UNKNOWN SIGNIFICANCE

Years of writing about genetic testing did not prepare me for my own foray into this rapidly changing world

By **Jennifer Couzin-Frankel**

Rarely could I be described in a headline in *The New York Times*, which explains why I lingered over one earlier this fall. "Study of Jewish Women Shows Link to Cancer Without Family History," announced the 5 September story. Uneasily, I read on: "Women of Ashkenazi Jewish descent who tested positive for cancer-causing genetic mutations during random screenings have high rates of breast and ovarian cancer even when they have no family history of the disease, researchers reported Thursday."

Hmmm.

Science has been my professional home for the past 13 years, and in that time I've written extensively about genetic testing and spoken with dozens of experts at the field's cutting edge. I've chronicled the scientific advances, the ethical quandaries, the lives testing saves, the angst it ignites. I had never turned the lens on my own DNA.

Abruptly, there was no escaping it. My parents are both of Ashkenazi descent. To my knowledge, no one on either side of my family has ever had breast or ovarian cancer. But suddenly I saw how a mutation in the genes discussed in that article, *BRCA1* and *BRCA2*, might have slipped unnoticed through my father's small family, heavy on the Y chromosome—through him; his older

The author and her two children at play. She sought genetic testing, as many do, in part to protect her own health as they grow up.

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brother; my three cousins, two of whom are male. I remembered that my paternal grandfather had suffered from prostate cancer, which eventually spread to his bones and killed him. My uncle had the disease, too. Along with their storied role in breast and ovarian cancers, *BRCA* mutations are associated with prostate cancer in men. I'd long known that Ashkenazi Jews are more likely to carry mutations in those genes. But that was as far as my knowledge went.

When I probed the numbers, they were not particularly reassuring. A quick Google search—why had I never done this before?—revealed that one in 40 Ashkenazis carry *BRCA* mutations, compared with as few as one in 800 in the general population. Like nearly all genes linked to cancer, *BRCA1* and *BRCA2* were first found in families riddled with the disease. But the September study, led by Ephrat Levy-Lahad, a medical geneticist at Shaare Zedek Medical Center in Jerusalem, argued that other families shared a similarly high risk if they carried the same mutations.

Several of the authors, among them Mary-Claire King of the University of Washington, Seattle, *BRCA1*'s discoverer, say all women regardless of family history should learn whether they carry dangerous mutations in *BRCA1* and *BRCA2*. Other experts are not yet convinced. Perhaps even more contentious is whom to screen for dozens of risk genes uncovered in the past decade, some only tenuously linked to cancer. I might have written a nuanced *Science* story laying out both sides of the debate. But when it came to my own health, 486 Israeli women with *BRCA* mutations, half without a family history but all highly vulnerable to cancer, was all I needed.

Time seemed of the essence. I am 38 years old; ovary removal in *BRCA* carriers is recommended by 40. I called the suburban Philadelphia hospital where my children, now 2 and 5 years old, were born and spoke with a genetic counselor. She took a family history and agreed that yes, *BRCA* testing was worthwhile, and yes, insurance would likely cover it in my case.

I booked an appointment. I was about to experience my own sliver of the brave new world of cancer genetic testing, which would take me beyond *BRCA* and into more uncertain terrain.

THE AUTOMATIC DOORS SWISH soundlessly open as I step into the hospital's cancer center. A genetic counselor with brown, curly hair and glasses approaches me, smiling, clipboard in hand. In her office, she pulls out a pedigree of my family sketched in pencil—squares for males, circles for females, diagonal slashes through anyone who has died with the cause of death jotted next to them. I thought I'd come prepared—after all, I'm here only for *BRCA* testing, and only because of my ancestry—but it turns out I haven't. Did my grandmother's hysterectomy include removal of her ovaries? (I hazard a guess and query family members after the fact; none knows whether I got it right.) Did my great-grandmother die of stomach or colon cancer? "She was in her 90s," I say. I still carry a dim memory of visiting her in the hospital, as a 3-year-old, shortly before she died. "Does it matter when someone is that old?"

The counselor pulls out a sheet of paper and lays it on the table. It's a list of 21 genes associated with breast and ovarian cancer. Eleven are shaded pink and labeled "high-risk"; three are in the purple "moderate-risk" category; and seven others are turquoise and described, obliquely, as "newer genes." This is the Breast/Ovarian Cancer Panel from the company GeneDx in Gaithersburg, Maryland, but as is often the case in oncology, many of the genes contribute to other cancers, too. One confers a 40% to 83% risk of stomach cancer. Stomach removal is recommended if you test positive. Another, *TP53*, confers a nearly 100% chance of cancer in women and a 73% chance in men; *TP53* cancers include brain cancers and sarcomas.

