing with their healthcare provider (Childers et al., 2017).

Several studies have evaluated effectiveness of NCCN guidelines' identification of individuals that would have benefited from genetic testing. Cropper et al. (2017) reviewed charts of 1,123 patients with breast cancer seen from March 31, 2013 through June 30, 2014, at the University of Texas MD Anderson Cancer Center. The patient's medical and family history were reviewed to determine which and how many of the NCCN criteria were met. This study showed that the diagnostic yield was higher when individuals met several NCCN criteria, compared to those that only met criteria due to a diagnosis of

breast cancer prior to age 45. In this study, 329 patients only met one criterion and 11 (3.3%) of these were found to be *BRCA1* and *BRCA2* positive. This was compared to the 644 individuals that met two or more criteria; 88 (13.7%) of these were found to be *BRCA1* or *BRCA2* positive (Cropper et al., 2017). Manickam et al. (2018) used cross-sectional analysis of individuals who volunteered for Geisinger's MyCode healthy genome study. Through exome sequencing of 50,726 samples, 267 samples were found to be carriers of a *BRCA1* and *BRCA2* mutation. Analysis of 122 pedigrees of *BRCA1* or *BRCA2* carriers revealed 63% (77/122) met NCCN criteria. Of the 89 individuals with a mutation in *BRCA1* and *BRCA2* who had not previously had genetic testing, 45 (50.5%) met NCCN criteria, while 44 individuals did not. These 44 individuals would not have been offered testing outside of this study because their family history was not concerning for hereditary cancer (Manickam et al., 2018).

Beitsch et al. (2019) conducted a multicenter prospective study of individuals with a recent or past diagnosis of breast cancer who had not previously undergone genetic testing. These patients were divided into two equal cohorts, those who met the 2017 NCCN guidelines for genetic testing and those who did not. The results showed the overall positivity rate on a multigene panel of 80 genes was 8.65% (83/959). The overall positivity rate for those that met NCCN criteria was 9.39% (45/479), while the overall positivity rate was 7.9% (38/480) for the participants that did not meet NCCN criteria. Although, when only considering *BRCA1* and *BRCA2*, the positivity rate of the patients that met criteria was four-fold of those who did not. When looking more closely at the individual genes that were found to have mutations, there was a higher rate of reduced penetrance genes in the group that did not meet criteria. For example, eight individuals tested positive for a single

pathogenic variant in *MUTYH*, which may increase the chance for colon cancer or breast cancer, but the data is not strong at this time (Beitsch et al., 2019; NCCN, 2021). Mutations in *ATM* and *CHEK2* were also detected more in the group that did not meet criteria (Beitsch et al., 2019). Both the *ATM* and *CHEK2* genes are considered reduced penetrance, and screening recommendations for cancers associated with *ATM* and *CHEK2* are less well-defined.

1.3 Role of Family History

As stated in the testing criteria, family history is an important tool in determining who meets current criteria for genetic testing. Genetic counselors annotate important genetic family history information into a pedigree, which is a visual representation of the family and the medical and biological relationships between individuals in the family. A pedigree provides a concise family and medical history summary with the important information easily obtainable in a glance (Bennett, 2010). A cancer-focused pedigree consists of three to four generations including both the maternal and paternal sides (Schneider, 2012). Cancer information is recorded including type of cancer, age at diagnosis, and treatment. The pedigree should include all individuals' current age or age of death, as well as the cause of death, regardless of reason.

A study conducted by Sussner et al. (2011) at Mount Sinai School of Medicine surveyed primary care providers (PCPs) including physicians and nurse practitioners (NPs) working in general medicine and obstetrics/gynecology (ob/gyn). This study identified that 25% of PCPs asked patients about cancer history in first- and second-degree relatives on both sides of the family, including type of cancer and age of diagnosis, to assess for hereditary cancer risk. They also assessed provider's confidence in making appropriate

genetic counseling referrals and their perceived skill level to conduct their own counseling about genetic testing. The group with the highest reported confidence was the ob/gyns and the lowest was NPs. Overall, 1.7% of providers perceived themselves as experts when it came to interpreting cancer risk based on family history (Sussner et al., 2011).

Studies have shown that oncologists are more familiar with breast cancer genetics than ob/gyns and general medicine physicians (Doksum et al., 2003). However, the quality of the family history recorded by oncologists through chart review was often incomplete (Jones et al., 2020; Wood et al., 2014). In Jones et al. (2020), 80% of the family histories contained only first-degree relatives (parents, siblings) and only 3% of patients had third-degree relatives (first cousins) documented on the pedigree. Wood et al. (2014) showed that of the patients who had cancer, 79.8% had a first-degree relative and 64.6% had a second-degree relative documented in their medical record. Depending on cancer type, the quality of family history documented in the chart differed significantly. For example, family histories for colorectal cancer were more likely to be incomplete. Fewer pedigrees included first- and second-degree relatives, and ages of diagnosis were missing for family members with a cancer diagnosis. This study also showed that of the people that met NCCN criteria for genetic counseling and genetic testing, 43% were referred for genetic counseling. The referral rate was higher for breast cancer compared to colorectal cancer (Wood et al., 2014).

