

The Three-Generation Pedigree: A Critical Tool in Cancer Genetics Care

Suzanne M. Mahon, RN, DNSc, AOCN®, APNG

Pedigree construction is an important component of cancer risk assessment and comprehensive genetic care. Pedigrees must be updated and re-evaluated on a regular basis. Complete pedigrees are needed to select genetic tests and interpret genetic testing results accurately, as well as to enroll patients and families in research and variant reclassification studies to advance the science of genetics. Identified barriers to pedigree construction and assessment are described with implications for nursing practice.

Mahon is a professor in the Department of Internal Medicine in the Division of Hematology/Oncology and a professor of adult nursing in the School of Nursing at Saint Louis University in Missouri.

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Mahon can be reached at mahonsm@slu.edu, with copy to editor at ONFEditor@ons.org.

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The family history, a rather low-tech tool, is the backbone of genetic assessment and guides risk assessment and genetic testing decisions. The importance of the pedigree and its application to genetic practice is often overlooked and underestimated. Unfortunately, particularly with electronic health records, standard pedigrees are not routinely constructed. A clear understanding of how pedigrees are employed in clinical oncology practice may lead to improved collection and use of family history data.

Standardized Pedigree Nomenclature

Family histories of disease have been recorded in standardized formats for centuries (Resta, 1993). In ancient Greece, the physician Hippocrates assembled family histories to understand disease prognoses (Hinton, 2008). In 1995, standardized criteria for the graphic presentation of data were published by the National Society of Genetic Counselors (NSGC) (Bennett, French, Resta, & Doyle, 2008). Pedigrees can be constructed with pencil and paper and scanned into the record. More commonly, a pedigree software program is used to construct the pedigree, making the process of updating it as more pertinent information becomes available an easier task.

American Society of Clinical Oncology and NSGC guidelines emphasize that the family history should be obtained and evaluated at the initial visit and should be reevaluated at least annually (Berliner, Fay, Cummings, Burnett, & Tillmanns, 2013; Lu et al., 2014). A pedigree should include three generations, ancestry from the maternal and paternal sides, current age and age at death, and, in oncology, information about malignancies and age of diagnosis.

Clinical Applications

Like many aspects of health care, collecting an accurate family history is a science and an art (Venne & Scheuner, 2015). Obtaining a family history provides a unique opportunity to connect with the patient on a different level and learn more about family dynamics and social norms, providing insight as to how the family may manage information gleaned from risk assessment and genetic testing. If patients know prior to their appointment what information is required from them, they can then provide a more accurate family history and will have greater confidence in their risk assessment and screening recommendations (Armel et al., 2009). This also communicates the importance of the family history in clinical decision making. Despite these benefits, in addition

Case Study

The proband presented for risk assessment and possible genetic testing. Her mother did not want to undergo genetic testing, and the family history was not overly suggestive of family risk. The proband's risk of breast cancer was calculated to be more than 30% by multiple models, and she opted to undergo screening with mammography alternating every six months with breast magnetic resonance imaging (MRI). During her first screening with breast MRI, the proband was diagnosed with breast cancer; the updated pedigree was now much more suggestive of hereditary risk. She underwent genetic testing with a panel of genes and was found to have an *ATM* mutation. Her mother and maternal aunt were also found to have the same *ATM* mutation, and testing is being offered to the proband's siblings and cousins. This case demonstrates how pedigrees can be used to calculate risk for developing a malignancy and guide personalized screening strategies. As demonstrated, pedigrees are dynamic, requiring ongoing updates, and they provide valuable insight into which other family members may benefit from testing based on their position on the pedigree, with the goal of ultimately decreasing the morbidity and mortality associated with malignancy.

