

Family history impacts patient care: how to recognize genetic risk

Joy Larsen Haidle, MS, CGC | Hubert H. Humphrey Cancer Center, Robbinsdale, MN

As the number of genetics tests and the demand for genetic services continue to grow, community oncologists will play an increasingly important role in accurately documenting family histories and triaging the appropriate patients into a cancer genetics specialty clinic. Patients with increased cancer risk, by virtue of either family history or the presence of a documented genetic mutation, are often initially identified in the community oncology setting. This is not a scenario reserved for the large academic medical centers. Instead the question becomes: Is genetic predisposition to cancer recognized? It is worthwhile to become well versed in cancer genetics, as genetic counseling assumes a greater part of the patient's care and cancer treatment plans. As genetic technology continues to advance, it will be important to identify qualified individuals for genetic counseling services in your area and use them. High-risk individuals can be helped by increased surveillance, chemoprevention, and risk-reduction options, which make family history assessment worth the effort.

Patients and their families are becoming more aware of the importance that family medical history plays in predicting their future health. As the number of genetic tests and the demand for genetic services continue to grow, community oncologists will play an increasingly important role in accurately documenting family histories and referring appropriate patients to clinics that specialize in cancer genetics.

A common problem faced by most healthcare providers is the limited amount of time they have to spend on each patient visit. Family history is often briefly documented, but it is difficult to factor its significance into a visit scheduled for a different purpose. When is the right time to elicit and discuss a patient's family history? At the time of cancer diagnosis? When the patient informs you a relative has been diagnosed with cancer? After the patient has received chemotherapy or radiation? Does the information obtained from a family medical history factor into the patient's treatment plan or perhaps the initial surgical decision? What pieces of information are important to triage patients and accurately assess their cancer risk? If a patient is referred for genetic counseling, what will happen during that appointment, and what information will be collected that is clinically relevant to the patient's care plan?

Patients with increased cancer risk, by virtue of either family history or the presence of a documented genetic mutation, are often initially identified

in the community oncology setting. This is not a scenario reserved for the large academic medical centers. Instead the question becomes: Is genetic predisposition to cancer recognized? Here is one family's story:

Tumor pattern offers telltale signs

In the early 1970s, a 25-year-old man collapsed suddenly and died, leaving behind four young children. On autopsy, bilateral pheochromocytomas and metastatic medullary thyroid cancer were found, and death was attributed to a catecholamine crisis. His physician recognized that this pattern of tumors might have a hereditary basis and suggested that other relatives could be at increased risk and should be screened. The family was told that this young man's siblings should undergo screening for the tumors, which they did on one occasion.

Twenty-five years later, his son collapsed and died en route to the hospital. He had a long history of bowel complaints, hypotonia, and poor coordination. An autopsy was performed. He, too, was found to have bilateral pheochromocytomas and metastatic medullary thyroid carcinoma. The autopsy report described a tall man with a pectus exca-

Manuscript received November 4, 2004; accepted December 2, 2004.

Correspondence to: Joy Larsen Haidle, MS, CGC, Genetic Counselor, Hubert H. Humphrey Cancer Center, 3300 Oakdale Avenue North, Robbinsdale, MN 55422; telephone: 763-520-3815; fax: 763-520-1976; e-mail: joy.larsen.haidle@northmemorial.com

Commun Oncol 2005;2:39-44 © 2005 Elsevier Inc. All rights reserved.

vatum, long fingers, full nodular lips, and a unilateral everted eyelid and neuroma. The pathologist suggested that the young man had multiple endocrine neoplasia type 2b (MEN2b) and recommended that his siblings and offspring be screened. The family was self-referred to genetic counseling 5 years later, when a sibling became concerned that one of his own children had features that resembled those of his brother and father. A review of the father's medical records revealed findings that were highly suspicious for MEN2b as well.

Although the term MEN2b had not been coined, parent-to-child transmission of this collection of tumors had been described in the literature as early as 1968.¹ The family had not been told to screen the offspring in the early 1970s. At the time, it was not known how often or what kind of screening would be appropriate in this setting, as the understanding about this disease was just beginning to evolve. The question weighing heavily on the family's mind was—why had the children not been screened for the collection of health problems that led to their father's demise?