Providers have expressed interest in tools to help assist in gathering family history information and studies have found that patients would like to have more time to gather the information about their family history prior to the appointment (Nathan et al., 2016; Sussner et al., 2011). Family history tools can serve as a prompt for the patient to know

what history is relevant (Hallowell et al., 1997; Pritzlaff et al., 2014). These tools can be in the form of paper family history questionnaires that are mailed or securely sent to the patient through the electronic medical record (EMR). There is also online software that asks family history questions and creates a pedigree based on the patient's answers. Studies have found these tools are an efficient and accurate way to help triage patients and provide adequate time for patients to obtain information from their family members (Armel et al., 2009; Vogel et al., 2012). Pritzlaff et al. (2014) studied the use of an online family history tool and found that it decreased the genetic counselor's time spent taking the family history by half. While there seems to be high satisfaction and efficacy with these tools, only 52.3% of individuals completed the questionnaire (Prizlaff et al., 2014). Previous studies have revealed that this low response rate could be due to several factors including familiarity with family history, being busy, procrastinating or forgetting, not receiving the mailed questionnaire, feeling overwhelmed or confused, age, and race (Appleby-Tagoe et al., 2012; Armel et al., 2011; Pritzlaff et al., 2014). Also, response rates differed between racial background as Native Hawaiian and Pacific Islanders (8.3%) were least likely to complete the form, while white (55.2%), Native American (53.3%), and Asian (52.6%) individuals were more likely to complete the questionnaire. Individuals with private insurance were more likely to complete the questionnaire than those with public insurance (Pritzlaff et al., 2014).

1.4 Rationale of Study

According to the literature, documentation of family cancer history is often incomplete, affecting ability to assess whether a patient meets NCCN guidelines for genetic testing. This means there may be patients that could benefit from a genetics evaluation and

testing that are not currently being identified. This study will provide an assessment of current identification of patients appropriate for genetic counseling and determine if more patients with a new breast cancer diagnosis meet criteria for referral than are currently being identified.

1.5 Objectives

1. Determine if a more thorough family history, such as that taken during a genetic counseling session, would capture more patients appropriate for referral to genetic counseling.
2. Evaluate two methods of gathering additional family history—phone call or online questionnaire—to determine effectiveness of each in identifying additional patients meeting criteria for referral for genetic counseling and testing.

1.6 Hypothesis

NCCN criteria for genetic counseling and testing have expanded, and there are likely more individuals who meet these criteria than may be identified by a limited non-genetics provider's intake of cancer family history. It is expected that a thorough family history, as gathered by a genetic counseling intern, will identify additional individuals who meet criteria for a referral for genetic counseling and testing.

CHAPTER 2

ASSESSING IDENTIFICATION OF NEWLY DIAGNOSED BREAST CANCER PATIENTS FOR REFERRAL TO GENETIC COUNSELING[1]

[1] Locke, C., Whitlock, S., Say, C., Parker, H. & Dobek, W. To be submitted to the *Journal of Clinical Oncology*

2.1 Abstract

Since 1998, the National Comprehensive Cancer Network (NCCN) guidelines have specified clinical indications for genetic testing for breast cancer susceptibility genes, but retrospective studies have shown that, despite meeting the NCCN criteria, patients are not always advised of the option of genetic testing. Further compounding this issue, studies have shown that cancer family history intake and documented family history can be incomplete even when taken by oncology providers. At this study site and other cancer centers in the country, patients with a new diagnosis of breast cancer are referred for genetic counseling by their cancer care team if they are deemed to meet NCCN criteria for genetic testing. For this study, the authors sought to explore if a family history, as gathered by a genetic counselor, will find additional patients who meet these criteria. Patients with a new diagnosis of breast cancer who were not referred for genetic counseling and testing were contacted and randomized to have their personal and family history collected via telephone or online questionnaire. Of the 64 patients contacted, 40 provided complete information about their personal and family history. The response rate was higher for the patients offered a pedigree assessment via phone (65.6%, n=21) compared to those offered the questionnaire (59.4%, n=19). In total, 11 (27.5%) individuals were found to meet NCCN criteria after the additional assessment—seven were detected by pedigree and four by online questionnaire. Of note, three of these patients were referred by their oncologist after consultation but prior to notification from the study team, meaning they were ultimately identified by the current system. Furthermore, two of the 11 patients did not meet

criteria after first contact with the genetic counseling team but met criteria after new information was obtained from discussions with relatives. The most common cancers in a family history that were overlooked by previous provider intake were pancreatic cancer (n=4) and prostate cancer (n=3). Since these two cancer types have been added to guidelines more recently, this indicates a need for better provider education following guideline updates. Adding a family history assessment tool to assist with identification of these patients is another avenue for exploration. However, when considering method of assessing patients, it is important to consider patients likelihood to respond. Further studies can build upon the data from this study to assess success of interventions and impact on patient care.