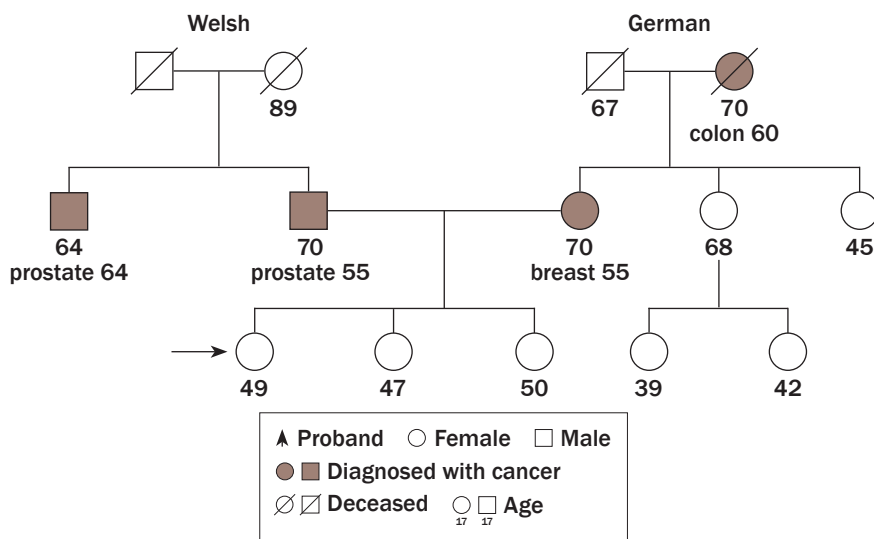


FIGURE 1. Using a Pedigree to Calculate Risk for Developing Malignancy

to others that include gathering critical information about potential cancer and genetic risk to guide recommendations, constructing a complete three-generation pedigree takes time, often as long as 10–15 minutes (Mahon, 2013).

Ongoing assessment and pedigree updates are important because family histories are dynamic. The pedigree should be updated on a regular (annual) basis or as more information becomes available (Berliner et al., 2013). A common scenario often detected on re-evaluation is that another relative is diagnosed with cancer and that the family history may be suggestive of genetic risk, necessitating genetic evaluation.

Reevaluation is also important because more testing may have become available in the interim since the last evaluation. In addition, some patients with cancer may be more motivated and able to learn more about their family history once they have shifted beyond the stress of their initial diagnosis and focused on providing useful information for other at-risk family members (Venne & Scheuner, 2015).

Pedigrees provide a wide range of information. The proband is the person for whom the risk is being calculated and who provides orientation for the pedigree regarding how relatives are related and possibly share the same risk of

disease. Cancer risk assessment depends on the construction of a pedigree. The more accurate and complete the pedigree is, the more accurate the assessment of the risk of developing cancer or the risk of having a susceptibility mutation (see Figure 1).

With the advent of next-generation testing for less penetrant and common genes, more variants of unknown clinical significance are detected (Mahon, 2015). To move forward and reclassify a variant of unknown significance, genetic testing laboratories will often want to test other family members who might provide valuable information about the variant based on their position in the pedigree. A standard pedigree is necessary for families who want to enroll in variant reclassification studies or studies that seek to identify less common susceptibility genes (see Figure 2).

Genetic testing results cannot be interpreted without an accurate and complete pedigree. Recommendations for care should include not only the results of testing, but also consideration of the family history of malignancy. This can be the case in positive and noninformative testing results.

Barriers and Limitations in Pedigree Assessment

Unfortunately, family histories are not always collected or are collected in such a way that they do not provide enough information to quantify risk. The visual format of the pedigree helps the health-care professional better recognize potential hereditary susceptibility. Without the visual representation, potential risk may be overlooked. An audit of 10,466 charts from 212 oncology practices found that the provider documented the presence or absence of malignancy in first-degree relatives in about 77% of all medical records and in

62% for second-degree relatives (Wood et al., 2014). In addition, the age of diagnosis, which is an important component in evaluating risk, was only present in about 31% of the records.

Barriers hinder implementation of the pedigree. Family communication and dynamics may limit the availability and the accuracy of the information (see Figure 3). Health-care providers may not have the time to accurately collect and document a pedigree, and they may not have the tools to create a meaningful and complete three-generation pedigree. Patient, provider, and system barriers are listed and described in Table 1.

Implications for Nurses

The three-generation pedigree is the key to calculating risk for developing cancer. Individuals whose pedigree suggests higher risk may benefit from modified guidelines for cancer prevention. The pedigree also provides the best means for identifying individuals and families who may benefit from genetic testing. Failure to identify at-risk families can result in less-than-adequate care and sometimes litigation (Robson et al., 2015).

