



Genetic Risk

Steps you can take if cancer runs in your family

MANY CANCERS begin as a fluke mutation in a single cell, but in about 10 percent of cancer cases one or more mutations wind their way through some family trees, with about a 50-50 chance of striking each new member. When mutations are deemed hereditary, they are present in every cell, including egg and sperm, and can thus be passed to offspring.

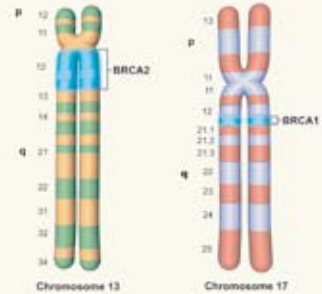
Each person has 46 chromosomes—23 from each parent—which contain 25,000 to 30,000 genes. These chromosome pairs allow for a backup, so a mutated gene's healthy counterpart can code for the correct protein. For cancer to develop, both copies of the gene must be mutated.

Inherited mutations will only make a person susceptible to cancer. Unfortunately, because the mutation is in every cell, the healthy gene will need to mutate in only one cell to jump-start cancer or lose the ability to suppress cancerous mutations from occurring in other genes. Because we are constantly bombarded with carcinogens (cancer-causing substances) and DNA-damaging substances, the probability of a second mutation is high.

Cancer Genes >

GENETIC TESTING is now available for dozens of hereditary cancer syndromes, most of which are caused by alterations in genes that suppress tumor growth.

TO DATE, the most commonly requested test is for **BRCA1** and **BRCA2**. Alterations in these two genes predispose individuals to breast, ovarian, and other cancers. Although these mutations can affect people of any race or ethnicity, they are found more frequently in families of



Ashkenazi Jewish descent. Among female carriers, BRCA alterations may confer a lifetime breast cancer risk of up to 85 percent (though new research suggests breast cancer risk varies among families and may only be as high as about 50 percent) and an ovarian cancer risk of up to 50 percent. Male carriers also have increased risk for breast, prostate, and other cancers.

Other frequently used genetic tests are for two colon cancer syndromes: **hereditary nonpolyposis colon cancer (HNPCC)** and **familial adenomatous polyposis (FAP)**. Both syndromes are associated with a high risk for colon cancer (80 percent and virtually 100 percent, respectively) and other cancers.

Recently, several familial syndromes have been linked to kidney cancer. In von Hippel-Lindau disease, patients inherit a defect in a specific gene called the **von Hippel-Lindau gene**, though people without the inherited disease can also have problems with the VHL gene. The VHL gene is a tumor suppressor gene, so inactivation of the gene can cause up to 80 percent of all sporadic (non-hereditary) clear-cell renal cell carcinomas, the most common type of kidney cancer. These discoveries provided researchers with a specific target for developing therapies to treat kidney cancer.

For those who test positive for a genetic mutation, increased screening is needed. Some patients may also consider chemoprevention strategies to help lower their risk of second cancers or recurrence. In other cases, cancer may be prevented altogether using prophylactic (preventive) surgeries. **■**

ILLUSTRATION BY ERIN MOORE

These inherited gene mutations can't be repaired—though such a repair is the hope for gene therapy of the future—but they can be found. Genetic testing requires little more than a simple blood draw, but learning about one's genetic status may open a Pandora's Box of personal and familial issues. For this and other reasons, the American Society of Clinical Oncology (ASCO) recommends testing be done only within the context of genetic counseling.

Genetic counselors help you decide whether to undergo genetic testing, and can help you understand your genetic testing results and put them into perspective. Counselors also facilitate communication within families, and though test results are delivered on an individual basis, seeing members together for the initial counseling can be helpful. Working with genetics professionals, you and your family can explore the possible consequences of genetic testing and develop realistic expectations of what may or may not be learned in the process.