2.2 Introduction

Hereditary cancer accounts for 5-10 % of all cancer (Garber & Offit, 2005; Lynch et al., 1995). Breast cancer is found to be hereditary in up to 10% of cases (Childers et al., 2017). The National Comprehensive Cancer Network (NCCN) publishes guidelines for

Table 2.1 NCCN Testing Criteria of High-Penetrance Breast Cancer Susceptibility Genes (Specifically *BRAC1, BRAC2, CDH1, PALB2, PTEN*, and *TP53*)

Personal history of breast cancer and…
Triple-negative breast cancer
Ashkenazi Jewish ancestry
≤ 45 years
46-50 years and
Unknown or limited family history
Multiple primary breast cancers (synchronous or metachronous)
≥ 1 close blood relative with breast, ovarian, pancreatic or prostate cancer at any age
≥ 51 years and
≥ 1 close blood relative with any:
Breast cancer at age ≤50 year or male breast cancer at any age
Ovarian cancer at any age
Metastatic, intraductal/cribriform histology, or high- or very- high risk group prostate cancer at any age
≥ 3 total diagnoses of breast cancer in patient and/or close blood relatives
≥ 2 close blood relatives with either breast or prostate cancer (any grade) at any age

genetic testing in specific individuals with breast cancer as well as management for those found to have a hereditary cancer syndrome (Table 2.1). The guidelines recommend a thorough evaluation of both personal and family history to determine if genetic testing is appropriate. The NCCN guidelines have become more widely utilized, but patients that may benefit from a genetics evaluation can still be missed in routine clinical practice when family history intake is less thorough (Alberty-Oller et al., 2021).

Alberty-Oller et al. (2021) used retrospective chart review of patients with a diagnosis of invasive breast cancer and found 21% (45/212) met NCCN criteria but were not referred to genetics. Of the individuals that were not referred despite meeting criteria, 41 out of 45 met criteria based on family history, rather than personal, factors (Alberty-Oller et al., 2021).

Similarly, Childers et al. (2017), in a review of the medical and family history from the National Health Interview Surveys (NHIS) found that fewer than 1 in every 5 individuals who met NCCN criteria for genetic testing had the testing performed and 81% had never discussed genetic testing with their healthcare provider.

Family history is an important tool in assessing cancer risk (Alberty-Oller et al., 2021; Childers et al., 2017). Family histories to assess this risk should include three to four generations, including first-, second- and third- degree relatives and have age of cancer diagnosis as well as current age or age of death. Despite the role it plays in determining cancer risk, family histories have been found to be incomplete when taken by non-genetic providers (Doksum et al., 2003; Jones et al., 2020; Sussner et al., 2011; Wood et al., 2014;). Studies have shown that oncologists are more familiar with breast cancer genetics than obstetricians/gynecologists (ob/gyns) and general medicine physicians (Doksum et al.,

2003). However, in Jones et al. (2020), 80% of the family histories contained only first-degree relatives and 3% of patients had third-degree relatives documented on the pedigree. Wood et al. (2014) showed that, of the patients who had cancer, 79.8% had a first-degree relative and 64.6% had a second-degree relative documented in their medical record. Depending on cancer type, the quality of family history documented in the chart differed significantly. For example, family histories for individuals with colorectal cancer were more likely to be incomplete; fewer pedigrees included first- and second-degree relatives documented, and ages of diagnosis were missing for family members with a cancer diagnosis. This study also showed that, of the people who met NCCN criteria for genetic counseling and genetic testing, 43% were referred for genetic counseling. The referral rate was higher for breast cancer compared to colorectal cancer (Wood et al., 2014).

Tools have been developed to aid in the process of collecting complete family histories such as questionnaires targeting the NCCN genetic testing criteria. Both providers and patients find completing a questionnaire ahead of time beneficial (Armel et al., 2009; Hallowell et al., 1997; Nathan et al, 2016; Pritzlaff et al., 2014; Sussner et al., 2011; Vogel et al., 2012). Studies have shown that providers believe that questionnaires aid in efficiency and help guide patients to relevant information and helps triage referrals. Patients benefit from time to gather the necessary information about their family prior to their visit and know what information is important.

This study explored the effectiveness of the current family history screening at one cancer center in Columbia, South Carolina and compared the utility of an online questionnaire based on NCCN guidelines compared to a family history taken by a genetic counseling intern on the telephone. NCCN criteria for genetic counseling and testing have

expanded and there is concern that individuals who meet these criteria are overlooked by limited cancer family history intake. It was expected that a family history, as gathered by a genetic counseling intern, would identify additional individuals who meet criteria for a referral for genetic counseling and testing.

2.3 Materials and Methods

This study was conducted at Prisma Health-Midlands in Columbia, South Carolina from September 2021 to February 2022. Participants in this study were women with a new diagnosis of breast cancer. Traditionally, at this center, a patient's surgeon, oncologist, and/or nurse navigator inquire about a family history of cancer throughout the patient's breast cancer treatment. After presentation at breast conference of the patient's personal and collected family history, typically including the history taken by the nurse navigator and surgeon, it is determined if the patient meets NCCN criteria for genetic testing. Patients that meet current NCCN guidelines for genetic testing are referred for a genetic counseling appointment.