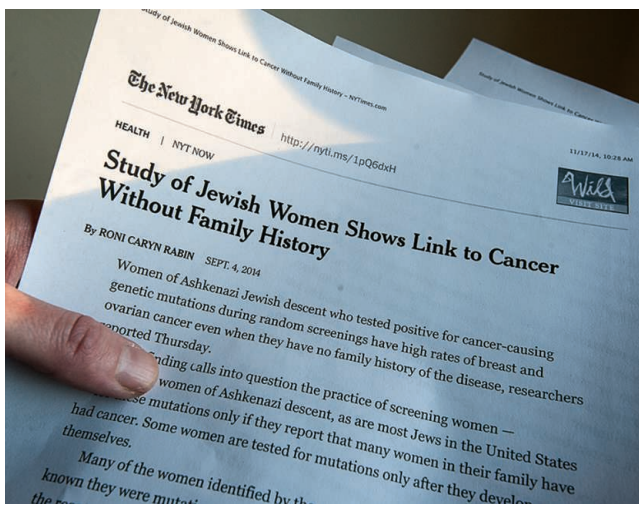
When it comes to two of the genes on the panel, *BRCA1* and *BRCA2*, there's little doubt that in cancer-prone families, testing saves lives: Extensive study of *BRCA* carriers has found that those who have their ovaries removed are 80% less likely to die from ovarian cancer and 50% less likely to die from breast cancer. Prophylactic mastectomy appears to cut risk of breast cancer by at least 95%.

But many other genes for which testing was discouraged just a few years back because their impact on health was uncertain are "now being routinely offered," says Kenneth Offit, chief of the clinical genetics service at Memorial Sloan Kettering Cancer Center in New York City. "This is the paradox we've fallen into." Just as more cancer risk genes were being uncovered, the cost of sequencing them plunged. The result is a proliferation of panels designed to decipher DNA.

How much each of these genes raises risk in individuals, and at what age, is often fuzzy. "The clinical work got out ahead of us," says Fergus Couch, an authority on *BRCA* and other breast cancer genes at the Mayo Clinic in Rochester, Minnesota. "The [sequencing] technology changed so quickly" that "we did not have time" to develop answers to the questions patients and doctors are now asking.

In the summer of 2013, GeneDx launched its Breast/Ovarian Cancer Panel—spurred partly by the Supreme Court ruling against the Myriad Genetics patent claims on the *BRCA* genes. Other companies, including Myriad itself and Ambry Genetics, along with academic medical centers, have jumped in with panels of dozens of genes linked to an array of cancers. "We're really looking at things that will provide the physician with the ability to make a treatment plan," for example, by adding increased surveillance, says Sherri Bale, managing director of GeneDx. The genes on the company's panels are "a moving target," she says, with culprits added and sometimes deleted based on the available scientific evidence. Bale believes the panels, which cost in the neighborhood of two or three thousand dollars, are suitable for high-risk families but not yet for the general population.

THE LIST OF 21 GENES sits between us, and I consider all I could learn by simply saying yes. The counselor isn't advocating I sign up for the full panel. But she draws my attention to one gene in the moderate-risk purple grouping, *CHEK2*. The list of cancers beside it is long: "Female Breast, Male Breast, Colon, Prostate, Thyroid, Renal, Endometrial (serous), Ovarian." I'm vaguely familiar with *CHEK2* as a breast cancer gene from my own reporting. "Is *CHEK2* more



The newspaper article that started it all, published in early September.

PHOTO: © APRIL SAUL

common in Ashkenazis?" I ask, still stuck on heritage as my cancer driver and the reason I'm in this room to begin with.

"No," the counselor replies. But in addition to prostate, my paternal grandfather had colon cancer. "He was in his 70s!" I protest. Nonetheless, *CHEK2* testing for me is worth considering, the counselor says. A *CHEK2* mutation could roughly double my risk of breast cancer, to at least 20%. Annual breast MRIs and mammograms would likely be recommended.

I'm stymied. Adding another gene for testing had never occurred to me. And yet, if the test is positive, the course of action sounds relatively benign and potentially lifesaving.

"Let's do it," I say. We've been talking for about 40 minutes.

The counselor pulls out a consent form. "There's one more thing," she explains. A block of text is titled "Variant of uncertain significance (VUS)." It reads, in part: "I may learn that a VUS was identified by this test. This means that a genetic change (variant) was identified, but it is unknown whether the variant may cause cancer." A given cancer gene can have thousands of variants, some showing up in just a handful of families worldwide. Certain variants are a major contributor to disease, whereas others are benign changes in DNA that, practically speaking, mean nothing.

