

ARTICLES

The Bridge From Genomic Discoveries to Disease Prevention

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Dedication

My presentation is dedicated to Susan Birnbaum; her sister, Sharon Luschen; and their families. Susan was a best friend of mine since junior high school who lost her long-fought battle with breast cancer on August 1, 2005, when she was just barely 46. The very day of Susan's funeral, her sister, Sharon, was hospitalized and diagnosed with brain metastasis. At the gathering at the house after Susan's funeral, their mother gave me a really tight hug and said, "You have to stay with me to help Sharon." Their mother knew exactly what was in store for her only other child. Sharon recently died at age 44, leaving her husband, five children, and a large extended family.

Even before Susan was diagnosed, she was a great listener who always offered encouragement and support, no matter what the situation. Susan was diagnosed in 1995, just a few years after I began my work in cancer genetics. Because I was new to the field and went "against the grain" most of the time, I frequently whined and talked to her about going back to general oncology nursing—my comfort zone. Susan always told me that she could see the passion I had for this work and reminded me that passion was crucial for me as well as the people with whom I work.

Susan, Sharon, and their families valued "their" nurses the most but also all nurses in general. They showed me how important the extra time we spend with patients is, even though we never really have extra time. Or how the smile we offer someone even when we are smiled out has a healing and lasting impact. They will forever remain central in my heart.

In April 2003, scientists from around the world gathered to announce the completion of the initial goals of the Human Genome Project, 50 years after the discovery of the first description of the DNA molecule. The same scientists worked together to unravel and record the entire set of

human genetic instructions, the human genome (McPherson et al., 2001; Venter et al., 2001). The achievement was lauded as the beginning of a new age of discovery sure to transform human health.

Many compared the full sequencing of the human genome to Neil Armstrong's landing on the moon in 1969 (Collins, 1999; Regalado, 2002)—what some say is the greatest scientific achievement of the 20th century. The unraveling of the human genome well may be the greatest scientific achievement of the 21st century. It undoubtedly will lead to other great scientific achievements. In 1969, people could not imagine today's scientific advancements related to and beyond space exploration. Even today, people cannot imagine the possibilities that knowing the human and other genomes will bring to health care and our world.

In a speech about space exploration, President John F. Kennedy retold the story of Irish writer Frank O'Connor's boyhood. As a boy, O'Connor and his friends would roam across the countryside of Ireland.

When they came to an orchard wall that seemed too high, and too doubtful to try, and too difficult to permit their voyage to continue, they took off their hats and tossed them over the wall—and then they had no choice but to follow them (Kennedy, 1963, p. 9).

Kennedy continued his speech by saying,

This nation has tossed its cap over the wall . . . and we have no choice but to follow it. Whatever the difficulties, they will be overcome; whatever the hazards, they must



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be guarded against. . . . We will climb this wall with safety and with speed—and we shall then explore the wonders on the other side (p. 10).

Kennedy's words of space exploration in 1963 fit perfectly with genomic medicine now. The cap has been thrown over the wall, and we must follow. Many scientists are already over the wall and far away from it by now, exploring the functions of genes and proteins, RNA mechanisms, and much, much more. Many healthcare providers also are over the wall and have incorporated genetics and genomics into their daily medical practice. But the average person and average healthcare provider are still looking at the wall and trying to negotiate it and make it over. Some have thrown their caps over and are trying to follow; others are still too reluctant to even throw their caps over.

Nurses are at the wall and will be there for our patients and each other to help people get over it. It fits our very job description, regardless of practice setting—nurses will help patients and the community climb the wall with safety and speed and allow the wondrous exploration of the other side.

Objective

The objective of this article is to get you excited about genomic medicine. I mean excited, down to your soul, excited as I am. Excited enough to get the books out and study basic biology. Excited enough to sludge through the hard science (Cannistra, 1997; Varmus, 2006) so you can understand how much genetics and genomics affect your nursing practice, right now, regardless of where you work or what you do. Genetics and genomics are now as fundamental to nursing practice as a blood pressure or a complete blood count (Baak et al., 2003; Varmus). The scope of this article is not to teach you these basics. It is to help you understand the importance of doing the studying yourself, in whatever way is best for you to learn.

Case Example—Part 1

Note. Patient names and pedigree details have been changed to protect anonymity. The physician in the case example is fictitious. The remaining details are true and are taken from my clinical practice.

This case presentation is about a high-risk family, comprehensive cancer risk assessment, evaluation, and management for a not uncommon single gene disorder. No matter where you work or what you do, you will be able to use information about this case in your practice. This case is *not* about how genomics has affected the diagnostic workup, molecular characterization of tumors, prognostic indicators, targeted therapies, response to treatment, symptom management, or long-term follow-up of a person with cancer. But a presentation on genetics could have been about all of those areas of oncology practice. The areas are well covered in many other educational sessions and materials. The genetic piece in other offerings may not be highlighted as forcefully as it will be here, but if you listen for it, if you pay attention with genetic ears, you will see how genetics and genomics are an integral part of all of cancer care. Your knowledge of cancer and the ability to appropriately take care of patients and answer their questions requires you to know the basic principles of genetics and the biology of cancer. You

can build on that solid foundation in all of these other areas of genomics and cancer.

Connie B. was 3.5 years out from her stage II breast cancer and was completely free of any disease. Her visits to her oncologist, Jennifer Swafford, MD, were every six months. Her life as a patient with cancer was in the past and one that she thought of only around her doctor visits and diagnostic tests. Her husband no longer had to take time off from work to accompany Connie to the office visits; Connie usually only had to take a long lunch hour to fit an appointment in her schedule.