All patients diagnosed with breast cancer received communication from the nurse navigator after their diagnosis. During this initial phone call, the nurse navigator prepares patients for what they can expect in the coming weeks, including genetic counseling. The patients are then presented at breast conference for multidisciplinary input on the patient's treatment plan, including and if they require a genetic counseling referral. For those that did not meet criteria from the history reported at breast conference, a phone call from the genetic counseling office served as the notification for the opportunity to be assessed for appropriateness of a genetic counseling referral. Patients were randomized to receive an online questionnaire about their family history or a phone call to collect their family

history. Patients were assigned a questionnaire or phone call based on the order they were presented at the conference. Patients were able to decline to share additional information about their family history. Family history gathered by phone followed guidance in Forman and Schwartz (2019) and National Institutes of Health consensus statement (Lu et al., 2014). The online questionnaire was designed by the genetic counselors and collected information about cancer in the family specifically targeted to the NCCN criteria. To increase the yield of completed online questionnaires, the genetic counseling office recontacted patients who had not responded and offered to complete the questionnaire over the telephone. Throughout this study, patient information used and stored was de-identified by using the case number given to patients at breast conference. All identifying information was stored in a secure, password-protected database. For those participants that met NCCN criteria for genetic testing after the pedigree or online survey, their providers were informed by a genetic counselor employed at Prisma Health through the electronic medical record (EMR) about the recommendation for a genetic counseling referral. Those who did not meet criteria also had a note placed in the EMR stating such.

This study was reviewed by Prisma Health IRB and was determined to not be research that required IRB approval.

2.3.1 Statistical Analysis

Descriptive statistics were used to highlight effects on genetic counseling referrals and describe trends in patients not initially targeted for referral. While one of the original objectives was to compare the two methods of data collection (phone call and online questionnaire), there was not a sufficient sample size to conduct statistical comparisons.

2.4 Results

2.4.1 Participants

There were 186 individuals with breast cancer presented during breast conference at Prisma Health-Midlands from September 2021 through February 2022. Of the 186, 65.5% (122/186) were determined to meet criteria for genetic testing at breast conference. The other 64 were contacted as part of this study; 24 were unable to be reached and did not return calls. The other 40 patients had their family history collected and reviewed.

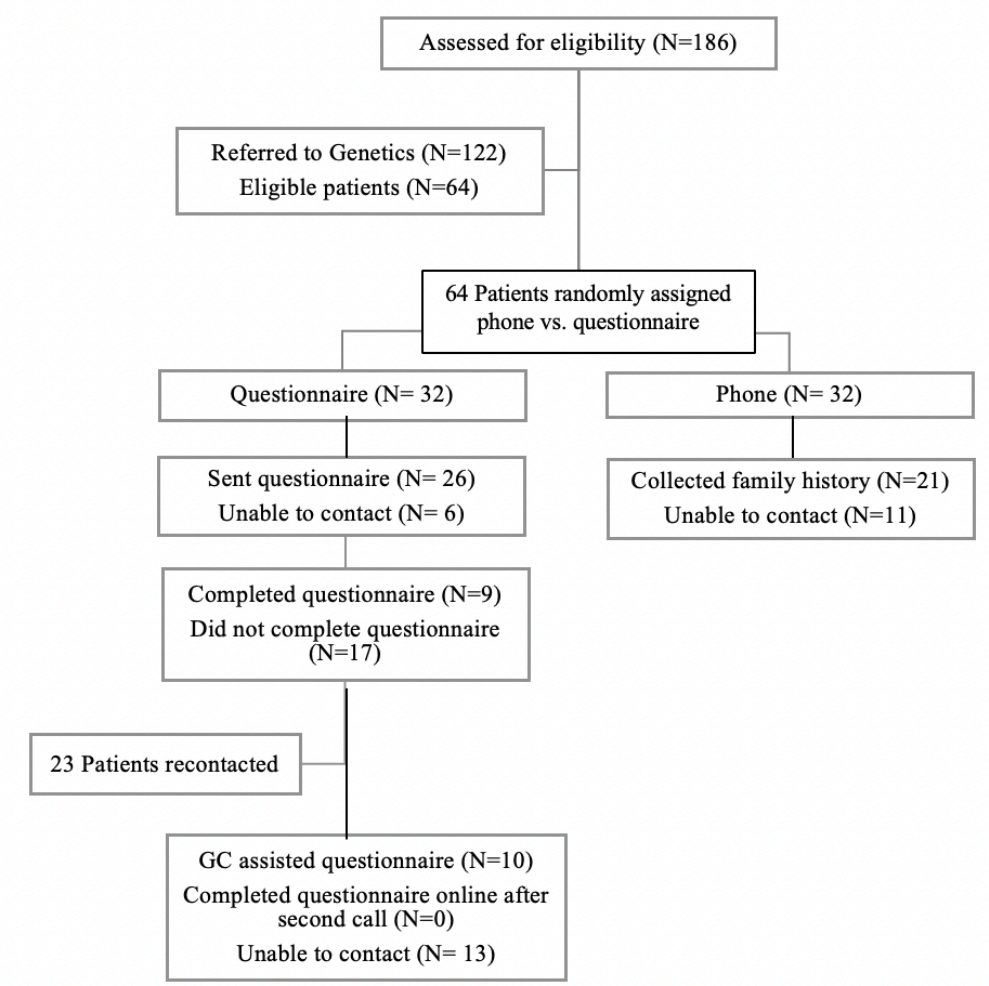

Figure 2.1 Participant ascertainment

Table 2.2 Demographics (N=40)

Age		
	Age Range	Total
	50-59	13 (32.5%)
	60-69	9 (22.5%)
	70-79	13 (32.5%)
	80-89	4 (10%)
	90-99	1 (2.5%)
Race		
	American Indian/Alaska Native	2 (5%)
	Black or African American	14 (35%)
	White	24 (60%)
Ethnicity		
	Hispanic or Latino	1 (2.5%)
	Not Hispanic or Latino	37 (92.5%)
	Unknown/ Not reported	2 (5%)

2.4.3 Comparing Tools

The response rate for the phone call was 65.6% (21/32). The initial response rate to the online questionnaire was 31.3% (10/32). An additional nine questionnaires were completed over the phone with the assistance of the genetic counseling office to bring the final completed questionnaire rate to 59.4% (19/32). Seven individuals met criteria after family history collection by a genetic counseling intern and four met criteria after completion of the online questionnaire (by either the patient or assistance of the genetic counseling intern). Because of the small sample size, we were not able to determine if methodology of gathering the family history made a statistically significant difference in identification for referral to genetic counseling. Figure 2.2 demonstrates the differences in response rate between tools.