As a result of advances in medical genetics, DNA testing is now available for MEN2b. DNA testing of the brother's normal tissue in a paraffin block remaining from the autopsy confirmed the diagnosis of MEN2b when the common mutation in the *RET* gene associated with MEN2b was identified. DNA testing could then be offered to the surviving siblings. None of them was found to have the *RET* mutation, and their children were no longer deemed to be at risk. Although tragedy had struck this family twice, the lessons learned from their story are invaluable.

This family could have presented to any community clinic. The collection of tumors in the father is characteristic of what is now a well-defined syndrome. Although rare, MEN2b can have significant and serious med-

ical results and must be monitored from the newborn period onward to offer the best long-term outcome. Although pheochromocytomas can occur sporadically, they are known to be associated with a hereditary predisposition, as is medullary thyroid cancer. Medullary thyroid cancer is the least common of the thyroid cancers and can be associated with mutations in the *RET* proto-oncogene, regardless of family history. Therefore, tumor type alone may be sufficient to raise suspicion of hereditary predisposition, even if there is not a family history of other cancers. Table 1 lists tumors known to be associated with a hereditary predisposition and includes many common cancers; further investigation is warranted in these cases, regardless of the family history.²

The other key features of MEN2b are physical characteristics. Individuals with MEN2b have a disproportionately tall, thin build that resembles Marfan syndrome. Often, an individual will have a pectus excavatum, full nodular lips, and eversion of the eyelids. Even newborns with MEN2b can have neuromas on the eyelid. To the family described here, the son resembled his father, and family members did not suspect that his health history was related to his father's condition. To the clinician, the physical appearance and family

TABLE 1

Tumor types that should prompt genetic referral regardless of family history

- Medullary thyroid cancer
- Retinoblastoma
- Paraganglioma (carotid body tumor)
- Cerebellar hemangioblastoma
- Pheochromocytoma
- Adrenocortical carcinoma
- Wilms' tumor
- Male breast cancer
- More than 10 colonic polyps
- Lhermitte-Duclos disease
- Acoustic neuroma

TABLE 2

Questions to elicit a cancer family history

All patients

- Age
- Routine medical history questions
- Biopsy history
- Personal history of benign or malignant tumors
- Organ removal/surgery
- Reproductive history
- Environmental exposures/risk factors
- Ethnicity

Individuals with a cancer diagnosis

- Age at cancer diagnosis
- Primary cancer diagnosis
- Number of tumors
- Pathology characteristics of tumors or hospital where treated to obtain medical records
- Treatment plan
- If deceased, the age at death and cause

Adapted from Trepanier et al³

history should initiate additional investigation and a referral to a cancer genetics program. Although some cancer predisposition syndromes have characteristic physical features, such as dermatologic changes or characteristic pigmentation patterns on the oral mucosa, face, and hands, several of the common cancer predisposition syndromes, such as BRCA1/2 and hereditary nonpolyposis colorectal cancer (HNPCC), do not have associated physical findings. Therefore, the clinical impression of physical features can provide helpful insight for further evaluation, but normal physical features do not necessarily rule out a hereditary predisposition.

Family history, family patterns

To fully stratify patients into a risk category, detailed personal and family histories should be obtained. The pedigree should span at least three generations. Table 2 reviews the information to be collected on each relative.³ Questions should be asked

regarding the number, age, and gender of the patient's offspring, siblings, and maternal and paternal aunts/uncles and their offspring. Information should be reviewed about the patient's parents and maternal and paternal grandparents. This level of detail will help determine the number of at-risk relatives and provide an impression of the family's level of risk.³ Families that are small or are mostly male may be uninformative to assess breast cancer risk. In this setting, the family may present with a single woman diagnosed with breast cancer at a young age. Although a family history may be absent, the young woman may still have a reasonable likelihood of a *BRCA1/2* mutation, and DNA testing may still be valuable. This level of detail will also capture most families with a hereditary colorectal cancer risk.