The cancer center staff had undergone typical personnel changes in the more than three years since Connie started going there. The nurses in the treatment area where she received her chemotherapy were busy taking care of other patients now, so Connie felt there was no reason for her to go say “hi” to them anymore. Even Dr. Swafford's primary nurse, with whom Connie was close, was no longer in the same position.

Connie's doctor visits fortunately had become pleasantly short. The personal connections in the cancer center were now with Dr. Swafford. This is not to say that Connie did not feel warmth and kindness from all of the cancer center staff, but she just did not know them anymore and, more importantly, did not need them anymore. These are all desirable developments. You all know patients like Connie. You see them on the patient list for the day, but they are not the patients you make note of or will likely interface with because they are no longer on any active treatment.

Dr. Swafford reacquainted herself with and updated Connie's family history. No pertinent changes existed in the family history. However, the review reminded Dr. Swafford that Connie's family history is significant for hereditary predisposition and that now was a good time to talk about genetic testing. Dr. Swafford checked the National Comprehensive Cancer Network (2006) *Clinical Practice Guidelines in Oncology* to confirm that the discussion would be clinically appropriate. She proceeded with a lengthy discussion with Connie about genetic testing for the *BRCA1* and *BRCA2* genes. Dr. Swafford explained that the testing involved a simple blood draw and could be done at the same time that blood was drawn for other laboratory tests. Connie was told that results of the testing would be available in 8–10 weeks. This included three weeks to obtain insurance authorization and approximately six weeks for the actual blood testing. Dr. Swafford told Connie that she would call her with the results as soon as she received them. Connie could then schedule an appointment to come back in for a more thorough discussion if she wanted.

The family history was significant enough that Dr. Swafford told Connie that she hoped testing would reveal a mutation so that other family members could be tested and “taken care of” as well. But Dr. Swafford mentioned that testing might not reveal anything either, and that also would be nice. This was confusing to Connie.

Dr. Swafford emphasized the importance of testing for both Connie and her family. The doctor offered several specific risk management changes for Connie to consider if a gene mutation was identified (see Figure 1). Dr. Swafford explained that a *BRCA* mutation would indicate that Connie was at significantly increased risk for both breast and ovarian cancer (Chen et al., 2006; Frank et al., 2002; Garber & Offit,

1. Prophylactic total hysterectomy with bilateral salpingo-oophorectomy
 - Scheduled at the patient's convenience
 - But as soon as possible
 - May be done laparoscopically.
2. Add breast magnetic resonance imaging to breast surveillance once per year.

Figure 1. Dr. Swafford's Management Recommendations If a *BRCA* Mutation Is Identified

2005; Metcalfe et al., 2004). She emphasized that ovarian cancer is not as likely to be cured as breast cancer, which is why she would recommend prophylactic oophorectomy. From Connie's perspective, the prophylactic surgery did not sound like a big deal.

Connie's breast cancer had been treated with breast conservation; therefore, she still had both breasts intact. Dr. Swafford said she would want to use breast magnetic resonance imaging and mammograms at least every year for breast surveillance. Again, Connie's impression was that this was not a big deal either. However, Connie also was a little confused because she thought her breast cancer was cured and was unsure why Dr. Swafford seemed concerned about both of her breasts and not just the unaffected breast.

Dr. Swafford gave Connie an educational booklet to read and gave her the option of having her blood drawn on the way out of the office or waiting until later. Dr. Swafford told her that her preference would be that Connie would get the testing started right away. Connie did have questions but could not think of them fast enough. Dr. Swafford had already spent 45 minutes with her and obviously needed to move on.

Dr. Swafford provided Connie with a consent form and told her that whenever she decided to undergo the testing she would need to sign the consent form before her blood was drawn. By this point, Dr. Swafford was standing at the door with her hand on the doorknob.

The setting for this discussion was in the room where Connie was examined. Connie had already changed out of her gown and was fully clothed and sitting on a chair next to a small side table. During the 45-minute conversation, Dr. Swafford answered one page and the staff interrupted the visit twice to ask questions about other patients.

Once Dr. Swafford was gone, Connie took her time leaving the examination room so that she could think about everything and try to decide whether she should go ahead and add genetic testing to her blood draw that day. The main thoughts going through Connie's mind at the time were that it was a simple blood test and something that was good for her and her sisters. Connie felt that if she needed more surgery, she would have it. She told herself she was making too big a deal out of the decision regarding genetic testing and she should be grateful she did not have cancer anymore. Connie finalized her decision just as she walked by the laboratory on her way out of the office and proceeded with genetic testing.

Cancer Genetics Review

In essence, all cancer is genetic, but not from one single gene mutation (Vogelstein & Kinzler, 1998, 2004). All cancers come about because of an accumulation of genetic mutations (Fearon, 1997; Kinzler & Vogelstein, 1997; Knudson, 2002; Lynch, Snyder, Lynch, Riley, & Rubinstein, 2003;

Merg, Lynch, Lynch, & Howe, 2005; Perera, 1997; Ruddon, 1995; Shields & Harris, 2000; Simpson, 1997; Vogelstein & Kinzler, 1998). Approximately 10% or less of all cancers are caused by germline mutations which arise in the egg or the sperm (Lindor & Greene, 1998; Lynch, Shaw, & Lynch, 2004; Lynch, Tinley, Lynch, & Attard, 2004; Mahon, 2003). These germline mutations are present in virtually every cell of the body. However, even with germline mutations, unlike single-gene disorders such as cystic fibrosis, hereditary cancers still entail many more mutations before cancer develops. The germline mutation predisposes certain tissues to the development of cancer; however, numerous additional mutations still are required to accumulate in the somatic cells of the tissue where cancer develops (Dolan DNA Learning Center, Cold Spring Harbor Lab, 2006).