The family history is a powerful tool for education and empowerment (Hinton, 2008) that should be shared with the patient (Lu et

al., 2014). For many patients, the visual presentation of the family history helps them to understand the magnitude of the risk and can be a motivator to engage in the recommended prevention and detection measures (Beadles et al., 2014).

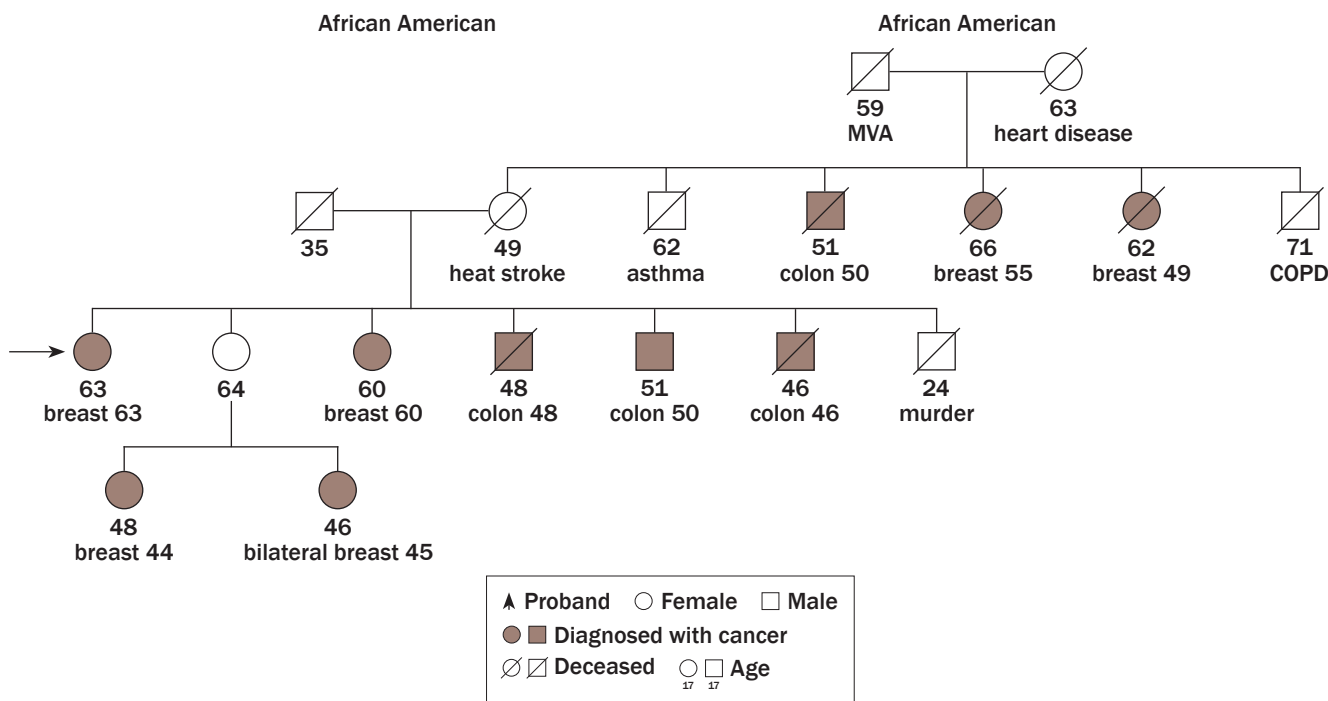
A need exists for tools that can assist patients and families with collecting information about family history. One such tool is the Surgeon General's My Family Health Portrait website (<https://familyhistory.hhs.gov/FHH/html/index.html>), which allows a family to store and share information about its history, as well as learn about its risk for genetic conditions (Owens, Marvin, Gelehrter, Ruffin,

FIGURE 2. Using a Pedigree and Genetic Testing Results to Provide Screening and Prevention Recommendations and Facilitate Enrollment in Variant Reclassification Studies