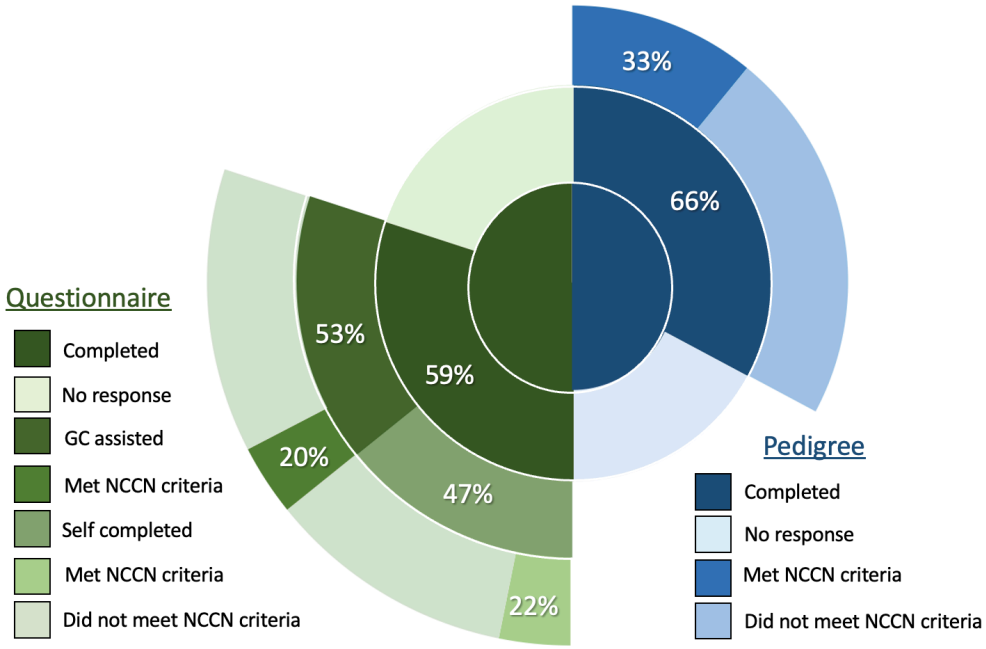

Figure 2.2 Contact methods and response rate

2.4.2 Identification for Referral

Of the 40 total participants, 11 (27.5%) were found to meet NCCN criteria after intervention. Statistical significance could not be determined due to small sample size. Data was collected on the individual's family history that was not noted during the initial intake of the affected patient. Most commonly, as shown in Figure 2.3, a family history of cancer was missed rather than personal characteristics. Personal characteristics include information about the patient's personal history that allows them to meet NCCN criteria (e.g. triple negative cancer, diagnosed at age 45 or younger, Ashkenazi Jewish ancestry) and family characteristics are items other than history of cancer such as an unknown or limited family history. Pancreatic (n=4) and prostate (n=3) cancers were the most common relevant family history that was not noted by the patient's initial intake.