Most cancers are sporadic in their etiology, with about 15%–30% described as familial (Antoniou & Easton, 2006; Baglietto et al., 2006; Lynch, Shaw, et al., 2004; Lynch, Tinley, et al., 2004; Sellick, Catovsky, & Houlston, 2006). Familial cancers are those with some inherited genetic component coupled with shared environmental exposure. The distinction between hereditary and familial predisposition is currently ambiguous but will become evident with continued genomic research. Familial cancer families exhibit more of the same cancer than would be expected over several generations, but these cancers do not typically occur at unusually young ages and involve more than one type of cancer observed, unlike patterns seen in hereditary cancer families.

Remember, germline mutations arise in the egg or the sperm and are present in virtually every cell of the body. They predispose people to hereditary cancer family syndromes, such as hereditary breast and ovarian cancer (HBOC) or Lynch syndrome (Garber & Offit, 2005). An accumulation of additional genetic mutations still is required to cause a malignancy to develop. Sporadic cancers, which are most of the cancers seen, are the result of multiple genetic mutations that occur only in the cells that eventually become the cancer (see Figure 2.)

The identified cancer family syndromes, the 10% piece of the pie graph shown in Figure 2, are numerous now and result from mutations in many different genes. Table 1 is a list of some of the genes associated with cancer etiology and hereditary cancer family syndromes (Genetics Home Reference, 2006). The hereditary predisposition syndrome that Dr. Swafford is suspicious of in Connie's family and wants to

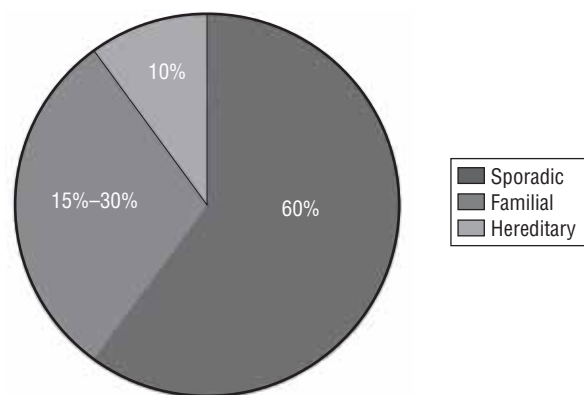


Figure 2. Cancer Etiology

Table 1. Sporadic and Hereditary Cancers and Their Associated Genes

Condition	Gene
Hereditary breast and ovarian cancer	<i>BRCA1, BRCA2</i>
Lynch syndrome, also called hereditary non-polyposis colon cancer	<i>MLH1, MSH2, PMS2, MSH6</i>
CoLoN—colon cancer, leukemia or lymphoma, and neurofibromatosis	Homozygous <i>PMS2</i> , homozygous <i>MSH6</i> , homozygous <i>MLH1</i> , homozygous <i>MSH2</i>
Turcot syndrome	<i>PMS2, MLH1, APC</i>
Muir-Torre syndrome	<i>MSH2</i>
Li-Fraumeni syndrome	<i>TP53</i> , possibly <i>CHEK2</i>
Increased breast cancer risk	<i>CHEK2, ATM, RAD51</i>
Sporadic breast cancer	<i>AR, DIRAS3, ERBB2, TP53</i>
Retinoblastoma and osteosarcoma	<i>RB1</i>
Costello syndrome	<i>HRAS</i>
Sporadic bladder and other cancers	<i>HRAS, FGFR3</i>
Neurofibromatosis (type 1)	<i>NF1</i>
von Hippel-Lindau syndrome	<i>VHL</i>
Sporadic clear cell renal cancer	<i>VHL, FLCN</i>
Familial adenomatous polyposis (FAP)	<i>APC</i>
Sporadic gastric carcinoma	<i>APC</i>
Autosomal recessive FAP (also called MYH-associated polyposis)	<i>MUTYH</i> (also called <i>MYH</i>)
Peutz-Jeghers syndrome	<i>STK11</i>
Cowden syndrome	<i>PTEN</i>
PTEN hamartoma tumor syndrome	<i>PTEN</i>
Sporadic prostate and endometrial, melanoma, glioblastoma, astrocytoma, and other sporadic cancers	<i>PTEN</i>
Multiple endocrine neoplasia (MEN) type 2	<i>RET</i>
Sporadic follicular thyroid carcinoma	Fused <i>PAX8-PPARG</i>
Sporadic papillary thyroid carcinoma	<i>RET</i>
MEN type 1	<i>MEN1</i>
Sporadic gastrinomas, insulinomas, and bronchial carcinoids	<i>MEN1</i>
Sporadic melanoma and pancreatic carcinoma	<i>STK11</i>
Sporadic colon or pancreatic carcinoma	<i>SMAD4, FLCN</i> (colon only)
Sporadic pediatric and adult leukemia	<i>PTPN11</i>

Note. This table is only a sample of known cancers and their associated genes.

confirm with genetic testing is the HBOC family syndrome associated with a *BRCA1* or *BRCA2* germline mutation.