COPD—chronic obstructive pulmonary disease; MVA—motor vehicle accident

Case Study

The 63-year-old woman with triple-negative breast cancer had a family history that was significant for breast and colon cancer. Genetic testing identified a *BRCA2* pathogenic mutation and variants of unknown significance in the *MSH6*, *APC*, and *SMAD4* genes. Based on the *BRCA2* mutation, she underwent bilateral mastectomies, total hysterectomy, and pancreatic screening; other family members were offered testing for the pathogenic *BRCA2* mutation. Based on the strong family history of colon cancer, colonoscopy was recommended at an interval of every two or three years for all family members, beginning at age 35 years. This recommendation was based on the family history, not on the presence of the three variants associated with colon cancer. The testing laboratory offered testing to the relatives with breast and colon cancer who were alive to better understand if the variants track with the cancer and the *BRCA2* mutation. The pedigree provided valuable information; about 13 months later, the laboratory reclassified the *MSH6* variant as a suspected pathogenic mutation.



& Uhlmann, 2011). Nurses need to encourage patients to accurately collect as much information as possible. Patients and families need to understand that the more accurate the information, the better the recommendations for genetic testing, prevention, and detection. The importance of a complete and accurate three-generation pedigree should not be underestimated.

Conclusion

Standard pedigrees provide a visual representation of a family history of cancer. They are dynamic and must be updated as family history changes or as more is learned about the family history of

malignancy. In addition, pedigrees provide an excellent teaching tool to demonstrate basic concepts of genetic transmission. Pedigrees also provide the backbone for cancer risk assessment, and the accuracy and completeness with which they are constructed can ultimately lead to better recommendations for cancer prevention and early detection, with the goal of decreasing the morbidity and mortality associated with malignancy.

Nurses need to be aware of the multiple ways that an accurate and well-constructed pedigree can influence patient care. For example, pedigrees can be used to calculate the risks of malignancy; when risks are elevated (typically

greater than 20%), screening recommendations can be modified from those used with the general public of average risk. Pedigrees provide information about the transmission of disease and can also offer information about which family member would be best to initiate genetic testing, with the objective of obtaining illuminating information about genetic risk. If a mutation is detected, the pedigree can be used to identify other family members at possible increased risk; these individuals should then be offered the option of testing. Accurate and well-constructed pedigrees also advance the science of genetics and are necessary when enrolling families in variant

FIGURE 3. Incomplete Family Pedigree

Case Study

The 19-year-old woman with breast cancer was initially offered genetic testing based on her very young age at onset and her maternal aunt with breast cancer. No paternal history was available at that point. She was found to have a pathogenic *BRCA1* mutation. Her sister and brother were also found to have the same mutation, assumed to be maternal transmission based on the aunt with relatively early onset breast cancer. However, the mother tested negative, suggesting paternal transmission. Some question of paternity existed; her father had been estranged from his family for more than two decades and was not aware of any family history of cancer. The proband's father was offered testing, and he was found to have the same *BRCA1* mutation, which also answered the paternity question. He agreed to contact one of his sisters and was surprised to learn she also had been diagnosed with breast cancer at age 40 years and had undergone testing with her oncologist, revealing the same *BRCA1* mutation. She had not shared this information with any of her siblings. Both of his other sisters were informed, and they also carry the *BRCA1* mutation, as do some of their offspring. This is not an uncommon example of poor communication among family members. Estranged families and poor communication can greatly limit the accuracy of the pedigree.