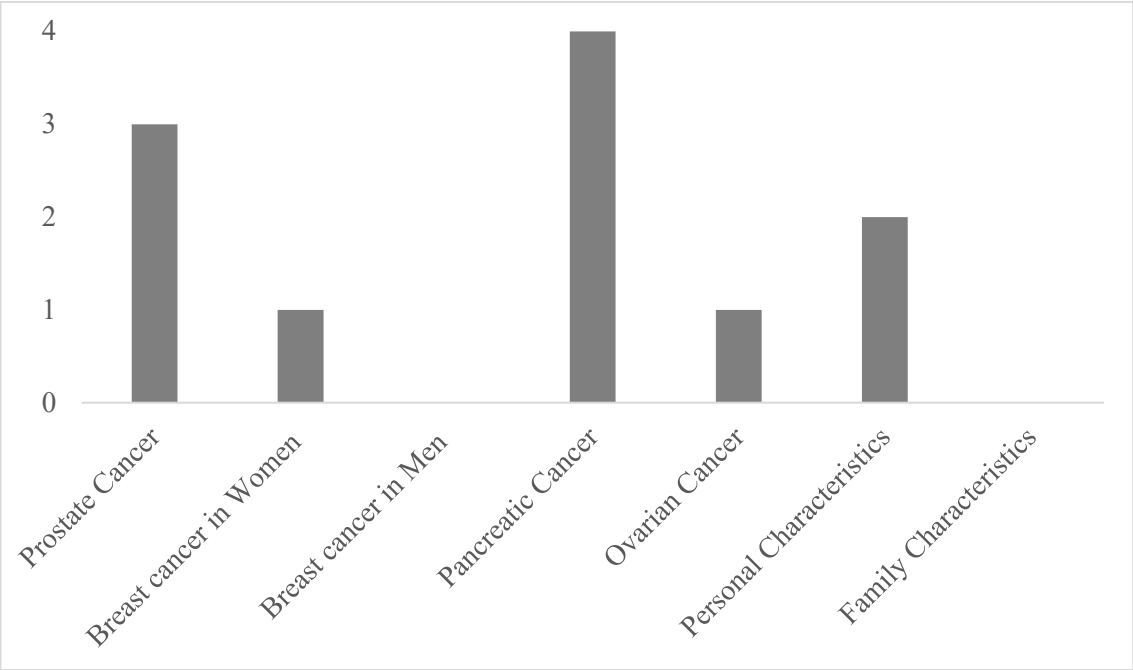

Figure 2.3 Relevant personal or family history in patients not referred on initial intake (N=11)

Three individuals who were not identified at breast conference as needing a referral were seen for genetic counseling following their consultation with their oncologist. For these patients, their oncologist correctly identified that they met NCCN criteria, and they were seen by genetic counseling prior to notification from the genetic counseling team working on this project. One of these individuals had triple negative breast cancer, one was found to have a family history of ovarian cancer, and the third had a more extensive family history of breast cancer than originally noted. After removing these patients from the study group as they were eventually identified by a healthcare provider, 21.1% (8/38) were only identified for genetic counseling after intervention by the genetic counseling team. Out of these nine remaining individuals, two went to their family and gathered more information following the phone call or online questionnaire. They recontacted the study team to update their history and were found to meet criteria at that time.

2.5 Discussion

Of the newly diagnosed breast cancer patients that were not identified upon initial intake, 27.5% met NCCN criteria upon review of their personal and family history by a genetics professional. This shows there are qualifying individuals that are not offered a genetic counseling referral. The most frequent missed cancer type in the family history was pancreatic followed by prostate. Only one of the individuals missed had a family history of breast cancer that met NCCN criteria, suggesting providers may be more likely to directly ask about family history of breast cancer compared to the other cancers. This could be because pancreatic cancer was first included in the NCCN guidelines in 2019, which is relatively more recent than other recommendations (Tempero, 2019). The most recent NCCN guidelines expanded testing criteria to include any close relative with prostate cancer for individuals diagnosed with breast cancer from 46-50 years of age, regardless of the features of this prostate cancer. Previously, prostate cancer had to be metastatic cancer (or Gleason score $\geq$ 7) to contribute towards the patient meeting NCCN guidelines regardless of age of breast cancer diagnosis. This most recent change may account for the limited identification of prostate cancer in family histories. Since the sample size in this study was small, it is difficult to determine if there would be a continuation of this trend in a larger sample size.

Two individuals that were not identified at breast conference as needing a referral were later referred for genetic counseling following their consultation with their oncologist. One of these individuals was found to have triple negative breast cancer shortly after the NCCN guidelines were updated in August 2021 to include all individuals with triple negative breast cancer. Previously, only individuals diagnosed with triple negative breast

cancer at less than 60 years of age met NCCN criteria for genetic testing. These findings support the need for genetic counselors to continue to stay up to date with the most current NCCN guidelines and provide that information to other providers as a valued member of the breast cancer care team.

Of the other individuals later referred to genetic counseling, one was found to have a family history of ovarian cancer and the other had breast cancer in a third-degree relative. Previous studies have shown oncologists are more familiar with NCCN guidelines than other providers (Doksum et al, 2003; Jones et al., 2020; Wood et al., 2014;). Though we were unable to determine if this trend would continue with a larger sample size, it seems that oncologists were more familiar with what family history and what degree of family history was important.

Two of the patients contacted during the study were found not to meet criteria when their family history was first taken. However, they recontacted the genetics office after the evaluation with additional family history information that led to them meeting NCCN criteria. This suggests that individuals may need prompting to know what questions to ask of their family members. Patients should also be encouraged to update their history with their medical team. Studies have found that tools, such as questionnaires or online platforms, are an efficient and accurate way to help triage patients and provide adequate time for patients to obtain information from their family members (Armel et al., 2009; Vogel et al., 2012).

The response rate was higher for phone pedigree compared to the online questionnaire. Several conclusions can be considered from this point. Multiple steps are involved in completing an online questionnaire compared to answering questions during a

phone call. Patients who had the online questionnaire had to look in their email for the invitation to complete the survey and then take the time to fill it out. Only one patient started the survey and did not complete it. Patients who were assigned a questionnaire and had not completed it were recontacted. To remove barriers and increase completion rate, the surveys were completed over the phone if the patient was reached. Through this process, an additional nine questionnaires were completed. No new patients completed the questionnaire after receiving a voicemail reminding them of the questionnaire. The response rate was closer to the pedigree response rate after the genetic counseling office recontacted patients. A response rate around 50% is consistent with other studies looking at utility of family history tools that similarly use online platforms (Armel et al., 2011; Pritzlaff et al., 2014). Unfortunately, there is a lack of data of how to increase the response rate because the individuals who do not respond are difficult to access (Armel et al., 2011).