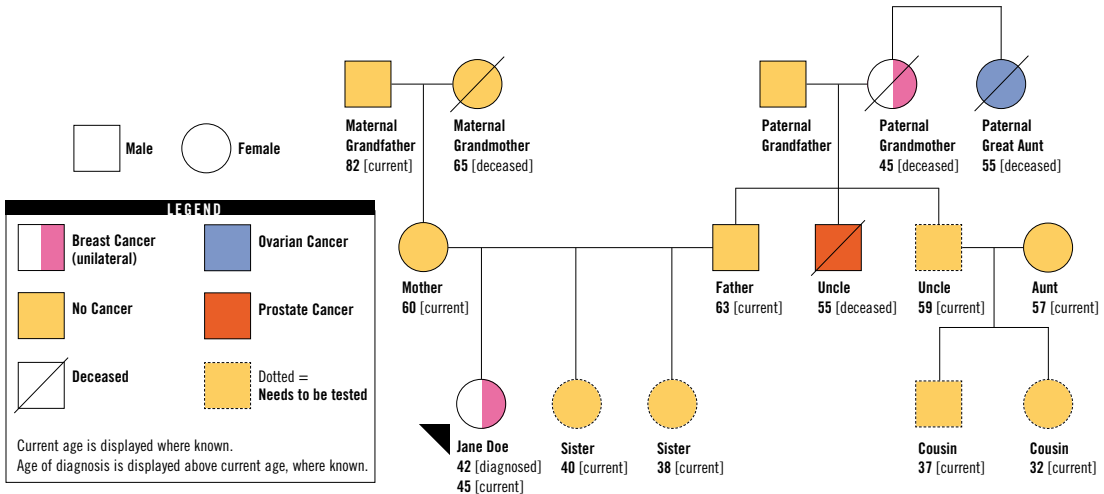
You may be an appropriate candidate for genetic testing if you have one or more of the following:

- ▶ Early-onset cancer (usually under age 50 for adult-onset syndromes)
- ▶ More than one cancer diagnosis
- ▶ A strong family history of cancer or the presence of rare cancers, such as male breast cancer and fallopian tube cancer

The details of what constitutes “early-onset” or “strong family history” will vary according to the type of cancer in your family or the specific gene being considered. A pedigree is created based on family history of cancer to determine who will most likely

FAMILY PEDIGREE FOR JANE DOE

GENETIC COUNSELORS work with patients to develop a **pedigree of family relationships** that uses lines and symbols to create a visual diagram of links among a family of a genetic disease, such as cancer.



benefit from genetic testing (see graphic).

Testing provides information that either confirms high-risk status or rules out the presence of a genetic alteration found in other family members. If you test positive, increased screening may detect cancer at an early stage when treatment is most effective, and may even allow you to avoid aggressive treatments like chemotherapy. In other cases, cancer may be prevented altogether using prophylactic (preventive) surgeries. Because gene alterations often predispose individuals to many types of cancer, identifying genetic status early can drastically affect long-term outcomes.

Some people who fit the criteria reject genetic testing for fear of genetic discrimination. But a number of laws, including the Americans with Disabilities Act, provide some protection regarding health insurance coverage and employment. Genetic testing is now available for dozens of hereditary cancer syndromes (see sidebar, page 91), most of which are caused by alterations in genes that

suppress tumor growth. The cost of genetic testing ranges from a few hundred to several thousand dollars, depending upon the number of genes tested and the number of sites analyzed within a given gene. For appropriate candidates, insurance often covers most or all of the cost of genetic testing.

But not everyone suspected to have a genetic mutation should necessarily have a test. If the results wouldn't alter your medical course—for example, if the gene raises risk of a disease with no reliable screening method or effective treatment—then the knowledge is of little benefit. In 2003, ASCO laid out three terms to be met before health providers offer genetic testing: a personal or family history suggestive of a genetic susceptibility; a test that can be adequately interpreted; and a result that will aid in diagnosis or medical decisions.

If genetic counseling is right for you, visit the National Cancer Institute's website at www.cancer.gov/search/genetics_services to find a genetic counselor in your area. **C**