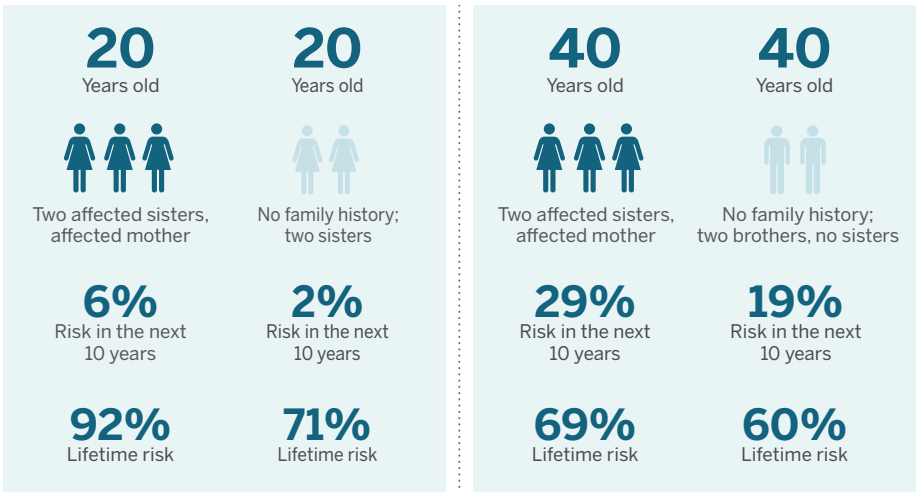
Again, my years of medical journalism have failed to prepare me. "How common are these in *BRCA* and *CHEK2*?" I demand. For *BRCA1* and *BRCA2*, the counselor explains, about 2% of people have a VUS. (I later learn that VUS rates fluctuate depending on the company offering the test.) She is not sure about *CHEK2* but is happy to find out. She stresses, too, that finding a VUS would not affect medical guidance and that the hospital will recontact me if a VUS is later reclassified as either harmless or pathogenic.

I push aside my hesitation, sign the forms, and am off to the lab for a blood draw.

Driving home, my intolerance for uncertainty rears its head. Do I really want to know if I have a VUS? What's the point? That afternoon, I send the counselor an e-mail. I tell her I'm worried that learning about VUSs "will cause me anxiety and there will be no benefit to having this information. I'm wondering whether it's possible not to receive information about any VUS that may turn up in testing. … Is this an option?"

The calculus of risk

How much a *BRCA1* mutation raises a woman's risk of breast cancer depends on her age, family history, and other variables, as the examples below illustrate.



Source: Courtesy of Antonis Antoniou/University of Cambridge/BOADICEA

> ***"People need to become more comfortable with uncertainty."***
>
> **Sharon Plon**, Baylor College of Medicine

She writes back quickly and kindly. She has checked with GeneDx and learned that, for regulatory reasons, they are obligated to share information if a VUS is found. She will ask her medical director whether the hospital can keep a VUS finding from me. But she wonders, too, whether "you will feel anxious not knowing whether or not you may be recontacted in the future regarding a reclassified VUS. … Chances are you will not have a VUS and then you may feel relief to know you do not have one."

Later, she writes to say that her medical director is comfortable withholding a VUS if no pathogenic variants turn up. And there's more good news: She has learned that the VUS rate for *CHEK2*, per GeneDx, is only 1.6%, far lower than she originally thought—although estimates vary depending on whom you ask. I shelve my inner dialogue over which information I want.

TWO DAYS LATER, while GeneDx is parsing my DNA**,** I'm on the phone with Susan Domchek, an oncologist studying breast cancer genes at the University of Pennsylvania. We are discussing cancer risk genes in people without a family history of disease. Unprompted, Domchek brings up *CHEK2* testing. "We don't know how to incorporate it into patient care," she complains, referring to women who test positive and their families. "What percentage of the time does it really add anything to the situation?" I don't mention that my own *CHEK2* test is in process. Instead, I inquire about the frequency of *CHEK2* mutations in the general population. Domchek's response that only about one in 200 people in the United States is a carrier helps me exhale.

Domchek is one of many researchers trying to illuminate the interplay between cancer genes and disease. Along with Offit, Couch, and others, she has developed an online registry called PROMPT that opened earlier this fall. It aims to register thousands of people who have had the panel testing offered by a host of companies, including GeneDx, Ambry, Myriad, Quest Diagnostics, and Pathway Genomics. Their goal is a database that will help them examine how specific gene variants affect health.

"We need to get the world's experience with all these panels," Couch says. He also points out an irony: Despite some uneasiness, scientists like him need panel testing to continue, because it's their best shot to gather enough data to tackle research questions. At the same time, "You don't want to do science … at the cost of the patient," he says. Couch is part of an international consortium called ENIGMA that's working to sequence breast cancer genes from 40,000 cancer patients and healthy people. The project will nail down the risk conferred by different mutations, and study the impact of VUSs on disease.

A menu of cancer genes

Multigene panels for cancer risk are proliferating and evolving, including this one of 21 genes associated with breast, ovarian, and other cancers, shared with the author prior to her own testing.

