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Gene Sleuth

Kevin Cool
Colby College

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gene sleuth

PATRICIA DAVIS MURPHY '68
TRACKS DOWN A CANCER-CAUSING
GENETIC MUTATION

BY KEVIN COOL

Patricia Davis Murphy's sister, Barbara, was 21 years old in 1974 when she was diagnosed with ovarian cancer. Three years later, she was dead. Murphy '68, who had two small children of her own, cared for her sister after her second surgery at Thanksgiving 1976, enduring the pain of her decline and eventual death and the frustration of a family blind-sided by a disease they assumed they had no reason to fear. She wanted answers.

"I decided that I would go into human genetics and that I was going to find out the basis of her disease," Murphy said. "It was a way of coping."

Barbara's death still tugs at Murphy; if only she knew then what she knows now perhaps her sister's life could have been extended. Murphy believes Barbara inherited a mutation of BRCA1, a cancer-fighting gene that checks the growth of tumors. A quarter century after burying her younger sister, Murphy is busy saving the lives of persons carrying those mutations.

Until recently scientists could only guess whether cancer was inherited, and there was no reliable method for testing persons whose family histories suggested they might be candidates for the disease. That changed when Murphy's research team two years ago made a revolutionary breakthrough. At Oncormed, a Gaithersburg, Md., company that develops and provides gene-based diagnostic and information services, Murphy headed the team that developed a process of testing for gene mutations that can lead to breast, ovarian and prostate cancer.

Murphy's work capitalized on previous research that had mapped some of the human genome. BRCA1 and BRCA2, identified in the mid-'90s, are genes that produce proteins that are important for the normal function of cells. A mutation in either of these genes can alter the protein and degrade its ability to fight tumors. The risk that a woman with a mutated BRCA1 gene will develop breast cancer can be as high as 87 percent, according to Murphy. Risks for ovarian cancer also are high in women with this genetic mutation, and men who have the mutation are at higher risk for prostate and colon cancer.

Murphy's team wanted a way to check BRCA1 genes for irregularities that might indicate a predisposition for cancer. They first had to figure out what a normal BRCA1 gene looked like—the sequence of "code" in a gene's DNA that can tell a scientist whether the gene is correct or flawed. This required isolating the DNA, then interpreting its biochemical structure. Their data allowed Murphy and her team to produce a blueprint of a healthy BRCA1 gene in the spring of 1996. Now, by comparing the profile of the normal BRCA1 gene with a patient's BRCA1 gene—taken from a blood sample—geneticists could identify mutations that signaled a risk of cancer. Murphy was thrilled.

"I knew this was going to save people's lives," she said.

Perhaps conditioned by the dark science-fiction fantasies of human engineering run amok or the macabre prospect of precisely replicated "Super People" populating the world, the public's conception of genetic research may be somewhat skewed, particularly following the successful cloning of sheep last year. That uneasiness may be understandable but should not inhibit potentially life-saving advancements in unlocking genetic secrets, Murphy says. Nor, she says, should it prevent companies from patenting their discoveries.

U.S. patent number 5,654,155 has Murphy's name on it; the correct sequence of the BRCA1 gene is a protected piece of property, part of the brave new world of genetic research. Unsettling? Only to those whose understanding of patents is limited to material inventions, says Murphy.

"The reason you patent something like this is so that there is a standard in the field that everybody can use," she said. "You must have zero tolerance for errors because patients will make decisions—whether to have prophylactic surgery, whether to have kids—based on the information they get." Murphy and Oncormed made the information available to the medical community to prevent sloppy clinical diagnosis of hereditary cancers, she says.

Murphy concedes that obtaining patents to secure proprietary rights to genetic information is controversial and that in the wrong hands genetic patents could delay positive scientific advancements. But patents allow companies to pursue new gene therapies without fear of losing their investments while also ensuring the integrity of the science, she says. "One of the reasons I was able to convince my company to pursue a patent was that the [previously] published sequence for BRCA1 was not correct," she said. "My fear was that women were getting bad information."

In March 1998, in recognition of the revolutionary nature of her work, Intellectual Property Owners, Inc., named Murphy "Inventor of the Year," an honor whose roster of previous winners includes the makers of the Jarvik Seven artificial heart and the developers of protease inhibitors that fight the AIDS virus. More important, Murphy says, women and men with cancer in their families' histories have a new, potent weapon to fight the disease before it strikes.

Without the genetic testing, men or women who carry the BRCA gene mutations would have fewer risk-prevention options and probably would not act until a tumor appeared. By then, medical intervention is less likely to work. But knowing well before any symptoms occur that the cancers may develop, which is what Murphy's test can predict, allows for aggressive surveillance and early detection.

"What the geneticist does is evaluate the pedigree," Murphy said. "If all of the breast cancer is on the father's side it can not be ignored because it can be carried through the father to a daughter. In my particular case the altered gene is likely to be coming through my dad. My grandmother had bilateral breast cancer in her fifties and died of colon cancer because they were not looking for it." The BRCA genes are called "breast cancer" genes, but they are general cancer genes that cause ovarian cancer, prostate cancer and colon cancer, according to Murphy.