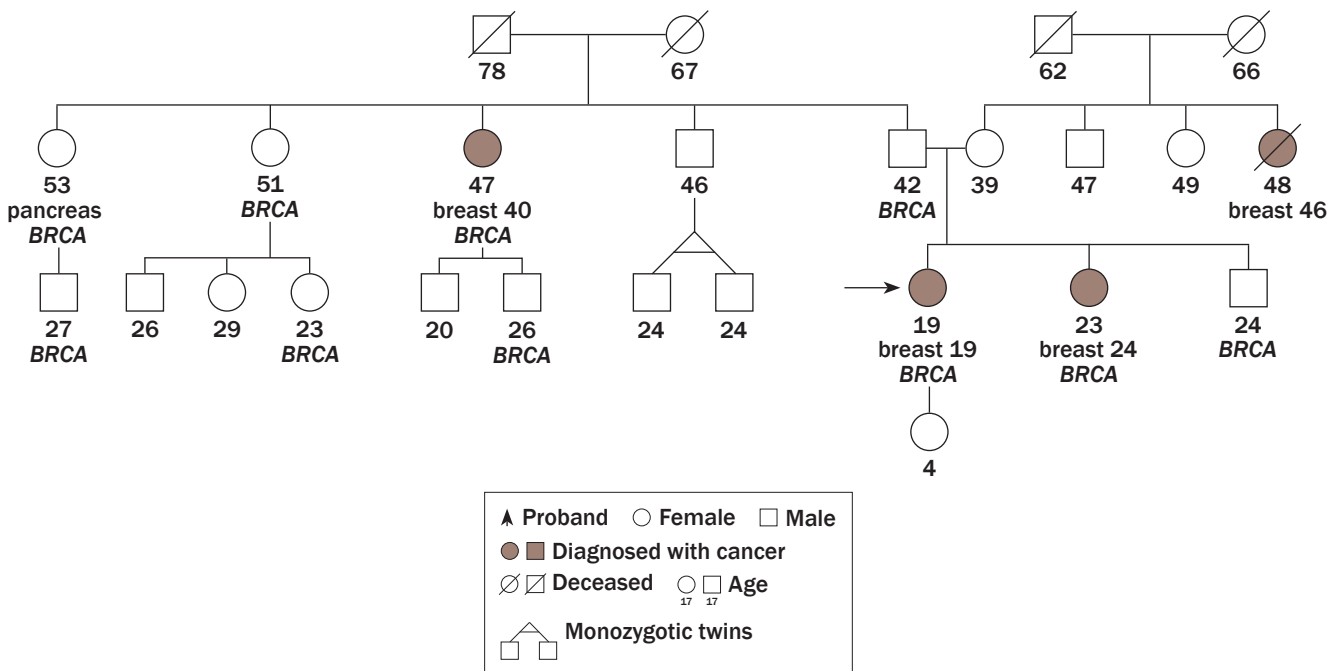


TABLE 1. Barriers to the Implementation of Quality Pedigrees

Barrier	Possible Remedy
Patient factors	
Inaccurate family history	Try to verify diagnoses with pathology reports, prior testing reports, or death certificates.
Lack of desire to explore family history	Educate the patient about why an accurate family history is important to constructing an accurate risk assessment and possibly ordering and interpreting genetic testing results.
Limited family history	Encourage the patient to reach out to other relatives prior to the appointment to try to obtain as much information as possible.
Patient adopted	No remedy; explain to the patient that risk assessment is difficult and that the interpretation of genetic testing results may be limited or noninformative.
Small family structure	No remedy; explain to the patient that this may limit the accuracy of the information.
Unknown paternity	No remedy; explain to the patient that risk assessment is difficult and that the interpretation of genetic testing results may be limited or noninformative.
Provider factors	
Failure to recognize subtle indicators of hereditary risk	Provide ongoing continuing information about emerging genetic syndromes.
Time required to construct pedigree	Have the patient gather some of the information prior to the visit, and document the information on paper or directly into a computer program.
System factors	
No inclusion of decision support and red flags for referral to genetics professional in electronic health record	Users identify criteria that must be collected and help to develop an interface that provides clinical decision-making support.
No reimbursement for time to collect accurate pedigree	Users need to lobby for changes in reimbursement that acknowledge the benefits of a comprehensive, accurate three-generation pedigree.
No visual representation in electronic health record	Users provide feedback to develop appropriate family history sections with a usable family history interface and produce a visual pedigree with standard symbols.
<i>Note.</i> Based on information from Armel et al., 2009; Beadles et al., 2014; Lu et al., 2014; Riley et al., 2012; Venne & Scheuner, 2015; Wood et al., 2014; Ziogas & Anton-Culver, 2003.	

reclassification studies, as well as studies intended to identify new genes associated with cancer risk. Nurses need to instruct patients about these numerous clinically important uses of the pedigree to engage them to provide the most accurate information possible.

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