Why focus on the smallest 10% piece of the cancer etiology pie graph? First, 10% of the common cancers—breast, colon, lung, and prostate—involve more than 77,000 people who will be diagnosed in the United States in 2006 alone (American Cancer Society, 2006). These technically rare cancer syndromes are part of all of your practices, no matter how small your office or unit might be. I am certain you already have taken care of patients, and will again, whose cancers are caused by hereditary cancer predisposition genes.

Second, the identification and management of high-risk patients and families no longer occurs just in specialty programs or by specialists such as me. Primary care physicians and subspecialists such as oncologists are incorporating genetics and genomics into their practice and, therefore, are taking care of high-risk patients themselves. They have gone over the wall and are exploring new territory. This is expected. However, where does the time to add genetic counseling and cancer

genetics expertise to oncology practice come from? Nurses, as patients' strongest advocates, must assist physicians and patients over the wall and into the unfamiliar territory. You cannot leave physicians or patients at the wall without help to fend for themselves. What Connie's case beautifully illustrates is that even the most straightforward cases are extremely complicated. Do not ignore or gloss over difficult areas just to make it easier on you. Know what you are doing, know when you need to seek additional help, keep your eye on patients, and do what nurses do best: Take care of your patients' physical, emotional, and family needs.

The last reason that you must know about the 10% group of patients from hereditary cancer families is because these individuals are at the greatest risk for developing cancer.

Because we are living in a time of personalized or individualized medicine, stratifying the degrees of risk and the individuals at the highest risk using specialized or intensified cancer prevention and screening modalities makes logical sense (National Comprehensive Cancer Network, 2006). These individuals may have different treatments to choose from when they are diagnosed with cancer. For example, a person diagnosed with an invasive colon cancer from a hereditary colon cancer family, such as hereditary nonpolyposis colon cancer (HNPCC), may choose to have his or her entire colon removed to the rectum instead of just the invasive colon tumor because of the significantly increased risk of a second colon cancer (Ricciardiello & Boland, 2005). Long-term follow-up and survivorship issues are much different for cancer survivors from hereditary cancer families than they are for average cancer survivors (Dove-Edwin, Sasieni, Adams, & Tomas, 2005). Our ability to truly prevent cancer or to make sure any cancer that develops is curable lies partly in these families who are at the greatest risk of developing cancer. We must appropriately identify and care for them.

Identification of High-Risk Families

Identification of high-risk patients and families begins with a family history. It is the easiest, most cost-effective, and most underused tool available to all of us. A family history is the ultimate genetic test. The history does not even have to be taken directly by a nurse. Have your patients provide you with thorough histories while they are waiting for their appointments or before they come in for their appointments. A history has to be completed and interpreted by a knowledgeable professional, and we have to make sure that we are asking the right questions on our forms, but much of the information gathering can be completed without even adding to your to-do list.

Elements of a Thorough Family History

A usable family history must have the following components.

- Obtain information about both sides of the family, not just the maternal side for female-only cancers such as uterine or ovarian or the paternal side for male-only cancers such as prostate or testicular, but rather both sides for everyone.
- Document all members of the family, not just those with cancer.
- Note the gender of each person in the family. For example, your patient is the only male of four sisters.
- Enter each person's current age or age at death.

- Gather, at a minimum, information about your patient's immediate family, including his or her spouse, children, siblings, and parents. To do any kind of cancer risk evaluation, you also need to know about your patient's aunts, uncles, and grandparents on both sides of the family. Going further and obtaining information about the patient's cousins is easy and useful. In more distant family members, you need to have a sense of how many cousins are in the family, their genders, and the presence of any cancers. For example, Aunt Susie had two sons and no daughters and none has cancer.
- For the family members with cancer, record the age that the person was diagnosed with cancer and the site of the primary cancer. Patients often report a history of liver cancer or bone cancer, which usually are metastatic diseases, not primary cancers. Ask leading questions to try to ascertain the site of the primary cancer. For example: Do you remember if your aunt ever had her breast removed?
- Report the presence of precursor lesions in family members. This is the number and type of colon polyps in a person or family with a colon cancer history, dysplastic nevi in a person or family with melanoma, or atypical hyperplasia or carcinoma in situ in a person with a mastectomy. Most people are not going to know this detail about their relatives, or even about themselves, but it can be pertinent information if you can gather it. This detailed information is more appropriately obtained during a more thorough cancer risk evaluation.
- Record the family's ancestry. Certain ethnic groups are at greater cancer risk by virtue of their ethnic ancestry alone. The most common pertinent example in this country is Jewish individuals whose ancestors came from Eastern Europe, known as Ashkenazi Jewish.

An example of a usable and meaningful family history is illustrated in Figure 3. Does this seem daunting or more than you can accomplish in your schedule? It should not. We