Gathering the family history is the first step, but determining its significance is the greater challenge. The patterns evaluated in the pedigree include multiple people in the family with the same or a related type of cancer (see Table 3), early age of onset (usually < 50 years of age), multiple primary tumors in the same individual, bilateral tumors in paired organs, presence of a rare tumor or a tumor in an individual who is typically not thought to be at risk (eg, male breast cancer or lung cancer in an individual without known exposure to environmental carcinogens), and/or an ethnic background known to have an increased gene carrier frequency or founder mutations (Ashkenazi Jewish, Icelandic). The cancers should occur in a cluster on one side of the family, and both the maternal and the paternal branches of the family should be addressed. Three of any given tumor type in a single branch of the family, in the absence of traditional risk factors, should be considered a high-risk cluster and evaluated by a cancer genetics specialist.

Although triage mechanisms vary

TABLE 3
Recognizable patterns of cancer and their associated syndromes

Cancer or tumor type	Syndrome
Colon/uterine/ovarian	Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome
Breast/thyroid	Cowden syndrome
Melanoma/pancreas	Hereditary melanoma (<i>CDKN2A</i>) ^a
Breast/ovarian	Hereditary breast and ovarian cancers (HBOC) (<i>BRCA1</i> or <i>BRCA2</i>)
Renal cell carcinoma/central nervous system	von Hippel-Lindau syndrome
Medullary thyroid cancer/pheochromocytoma	MEN2a or MEN2

^a *CDKN2A* = cyclin-dependent kinase inhibitor 2A

around the country, Hampel et al have proposed a comprehensive and valuable set of criteria, including guidelines to help stratify patients into a risk category and an explanation of when and how to use the common risk-assessment models to determine cancer risk.² These characteristics are summarized in Table 4. Patients who meet these criteria due to a personal history, family history, or a combined personal/family history would benefit from a consultation with a genetics professional.

Genetic counselors possess a unique skill set that facilitates patient education, and their understanding of complex molecular and genetic information, combined with counseling skills, is invaluable in assessing

TABLE 4
Characteristics of hereditary cancer predisposition

- Bilateral cancer in a paired organ
- Early age of onset (< 50 years)
- Multiple primary tumors in an individual
- Multiple people in the family with the same or related tumors (all on one side of the family; maternal or paternal)
- Cancer in a person not thought to be at risk or absence of known environmental exposures
- Presence of a rare tumor
- Ethnic background with high gene carrier frequency or known founder mutations
- Three of any given tumor type in one branch of the family

and addressing psychosocial issues. The genetic counselor will obtain a detailed family history, usually spanning three to four generations, and verify the history in key relatives with medical records whenever possible.³ The documentation of family history, tumor type, and age of onset is extremely important for an accurate risk assessment. The patient should receive a formal risk assessment that addresses the likelihood of developing a given cancer based on the individual and family histories, the likelihood of a gene mutation causing the cancers within the family, and recommendations for appropriate genetic testing strategies. This complex information must be presented in a meaningful way, as it is often an emotionally charged conversation, because the information not only impacts the individual but also the family. If the patient chooses to proceed with DNA testing, the genetic counselor should identify a reputable laboratory, obtain informed consent, and facilitate testing on the patient's behalf.³

All of this information should be communicated to the primary care physician, as the patient will often return to his or her physician for additional discussions about management decisions and the physician's opinions about testing. The genetic counselor will also interpret the test results in the context of the family history, offer enrollment of the patient into an

appropriate genetic research study if clinical testing is not available, and provide a review of the literature summarizing the surveillance strategies for a given diagnosis. The genetics team will provide the consultation and serve as an ongoing resource, as the knowledge and utility of cancer genetics are changing rapidly.

Cancer genetic counselors historically worked at major academic centers. However, a recent survey has shown that more cancer genetic counselors are working in the community setting.⁴ Several organizations will help locate qualified genetics professionals, including the National Society of Genetic Counselors, GeneTests, the American Society of Human Genetics, and the American College of Medical Genetics (see the box "Resources on the Web").

Waving the red flag

Although MEN2b is rare, the following two cases are much more likely to present in the routine community oncology setting. A 35-year-old woman presents with rectal bleeding 4 years after a normal colonoscopy. Colonoscopy was recommended to her every 5 years because she had a family history of colon cancer. A review of the family history prior to her own colon cancer diagnosis showed a sister who had been diagnosed with colon cancer at 25 years of age and a new colon primary at 32 years. Her father was diagnosed with colon cancer at the age of 46 years. Her paternal uncle was diagnosed with colon cancer in his 40s and again at 60 years.