Dr. David Sidransky, a cancer researcher at Johns Hopkins University School of Medicine, sees great promise in the use of tests like Murphy's to increase cancer survival rates. Writing in *Scientific American*, Sidransky noted that genetic testing "will save the most lives in the years to come by making it possible for existing therapies to be applied at the time when they can be most effective."

a physics major at Colby, Murphy became interested in genetics while working at the Jackson Laboratory in Maine, where she spent two years shortly after graduation. The biologists at the Jackson Lab "changed my life," Murphy said. "They sold me on the idea that science could be fun."

But Murphy attributes her success as a scientist to the grounding she received at Colby. The only physics major in her class, she got one-on-one instruction from Dennison Bancroft, chair of the Physics Department. "That personal attention gave me the confidence to pursue any goal I chose," Murphy said. "To this date, no task is too large."

She remained close to Bancroft, who died in January. Bancroft for several years treated Murphy and her husband, Donal, and their two children, Michael '95 and Lori, to sailing excursions on Penobscot Bay near his home. "He was one of the most influential people in my life," Murphy said.

Her physics training prepared her for genetic research because of its emphasis on inferential methods, Murphy says. "I worked with small-particle physics at Colby. I had to infer that they were there, design experiments, get an answer and be able to interpret it. The skills I learned in physics I just simply lock, stock and barrel picked up and moved to this brand new field called human genetics."

After attending graduate school at the University of Michigan from 1970 to 1973, Murphy devoted the next few years to raising her children, always sure that she would return to school. The combination of becom-



ing a mother, her exposure to mentors in genetics research and her sister's death in 1977 clarified her career path. "I hadn't realized what Mother Nature could do to people and that you could control that to a certain extent," she said.

In 1978 she enrolled in the Ph.D. program in human genetics at Yale. After earning her degree in 1984, she immediately began a postdoctoral fellowship at the Yale School of Medicine, where she worked in the cytogenetic lab and later in the child study center. In 1988 she left to become director of a DNA diagnostic lab at the New York State Department of Health. It was there that Murphy, motivated by her desire "to do good" while also advancing the science in her field, embarked on an ambitious project to write regulations governing genetic testing. Eleven years later they remain the only national standard used in the U.S. The regulations are crucial to protect patients from poor diagnostic testing that could either fail to detect a genetic mutation or misinterpret a test and falsely label a patient as a potential victim, Murphy says.

Subsequently, she has pushed for more standardization in genetic counseling, which she sees as an important component of managing genetic-based diseases. Women who test positive for the BRCA1 mutation carry a daunting psychological burden, she says. "They know they carry an altered gene," she said, "but we cannot tell them *when*, or even *if*, they will get breast cancer. Our task is to monitor them carefully so that cancer can be detected early, at a treatable stage."

Furthermore, women's test results could be used against them by insurance companies or employers who wish to deny medical coverage. "Fear of discrimination is very real," Murphy said. "If you have a genetic predisposition, even though you are perfectly healthy, a company or insurer can perceive that as a time bomb. They can say, 'Aha, she's screwing up our overall costs, let's get rid of her.' They find ridiculous causes to fire these women."

Murphy has been a leading advocate for keeping genetic records confi-

dential and out of medical files. She testified at Senate hearings in 1996 during debate about the Kennedy-Kassebaum bill, which protects individuals from discrimination by insurance companies. Now she hopes to push through legislation that makes genetic counseling mandatory to ensure that patients and their families are given appropriate information before, during and after tests. "Anybody who wants to license the BRCA1 test has to agree to do the counseling," Murphy said. Imposition of that requirement was made possible by the patent awarded for the test.

Murphy's latest goal is to convince insurance companies that they should neither fear genetic testing nor target patients who have undergone such testing. Last fall she met with medical directors of insurance companies from across the country to teach them the science involved in the testing. "They think genetics will bankrupt the life insurance industry; I tell them they should be thanking me because we are improving life expectancy," Murphy said.

Currently director of the Hereditary Cancer Screening program at Albany Medical Center, Murphy oversees a comprehensive program of testing and counseling for men and women who may carry the BRCA1 or BRCA2 mutations. She encourages patients to seek genetic counseling if they have a relative who had cancer under the age of 50, if they have had three or more relatives with any kind of cancer, or if cancer has occurred in two successive generations of their families.

Though her work helps break the cycle of pain caused by cancer in some families, Murphy acknowledges that science's ability to eradicate hereditary diseases is limited. "As soon as we

figure out one mutation and find a way to deal with it, something else mutates and creates a whole new problem," she said.

But she also realizes that more lives will be extended thanks to her research and that her sister's early death may have helped plant the seed that led to Murphy's discoveries. "I think Barbara would be proud of me," she said.

The death of Murphy's sister, Barbara (opposite), still tugs at her. But she realizes that more lives will be extended thanks to her research and that her sister's early death may have helped plant the seed that led to her discoveries.