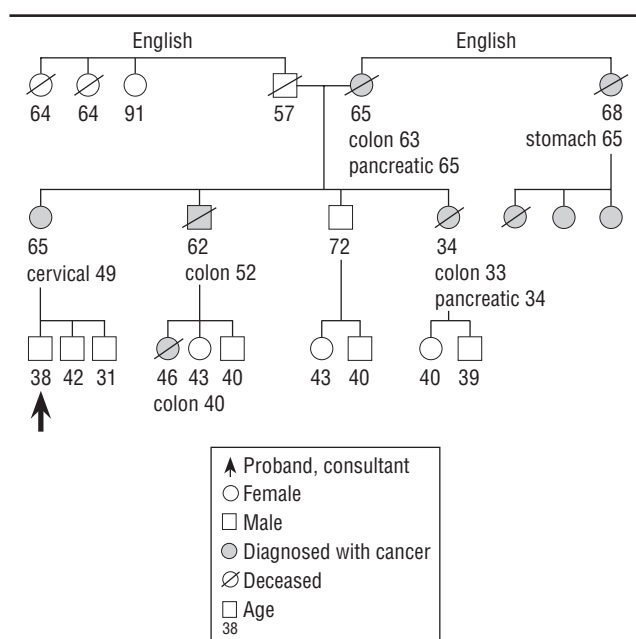


Figure 3. Example of a Family Pedigree: Clinical Evidence of Hereditary Nonpolyposis Colon Cancer

cannot adequately take care of patients without knowing this information. Just as you would never give chemotherapy without checking the patient's temperature and blood count, you should not let new patients or follow-up patients be evaluated without a thorough and updated family history. If a physician forgot to order a blood count, you would still not move forward with therapy until you verified that the blood counts were safe to proceed. Order or no order, you would check the counts. Do not minimize the importance of an accurate and current family history.

Work with your physician partners and nurse colleagues to make obtaining a family history routine. If your role is giving chemotherapy, then help the physicians or nurse practitioners who examine patients and figure out how to make this happen. In other words, even if you will not be the person gathering patients' histories, ensure that it is done for all of your patients. Learn the symbols used for drawing family trees (Bennett, 1999), called pedigrees in genetics, because this allows you to gather and interpret histories more quickly. All you have to do to learn the symbols is to practice using them, probably on your own time with family and friends. All of this information is absolutely necessary for risk assessment and the identification of high-risk individuals and families.

Identifying the Red Flags of Hereditary Predisposition

Once you have a thorough family history, identifying high-risk families is much easier. The characteristics of inherited cancer families include the following.

- **Early age at diagnosis:** This is why you need to find out about the age that kin were diagnosed with cancer when you are getting the family history. Early is a relative term and varies depending on the cancer, but use what you know about the epidemiology of cancer or your common sense. Does the patient in front of you seem younger than most of the patients you see with the same type of cancer?
- **Multiple family members on the same side of the family with the same or related cancers:** Certain types of cancers cluster together in a family with hereditary cancer family syndrome (Barse, 2003; Garber & Offit, 2005). A family with early-onset colon and uterine cancer is illustrated in Figure 3. These two types of cancers go together in the inherited form. This pedigree is indicative of Lynch syndrome or HNPCC.
- **The presence of rare cancers:** The same family shown in Figure 3 has been changed in Figure 4 to show the presence of a rare cancer. The family now shows two cases of ureteral cancer. This history is a real family. How many patients have you had with ureteral cancer, let alone two in the same family and both at such young ages?
- **The presence of two or more cancers diagnosed in the same person,** regardless of his or her age, is a red flag.

Someone who knows very little about hereditary cancer syndromes but knows basic cancer genetics and cancer biology would be able to identify that the family in Figures 3 and 4 has a hereditary predisposition. In fact, an office nurse of this patient's oncologist referred the family to me. That nurse indicated that she was not sure whether the patient was appropriate for me to see, but a 37-year-old with ureteral cancer seems to be a red flag. It is not that the patient's oncologist did not know that the family history was suspicious; it is just that the oncologist was focused on treating the cancer.

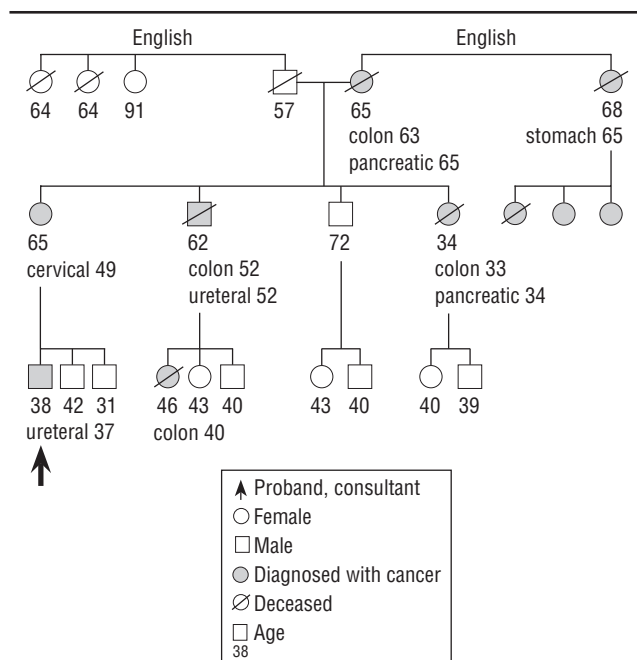


Figure 4. Example of a Family Pedigree: Hereditary Cancer Syndrome With Rare Cancers

Consider all of the healthcare professionals who interfaced with the family and did not identify the significantly increased cancer risk. What if someone had intervened with the patient's maternal uncle or maternal aunt instead of this young man, which is not unreasonable to expect from nongenetic specialists? What if the family was already identified to be at risk and all at-risk relatives were notified and kept under intense surveillance for the appropriate cancers? Perhaps then the patient I saw would have been seeing a urologist every six months and having his urine checked for hematuria. This cheap and easy screening likely would not have prevented his cancer from occurring, but it possibly could have allowed diagnosis at an earlier stage, one more likely to be cured than the stage IIIB tumor he was actually diagnosed with. What if the nurse ignored the patient's rare cancer and his family history because the oncologist failed to order a referral for genetic counseling?