This family history meets the Amsterdam criteria for consideration of a diagnosis of HNPCC or Lynch syndrome. The American Gastroenterologic Association and the American Cancer Society guidelines are meant for an individual at moderate cancer risk due to a first-degree relative with colon cancer. They are not intended for persons at high hereditary risk.^{5,6} This young woman's family history

suggests that she would benefit from high-risk surveillance, which includes a colonoscopy every 1–2 years until the age of 40 years and then annually after 40 years and an upper endoscopy, in addition to screening for uterine and ovarian cancer. This was a potentially preventable cancer if the appropriate screening had been done (Figure 1).

A 36-year-old woman was diagnosed with stage IV breast cancer after years of requesting a mammogram due to a strong family history of breast cancer. She had a nonpalpable breast tumor and presented with a lump in her neck. Mammograms had not been ordered, under the guise that she was not at increased risk because the history was on her father's side.

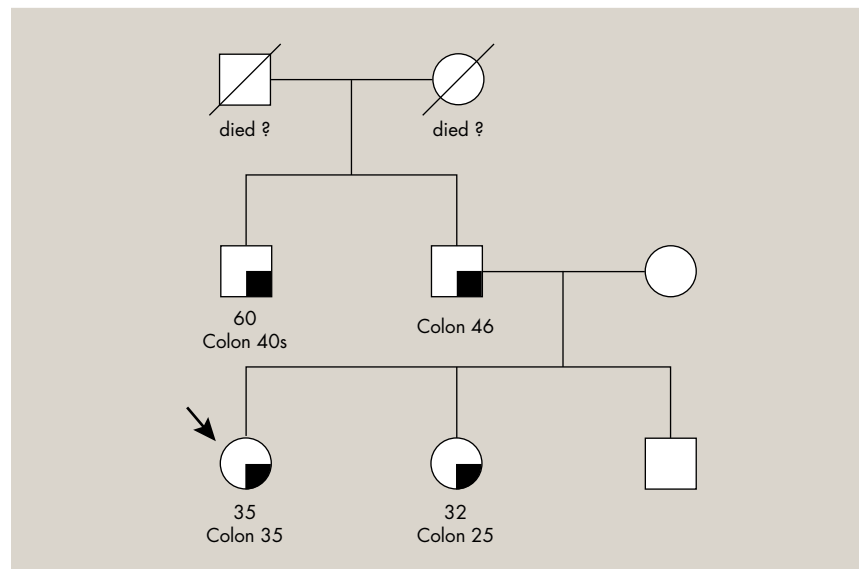


FIGURE 1 Pedigree of a three-generation family with a history of hereditary nonpolyposis colorectal cancer (HNPCC). The proband (index case) is arrowed.

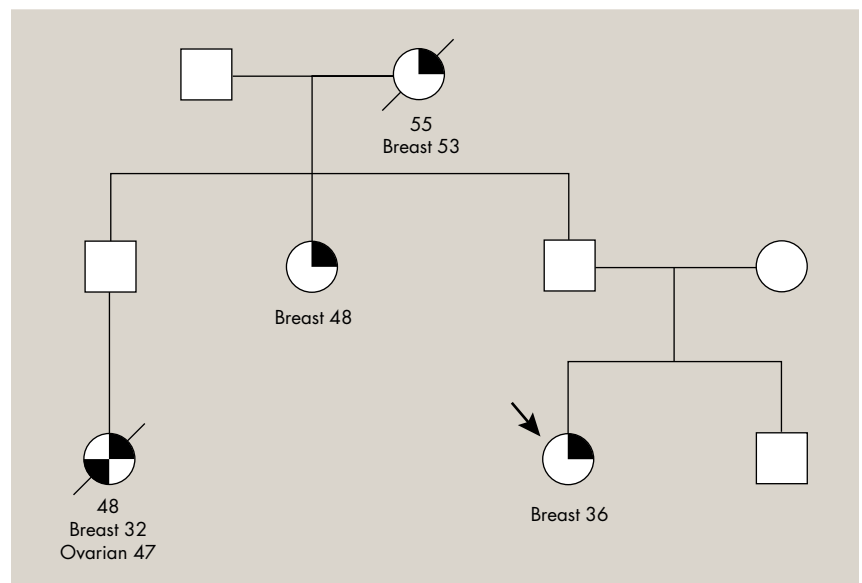


FIGURE 2 Pedigree of a three-generation family with a history of breast cancer due probably to inheritance of a *BRCA1* or *BRCA2* mutation. The proband (index case) is arrowed.