While patients were captured using both methods of contact, taking a complete pedigree takes more time than the questionnaire. Pedigrees typically took 15 to 20 minutes to collect, putting a time burden on both the provider and the patient. Currently, it would not be practical for genetic counselors to contact every patient with a new diagnosis of breast cancer at this institution. The low initial response to the online questionnaire also puts in question the utility of that tool for this population. Because of both of these concerns, other routes of intervention may be preferred such as adding a tool to the physicians' practices to aid in identification. This may take the form of a questionnaire sent out via the EMR or a questionnaire while waiting on the appointment with their physician. Both methods could have a benefit over the emailed questionnaire sent in this study, since emails, especially those not associated with the physician's office, may be overlooked.

It will also be important to track the genetic testing results in the 11 patients who were recommended to seek genetic counseling as a result of this study. If the results show that genetic testing would have changed medical management through a positive genetic test result, then that further supports the importance of considering intervention and future implementation of such tools. Studies have shown 10-12% of individuals who meet NCCN guidelines have a positive genetic testing result that will impact management (Kurian et al., 2018; Couch et al., 2017).

2.5.1 Study Limitations

The small sample size was a limitation for this study. We were unable to determine if age of the patient, their race, and/or what cancers in the family could have contributed to the identification for genetic counseling referral. It is also unclear why there was a low initial questionnaire response compared to taking a family history over the phone. This study's response rate was lower than the 50% seen in other studies regarding electronic family history questionnaires (Armel et al., 2009; Armel et al., 2011; Pritzlaff et al., 2014). This could be due to these tools being used prior to genetic counseling appointments. Both studies by Armel et al. (2009, 2011) required a completed family history questionnaire prior to scheduling a genetic counseling appointment. The patients in these studies may have a higher perceived risk and motivation than patients determined not to need genetic counseling by their other medical providers.

2.5.2 Future Directions

Future studies need to be done to understand why some patients are not being identified as appropriate for genetic counseling referral. Continuing data collection over several years would allow for an increase in the sample size to determine broader trends.

A future study could utilize an intervention, such as a review of NCCN guidelines with the breast care team, followed by a similar review of rates of identification and referral to genetic counseling.

Future studies could also assess the success of another implemented family history tool such as an EMR questionnaire or physical form in the surgeon's office. This study's questionnaire was not validated. Studies of the accuracy of questionnaires used to take family histories showed 92% of the pedigrees required changes when reviewed with a genetic counselor (Armel et al., 2009). To assess the accuracy of the survey tool, it would be beneficial to review the pedigrees taken during the genetic counseling session of those who met NCCN guidelines via the questionnaire.

CHAPTER 3

CONCLUSIONS

This study evaluated if all women with a new diagnosis of breast cancer at Prisma Health-Midlands were being appropriately identified for referral to genetic counseling. Patients who were determined to not meet NCCN criteria after initial presentation at breast conference were contacted by a genetic counseling intern to review their family history. We also explored the use of an alternate tool to taking a full family history via an electronic questionnaire based on the current NCCN guidelines. The sample size was too small to determine statistical significance of referral rates, but we did identify 11 patients (27.5%) who were missed during the breast conference that ultimately did meet criteria for genetic testing. The most common missed criteria were a family history of pancreatic cancer or prostate cancer. The number of patients found to meet criteria is indicative that further intervention may be beneficial to identify all patients who meet NCCN criteria for a referral for genetic counseling. This information is expected to improve protocols internally at Prisma Health-Midlands. The genetic counselors plan to collaborate and provide updated questionnaires to be used by the breast surgeons to include more of the NCCN criteria in hopes of identifying more family history information prior to the breast conference. Further studies can build upon the data from this study to assess success of interventions and impact on patient care.