Case Example—Part 2

Connie B.'s family history is depicted in Figure 5. Connie is called the proband in genetics and is depicted with an arrow. The proband is the person who brought the family to the practitioner. Connie is one of eight siblings, four girls and four boys. Connie is sixth in birth order and has three children, two boys and a girl, all younger than age 14. Connie is now 41 and was diagnosed with unilateral, stage II, estrogen- and progesterone-negative, HER2-positive breast cancer at age 37. She was treated with a lumpectomy, four courses of adjuvant chemotherapy, adjuvant trastuzumab, and radiation therapy to the affected breast. Connie is the only person in her generation diagnosed with cancer.

Connie's mother was diagnosed with unilateral breast cancer at age 57 and died at age 58. Connie and her younger sister were

the most involved (compared with the rest of the siblings) in the day-to-day care of their mother throughout her entire cancer trajectory. Connie's mother's only sibling, Connie's aunt, was diagnosed with breast cancer at age 57 and died at age 64. None of the aunt's children have been diagnosed with cancer. Connie's maternal grandmother was diagnosed with ovarian cancer at age 47 and died at age 49. Connie's grandmother's ovarian cancer was confirmed on her death certificate.

Is This Hereditary Predisposition?

Does the family seem like one that is appropriate to evaluate for hereditary predisposition? Would you, like Dr. Swafford, have thought to bring up the subject of hereditary predisposition? Would you have reminded Dr. Swafford to talk about it if she had not already? I hope so, because the family meets several red flag criteria that we have discussed.

- Connie and her grandmother had early diagnoses at ages 37 and 47, respectively. Connie's mother's and maternal aunt's ages at diagnosis are not suspicious in and of themselves.
- Two or more generations have had the same or related cancers. This is present with three generations affected with three breast cancers and one ovarian cancer. Breast and ovarian cancers are related in the inherited form. You also can look at the pedigree without even reading the details and be able to tell that the family has more cancers than would be expected.
- The family has no rare cancers, no suspicious ethnicity or ancestry, and no individual with more than one primary cancer.

Connie's family history is diagnostic for HBOC, and that is what I discussed with her. I must emphasize that I am saying it is appropriate to discuss the diagnosis of hereditary predisposition with Connie even though I have not yet said anything about genetic testing. Genetic testing and a diagnosis of hereditary predisposition are two separate topics. They are

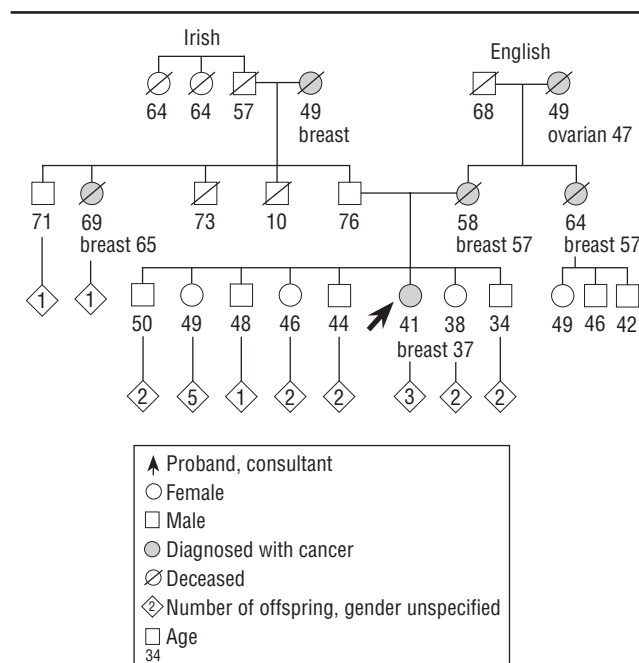


Figure 5. Connie B.'s Family Pedigree

not equivalent. One of the most common errors I see is that patients are counseled to get genetic testing instead of or before a hereditary cancer syndrome diagnosis is made. Genetic testing is often part of the discussion of hereditary predisposition, but patients need to understand that the diagnosis of hereditary predisposition is not necessarily determined by genetic testing. The discussion should begin with the likely or possible diagnosis of a hereditary cancer syndrome and then logically move to confirmation and treatment.

The reason that the diagnosis of hereditary predisposition cannot be absolutely confirmed with genetic testing is that testing for HBOC and other cancer predisposition syndromes is not good enough. The tests still have too many false negatives to absolutely rule out the diagnosis in families whose history, like Connie's, is strong enough to make the diagnosis. Said differently, even if Connie's genetic test results do not reveal a deleterious mutation, Connie and her close relatives still should be considered at significantly increased risk and managed accordingly. The difficulty in not finding a deleterious mutation in a family is that differentiating who in the family is at the highest risk for cancer from those who are essentially at population risk cannot be done. Then, the question becomes how aggressively should at-risk family members, like Connie's sisters, be screened and whether preventive treatment is indicated. Is prophylactic surgery, such as that recommended by Dr. Swafford, appropriate for Connie's sisters if a mutation cannot be identified in the family? I cannot answer that here, but it should at least be considered and discussed. This illustrates how complex cancer risk assessment and evaluation quickly become.

Critique of the Genetic Testing Discussion

I would like to go back and critique Dr. Swafford's discussion with Connie regarding hereditary predisposition.

What was positive about the discussion?