HIGH-RISK GENES

GENE	ASSOCIATED CANCERS AND RISKS
BRCA1	Female breast (57–84%), ovarian (24–54%), prostate (16–20%), male breast (4%), pancreatic (3%), melanoma, fallopian tube, primary peritoneal, endometrial (serous)
BRCA2	Female breast (41–84%), ovarian (11–27%), prostate (20–34%), pancreatic (5–7%), male breast (4–7%), melanoma, fallopian tube, primary peritoneal, endometrial (serous)
CDH1	Female breast (39–52%), diffuse gastric cancer (40–83%), colon
EPCAM *MLH1* *MSH2* *MSH6* *PMS2*	Ovarian (4–24%), colorectal (20–80%), endometrial (12–60%), stomach, pancreatic, biliary tract, urinary tract, small bowel, brain, sebaceous neoplasms
PTEN	Female breast (25–50%), thyroid (10%), endometrial (5–10%), colon, renal, melanoma
STK11	Female breast (32–54%), ovarian tumors (21%), colorectal (39%), pancreatic (11–36%), gastric (30%), lung (15%), small intestine (13%), cervical (10%), endometrial (10%), testicular tumors (9%)
TP53	Female breast, ovarian, soft tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma; overall risk for cancer: nearly 100% in females, 73% in males

MODERATE-RISK GENES

ATM	Female breast, colon, pancreatic
CHEK2	Female breast, male breast, colon, prostate, thyroid, renal endometrial (serous), ovarian
PALB2	Female breast, male breast, pancreatic, ovarian

NEWER GENES

BARD1	Female breast, ovarian
BRIP1	Female breast, ovarian
FANCC	Female breast
NBN	Female breast, melanoma, non-Hodgkin lymphoma
RAD51C	Female breast, ovarian
RAD51D	Female breast, ovarian
XRCC2	Female breast, colon, pancreatic

DATA: GENEDX ONCOLOGY PROGRAM

Outside the United States, panels of cancer genes are largely restricted to research settings, and investigators often don't share information about mutations that carry a modest or unknown risk. There's much debate over what to tell volunteers. "We struggle with it," says Hans Ehrencrona, a clinical geneticist at Lund University Hospital in Sweden. "Where to draw that line, no one knows for sure."

Every woman in Sweden who receives *BRCA* testing is now also offered the chance to sign up for a study in which she's tested for 63 other cancer genes. Results from only seven of those are shared with the participants. Many moderate-risk genes are not on the list, says Ehrencrona, who's helping lead the effort. As an example, he points out, "*CHEK2* is quite common in Sweden. We do not return it."

ONE TUESDAY MORNING IN OCTOBER, minutes after a work conference call ends, my phone rings. "I have your results," the counselor announces. It's been 19 days since I met with her. "What do you want to know?"

Well, the pathogenic mutations, of course, I say.

There's great news, she tells me: No pathogenic mutations were detected in any of the three genes.

Relief rushes through me. "Do you want to know about any VUS?" she asks. I think about *CHEK2*, and the 1.6% VUS rate she quoted. What are the chances? "Sure," I say.

"There were no variants of unknown significance detected in *BRCA*, but a variant of unknown significance was detected in *CHEK2*," she tells me. Reading from the GeneDx report, she explains that my VUS is a deletion of 15 DNA nucleotides. The variant has been found in two men with prostate cancer, and in vitro analysis suggests it causes a partial loss of function of the gene.

I expected distress, a ringing in my ears, fear coiling in the pit of my stomach. Instead, I'm almost laughing. I think, "That's it? That's what's being shared with patients these days?" Two men with prostate cancer, cells in a petri dish, a loss of function that may or may not translate into pathogenicity: This does not merit my mental energy.

"People need to become more comfortable with uncertainty," Sharon Plon, a clinical geneticist at Baylor College of Medicine in Houston, Texas, tells me a few days later. But she stresses that acknowledging uncertainty "does not mean that we don't know anything." For many families with cancer, large panels provide constructive guidance.

I write to my cousin in San Francisco to share my test results; she is the only close female relative on my father's side, where the cancer cases cluster. And she's more familiar than most with the panels: Her mother, my nonbiological aunt, is fighting ovarian cancer and signed up for a panel of 41 genes offered by the University of Washington, Seattle. She tested negative for all of them.

My cousin had urged me to consider the same panel, which has now expanded to 48 genes. In the end, I explain in my message to her, it wasn't something I wanted. "I know the panels are often discouraged," she writes back. It's a view she doesn't share. Even without a clear-cut action plan, she wants to know whatever message her DNA carries for her future. The only reason she's eschewed testing for herself is because insurance is unlikely to pay for it. "Knowledge is power," she writes. "I don't see any downside at all." ■

Unknown significance

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