The father's family met the criteria for a hereditary predisposition and had a strong likelihood of a *BRCA1* or *BRCA2* mutation (Figure 2).

These cases exemplify several points. The first case reviews the classic criteria for hereditary risk of HNPCC and demonstrates the need for heightened surveillance. The second case demonstrates that hereditary risk can come from either side of the family. The father's family history is equally important to assess in the breast cancer setting. Contrary to common myth, it does impact risk.

When to refer

Genetic testing would be beneficial in both of these families, but when is the right time to refer the patient? The first patient described here might benefit from an immediate cancer genetics referral, as surgical decision-making may be impacted by the results of genetic testing (in some instances, it is possible to receive rapid test results). For example, if she was found to have HNPCC, she might wish to consider a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) at the time of the tumor resection.

The medical management of the woman described in the second case may not be altered by DNA testing, because she has stage IV disease. However, she is an ideal candidate to pursue DNA testing, as her test results may impact the medical management of her relatives. In some cases, a woman may consider a bilateral mastectomy and/or risk-reducing TAHBSO if she was found to carry a *BRCA1* or *BRCA2* mutation. If the results of the testing would impact the patient's surgical decision, an immediate referral is recommended. If the results of DNA testing might impact the long-term management of the patient or management of the patient's relatives, then referral when the treatment is complete may be appropriate.

Referral in the end-of-life setting

is a challenge for all involved, but patients are often worried about their surviving relatives and may benefit from the consultation by documenting their family history and banking a sample of DNA for future use by relatives.

To test or not to test?

The American Society of Clinical Oncology issued a policy statement on genetic testing.⁷ Genetic testing is appropriate when the patient has a personal or family history suggestive of a hereditary predisposition, a test exists that can be adequately interpreted, and the result of which will impact the medical management of the patient or the patient's relatives.

Genetic testing is most useful when an affected relative is tested first and a mutation is identified. In this setting, accurate and relatively inexpensive DNA testing is available for at-risk relatives to determine their degree of risk. DNA testing is available, too, for some conditions in which the benefit gained from the testing is limited, as medical management will not yet differ based on the test results. Testing of children should not be done for adult-onset conditions. Genetic testing of children is typically reserved for conditions in which medical management will change prior to the age of 18 years, such as retinoblastoma, familial adenomatous polyposis, MEN2a, MEN2b, and von Hippel-Lindau syndrome. Several position statements exist on the appropriate use of genetic testing in childhood.^{8,9}

Why put so much effort into stratifying families into risk categories of high, moderate, or average risk? The answer is simple—it saves lives and it saves unnecessary surveillance/expense for those who are not at increased risk of developing cancer based on DNA testing and those whose cancer risk is much less than their perceived risk. If one individual is identified, then an entire family unit can benefit from increased cancer

Resources on the Web

American Board of Genetic Counseling
Web site: www.abgc.net

American Board of Medical Genetics
Web site: www.genetics.faseb.org/genetics/abmg/abmgmenu.htm

American College of Medical Genetics
Web site: www.acmg.net

American Society of Human Genetics
Web site: www.genetics.faseb.org/genetics/ashg/

GeneTests
Web site: www.genetests.org

National Cancer Institute
Web site: www.nci.nih.gov/search/geneticsservices/

National Society of Genetic Counselors
Web site: www.nsgc.org

surveillance and/or appropriate DNA testing to determine which members are not at increased risk of developing cancer. Family history is a cost-effective screening tool to help determine the risk category. Referral to a genetic counselor or cancer genetics program is a cost-effective method to evaluate the patient/family with DNA testing and assess the surveillance needs of the individual.^{10,11}

Because of the increasing availability of information and education about cancer genetics, primary care providers are becoming more comfortable caring for individuals with common genetic conditions. However, consultation with and referral to a medical geneticist continues to occur regularly in situations where rare, complicated, or unknown diagnoses exist. Currently, high-risk breast and ovarian cancers (HBOC) are primarily seen in the cancer genetics clinics for evaluation. In time, HBOC will likely move

to the community oncologist for surveillance and risk-reduction/management, as HBOC will likely become a “common” occurrence and not perceived as a “rare” one.