- A lengthy conversation took place in a relatively quiet and uninterrupted space. Connie was sitting at an equal level with Dr. Swafford, she was completely clothed, and both were sitting in comfortable chairs around a small examination room desk.
- The significant family history was reviewed.
- Connie was instructed about her significantly increased risk for a second primary breast cancer or ovarian cancer.
- Connie was informed of the significant impact on not just herself but her entire family.
- Connie was told of the signed consent form requirement.
- Written educational information was provided.
- Connie was instructed about the length of time before results would be available.
- Dr. Swafford discussed how the results would be provided and offered a face-to-face follow-up visit.
- Connie was informed of the possibility of either a positive or negative result and the implications of each related to her risk management.
- Dr. Swafford was clear in the discussion about what she would recommend to Connie if a mutation was identified.
- The entire process was framed positively, regardless of test results.
- Connie was told that insurance coverage would be sought and probably obtained.
- Connie was offered the ability to postpone testing for another time.

This is a long list of positive features of the discussion, and sadly, much more than some patients are given. In fact, I cannot criticize the discussion except that Connie should have been referred to someone who could help her understand HBOC and the ramifications of genetic testing before testing was undertaken. That is where nurses come in. A nurse could talk to Connie, initiate a referral, or take care of her if the nurse is competent to do so. If a referral is not possible, then the nurse or Dr. Swafford have to do more.

What was missing in the discussion?

- The setting—we are all familiar with it—was not the best physical environment for a long discussion and not completely uninterrupted. A better setting would have been in a more private and comfortable area with no interruptions, but this setting was still satisfactory.
- Most importantly, Connie had no one to talk to before she went to the laboratory and had her blood drawn. No one accompanied her to her appointment, and she did not know anyone in the office well enough to ask for guidance—she had no one to even ask if she should wait and think about it more.
- Dr. Swafford reinforced the simplicity and the need to move forward with testing (which is not necessarily wrong in the right context), and Connie was appropriately offered a choice to postpone if she wanted to. But few patients will go against that implied pressure, especially from someone they trust so much.
- Connie had no time to read the written material. If all of the pertinent issues are not discussed in person, patients should at least be given the materials and an opportunity to read more. It was positive that she received reading material, but, obviously, Connie was not able to read through the material before proceeding.
- Connie signed a consent form but probably was not actually fully informed to give consent. Information in the consent form was not actually discussed. We are not sure if Connie even read the consent form.
- No discussion of the diagnosis of hereditary predisposition took place, just a discussion of genetic testing.
- Connie's or her family's prevention or surveillance options if testing was not done or if the findings were not informative were not mentioned.
- The likelihood of receiving uninformative results was not discussed. The possibility of receiving a "variant of unknown significance" result was not mentioned. This is one of the pieces in the consent form that was not addressed.
- No discussion took place on the details of the impact on the family. Connie was told that her sisters would benefit from testing, but the totality of impact was not explored. Connie had no way of understanding the possible outcomes of the testing without either time to figure it out on her own or being told. Her sisters and the entire family were mentioned, but did Connie understand what testing also meant for her brothers, nieces, and nephews, or even her father? How would Connie know that her father might react to the information with guilt or anger? Connie's father lost his wife to breast cancer, and one of his daughters has the same disease. Now Connie may tell him more directly who else is at significantly greater risk.
- Connie's husband and their children were not mentioned. Usually, patients' children will motivate them to either undergo or avoid genetic testing.

- Obviously, Connie had no time to discuss the HBOC diagnosis, testing, and its potential impact on her family before proceeding. This is one part of genetic testing that is so vastly different than any other kind of diagnostic or screening testing we have today. Connie's testing will tell us not only about Connie, but also about current, past, and future generations.
- The risk-management options were mentioned but not thoroughly explored. For example, does Connie know that removing her ovaries (described as a simple surgery) will put her into immediate menopause? Would Dr. Swafford recommend hormone replacement? Does Connie understand that this will become pertinent and a serious issue if she proceeds with prophylactic oophorectomy?

You may be saying to yourself, why think about all of this before genetic testing has even been done? You also may be saying to yourself, just like physicians have told me, that I am making the genetic testing process more complicated than it really needs to be.

Connie's Current Life

Remember the description of Connie's current life when she arrived at her appointment. Her life no longer revolved around her cancer diagnosis; she had moved on. She no longer had any resource people to turn to. Unlike breast cancer groups, communities rarely have support groups for high-risk individuals, let alone one that Connie could find. A wonderful Internet support group, called FORCE—an acronym for Facing Our Risk for Cancer Empowered (www.facingourrisk.org)—could help Connie, but how would she find that resource?

Is Connie ready for another intensive round of doctor appointments, second opinions, taking time off from work, and the process of tough choices and decision making? Unlike cancer, hereditary predisposition is something that does not need to be treated immediately, and it is not even something that people or families must deal with if they choose not to. As healthcare professionals, we may see the value of all of this for our patients, but we cannot live their lives or make decisions for them.

The Case Continues

You already know that Connie had her blood drawn on her way out of the office. Connie decided that because she would receive the results in about two months, and her whole family would be together for Thanksgiving, which was 12 weeks away, she would just talk about the genetic testing then, with the entire family at once. She did not discuss anything with even her closest sister.

Connie started to read the educational booklet about HBOC, but it made her too anxious to continue, so she put it away. She did not think that her husband would be thrilled with the idea of more surgery and treatments, and she really did not want to have to talk about it, so she chose not to even tell her husband about the testing. Essentially, Connie told no one about the genetic testing.