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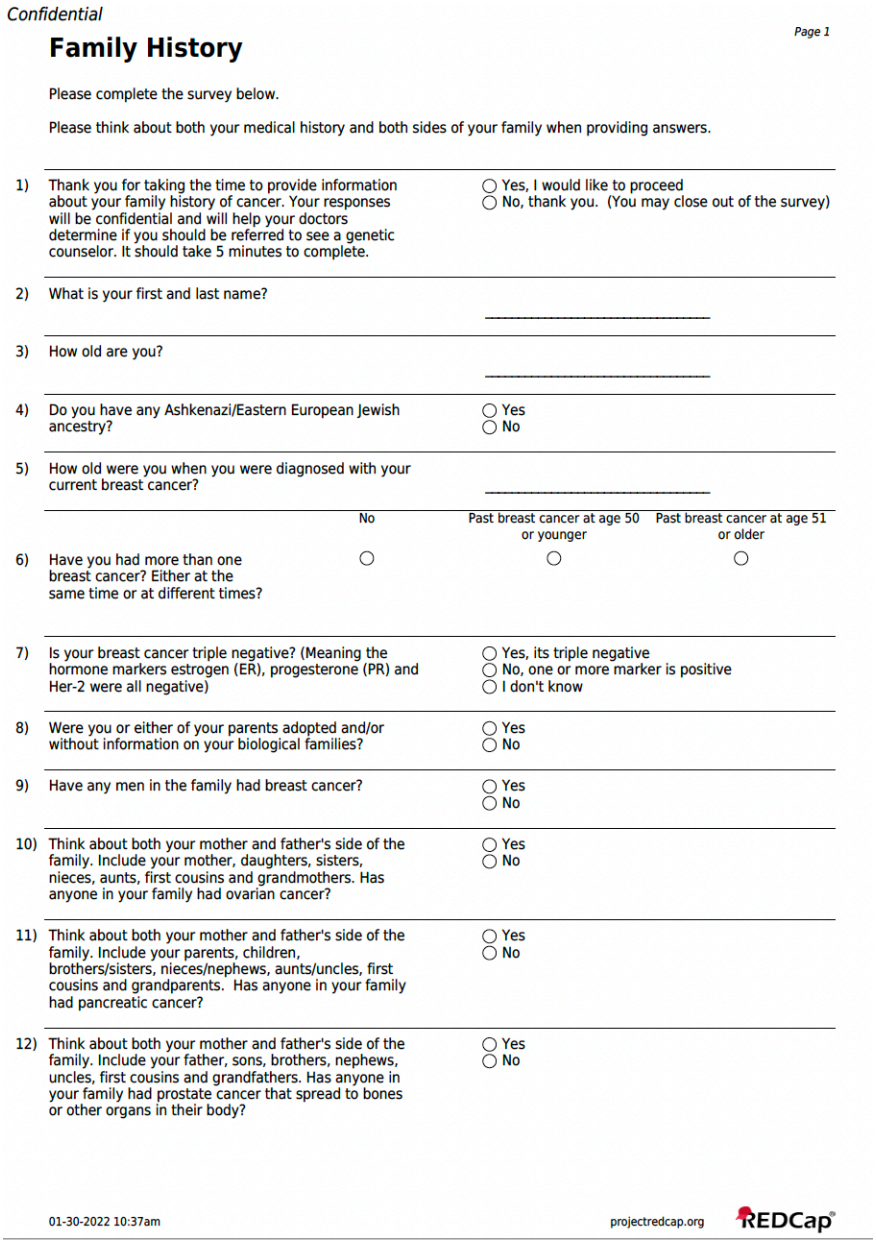
APPENDIX A:

FAMILY HISTORY QUESTIONNAIRE



Confidential

Page 1

Family History

Please complete the survey below.

Please think about both your medical history and both sides of your family when providing answers.

1) Thank you for taking the time to provide information about your family history of cancer. Your responses will be confidential and will help your doctors determine if you should be referred to see a genetic counselor. It should take 5 minutes to complete.
   - ◯ Yes, I would like to proceed
   - ◯ No, thank you. (You may close out of the survey)

2) What is your first and last name?
   _____

3) How old are you?
   _____

4) Do you have any Ashkenazi/Eastern European Jewish ancestry?
   - ◯ Yes
   - ◯ No

5) How old were you when you were diagnosed with your current breast cancer?
   _____

	No	Past breast cancer at age 50 or younger	Past breast cancer at age 51 or older
6) Have you had more than one breast cancer? Either at the same time or at different times?	◯	◯	◯

7) Is your breast cancer triple negative? (Meaning the hormone markers estrogen (ER), progesterone (PR) and Her-2 were all negative)
   - ◯ Yes, its triple negative
   - ◯ No, one or more marker is positive
   - ◯ I don't know

8) Were you or either of your parents adopted and/or without information on your biological families?
   - ◯ Yes
   - ◯ No

9) Have any men in the family had breast cancer?
   - ◯ Yes
   - ◯ No

10) Think about both your mother and father's side of the family. Include your mother, daughters, sisters, nieces, aunts, first cousins and grandmothers. Has anyone in your family had ovarian cancer?
    - ◯ Yes
    - ◯ No

11) Think about both your mother and father's side of the family. Include your parents, children, brothers/sisters, nieces/nephews, aunts/uncles, first cousins and grandparents. Has anyone in your family had pancreatic cancer?
    - ◯ Yes
    - ◯ No

12) Think about both your mother and father's side of the family. Include your father, sons, brothers, nephews, uncles, first cousins and grandfathers. Has anyone in your family had prostate cancer that spread to bones or other organs in their body?
    - ◯ Yes
    - ◯ No

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Figure A.1 First page of family history questionnaire

	How many female relatives in your family have had breast cancer?	No known relatives	One relative	Two or more relatives
13)	Sisters, daughters, and/or nieces	○	○	○
14)	Mother's side (mom, aunts, first cousins, grandmother)	○	○	○
15)	Mother's side (great aunts and/or great grandmother)	○	○	○
16)	Father's side (aunts, first cousins, grandmother)	○	○	○
17)	Father's side (great aunts and/or great grandmother)	○	○	○

18) If you have any great aunts or grandmothers with breast cancer, can you tell us specifically how you are related to that individual? (example: my mother's mother's sister or my maternal grandmother's sister) _____

	How many people in your family have had prostate cancer?	No known relatives	One relative	Two or more relatives
19)	Brothers, sons, and/or nephews	○	○	○
20)	Mother's side (uncles, first cousins, grandfather)	○	○	○
21)	Mother's side (great uncles and/or great grandfather)	○	○	○
22)	Father's side (father, uncles, first cousins, grandfather)	○	○	○
23)	Father's side (great uncles and/or great grandfather)	○	○	○

24) If you have any great uncles or grandfathers with prostate cancer, can you tell us specifically how you are related to that individual? (example: my mother's mother's brother or my maternal grandmother's brother) _____

Figure A.2 Second page of family history questionnaire