It is worthwhile to become well versed in cancer genetics, as genetic screening and DNA testing will become a greater part of the patient’s care and cancer treatment plans. The community oncologist will need to recognize hereditary cancer patterns and be prepared to discuss surveillance for all cancers in the tumor spectrum if the treatment plan, surgical decisions, and other aspects of a patient’s care are affected. (For example, some patients predisposed to cancer need to avoid radiation therapy, such as those with *p53* mutations and those with Gorlin syndrome.) At this time, it is important to step back and look at the patient and the family medical history as a whole, in addition to focusing on the characteristics of the current cancer. Long-term planning will pay off in improving quality of life, satisfaction with treatment, and perhaps compliance with surveillance for both the patient and family members.

Family histories are dynamic. The history must be reviewed at regular intervals to identify components that elevate the suspicion of a hereditary cause to the cancer or components that suggest that surveillance recommendations should be reconsidered based on new information. The family history will help guide surveillance for moderate-risk patients, identify

high-risk individuals, and may offer reassurance to those at average risk.

Conclusion

The ability to identify individuals and families at increased cancer risk is a valuable skill set that is becoming a necessary component of patient care. DNA testing impacts patient care, and the testing options are expanding rapidly. DNA banking is a valuable resource for families that will allow them to pursue testing when technology fits their needs. The timing of the referral to a cancer genetics specialist will vary by provider and the patient’s situation. As technology continues to advance, it will be important to identify qualified individuals for genetic counseling services in your area and use them. High-risk individuals can be positively impacted by increased surveillance, chemoprevention, and risk-reduction options, which make family history assessment worth the effort.

Acknowledgments: The author would like to thank Jade Anderson, MD, and V. Kim Norton, RN, MS, CGC, for their careful review of the manuscript.

References

1. Bartlett RC, Bean LR, Mandelstam P. Hereditary study of neuroendocrine dysplasia in six generations [abstract]. *Int Assoc Dent Res*, San Francisco 36, 3/1968.
2. Hampel H, Sweet K, Westman JA, et al. Referral for cancer genetics consultation: a review and compilation of risk assessment criteria. *J Med Genet* 2004;41:81–91.
3. Trepanier A, Ahrens M, McKinnon W, et al. Genetic cancer risk assessment and counseling: recommendations of the National Society of Genetic Counselors. *J Genetic Couns* 2004;13:83–114.
4. National Society of Genetic Counselors. Professional status survey 2002: Cancer genetics analysis. 2003:1–8. Available at: http://www.nsgc.org/pdf/PSS_2002_addendum.pdf. Accessed November 8, 2004.
5. Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. *CA Cancer J Clin* 2001;51:38–75.
6. Winawer S, Fletcher R, Rex, D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. *American Gastroenterological Association. Gastroenterology* 2003;124:544–560.
7. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 2003;21:2397–2406.
8. McKinnon W, Baty B, Bennett R, et al. Predisposition genetic testing for late-onset disorders in adults: a position paper of the National Society of Genetic Counselors. *JAMA* 1997;278:1217–1220.
9. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. *Am J Hum Genet* 1995;57:1233–1245.
10. Murff HJ, Spigel DR, Syngal S. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. *JAMA* 2004;292:1480–1489.
11. Balmana J, Sanz J, Bonfill X, et al. Genetic counseling program in familial breast cancer: analysis of its effectiveness, cost, and cost-effectiveness ratio. *Int J Cancer* 2004;112:647–652.

In a future issue, Ms. Larsen Haidle will discuss the psychosocial issues associated with genetic testing and genetic risk assessment.

ABOUT THE AUTHOR

Joy Larsen Haidle, MS, is a certified genetic counselor with the Hubert H. Humphrey Cancer Center, Robbinsdale, MN.