As the eight-week mark approached, Connie was surprised by her attention to the date and the phone ringing. She had mostly forgotten about it until week seven; then, getting her results was prominent in her thoughts. After week eight passed and she had not heard anything, she told herself that the testing was just taking longer than the doctor thought. She would try to be patient and forget about it again.

That did not happen; the testing remained prominent in her mind until the phone call came. It was 10.5 weeks after she had her blood drawn and a Friday afternoon when she received her results. As Connie feared, her results were positive. Connie felt sick to her stomach, but Dr. Swafford seemed pleased with the results, which helped her feel better. Dr. Swafford kept the conversation short and transferred Connie so that she could make an appointment to come in and talk more about the surgery and what else needed to be done. All Connie had before her appointment with Dr. Swafford, which would not occur for two weeks, was the booklet that she had been given.

Fast Forward to the Present, Three Years Later

Connie and all three of her sisters are carriers of the same deleterious *BRCA2* gene. Connie had a total hysterectomy and bilateral salpingo-oophorectomy the summer following her testing. After seeing several doctors and getting numerous opinions, she decided to take estrogen replacement beginning immediately following her surgery.

Before her hysterectomy, Connie had a mammogram with normal results. She also had bilateral magnetic resonance imaging because of her confirmed significantly increased risk. The radiologist detected something in her unaffected breast. The consensus was that it did not represent a cancer, but no one could be sure. A biopsy was not possible because the abnormality could not be visualized by ultrasound or mammography, and magnetic resonance imaging-guided biopsy was not available at the time. Connie could not live with that uncertainty, especially in the face of her significant risk of another breast cancer, so she decided to have bilateral mastectomies with immediate breast reconstruction.

Connie's husband turned out to be very supportive and, in fact, wanted her to be as aggressive as she could be to save her life. But Connie believed that it changed their relationship in a way that was difficult for her to articulate. Connie expressed that her positive test results were a huge burden on her immediate family for about two years.

Connie's now-14-year-old daughter coped very well during Connie's cancer treatment but did not do as well with Connie's preventive surgeries. Connie put her daughter in counseling to assist her in coping. Her daughter thought that Connie was not being truthful about undergoing all of the surgery preventatively, and she was fearful that her mom had cancer again. Connie's daughter also was just going through puberty and would say that she did not want breasts. She wished she could just have her breasts removed.

I know, now you are thinking, "Our patients don't have this much trouble with all of this." "Our patients do really well with it all." Actually, no one would have ever known Connie was struggling with all of these issues without asking. Outwardly, she appeared to be the perfect patient and was coping beautifully. She did not decompensate, she did not become nonfunctional in any way, and she never missed work, lost friends, or severed family relationships as a result of the high-risk identification process. She never gained or lost weight, she was always impeccably dressed when she came for appointments, and she did not start drinking alcohol excessively or taking drugs of any sort. Connie only rarely called with questions or asked for help from the office. How do we really know how well our patients cope? Do you ask, and do you give them time to answer?

All three of Connie's sisters also chose to have prophylactic oophorectomies, total hysterectomies, and bilateral mastectomies. One of her sisters had numerous problems with hormone deprivation following her oophorectomy. That sister chose not to take estrogen because her doctors said it was not safe. Another sister had postoperative complications with her breast reconstruction. As close sisters will when they get together, they all undressed and compared their breasts. All of the sisters agreed that Connie's breasts looked the best and were the "perkiest." Connie's closest sister had the most complications and said on several occasions that she wished she had not had the bilateral mastectomies. Imagine how Connie must feel when she hears that or when she sees that her physical outcome was better than her sisters' outcomes.

None of Connie's four brothers has undergone genetic testing. One of Connie's nieces, the daughter of Connie's oldest brother, is in her late 20s and, Connie was told, at an age where she should begin breast screening and possibly other risk-reduction actions. Connie does not know whether she should bypass her brother and speak directly with her niece and encourage her to undergo testing. Fortunately, Connie remains in complete remission, and no one else in the family has been diagnosed with cancer.

Lessons Learned

Is Connie's story tragic? No. Would Connie and her family have done things differently if Connie was better informed about HBOC? Who knows? What could a referral to cancer genetic experts or even you knowing more about all this and intervening with Connie accomplish? I am obviously biased, but a long list of interventions partially includes

- Further explanation, leading to a better understanding of HBOC syndrome
- Time to discuss and inform family members of the potential impact to them. This would help Connie know where to get support and where the land mines in the family are.
- A plan for her own children
- A list of other women who are gene carriers with whom she could connect

- Someone to talk to who would not minimize the impact all of this has on her and her family
- Someone who acknowledges her guilt and helps her cope with it effectively
- Someone who could acknowledge and inform Connie about the meaning of her family's behavior, such as her father's guilt or her brothers' denial.
- A long-term resource for her as new issues arise related to hereditary predisposition.

Connie's family is actually easy compared to some others I have worked with. Connie was close to and spoke with all of her siblings and cousins. The family was as functional as any family can be. They obviously had financial resources to obtain second opinions, take time off from work, and consider prophylactic treatment. The family had no multiple marriages, estranged family members, children with unknown fathers, kids adopted out of the family, family members marrying other family members, unidentified paternity (in other words, the father is not the father), and the list goes on. These are all the issues that may arise when the family, not just the individual, is your patient.

Please be the nurse who identifies and takes care of high-risk patients and families. Be the nurse at the wall, helping patients and colleagues over and past the wall to get their caps. Go home and find the experts you need to refer to, learn from, and work with. Help your physician partners know that the complex issues must be addressed and considered. None of this is as simple as it seems, but it could possibly save the most lives.

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