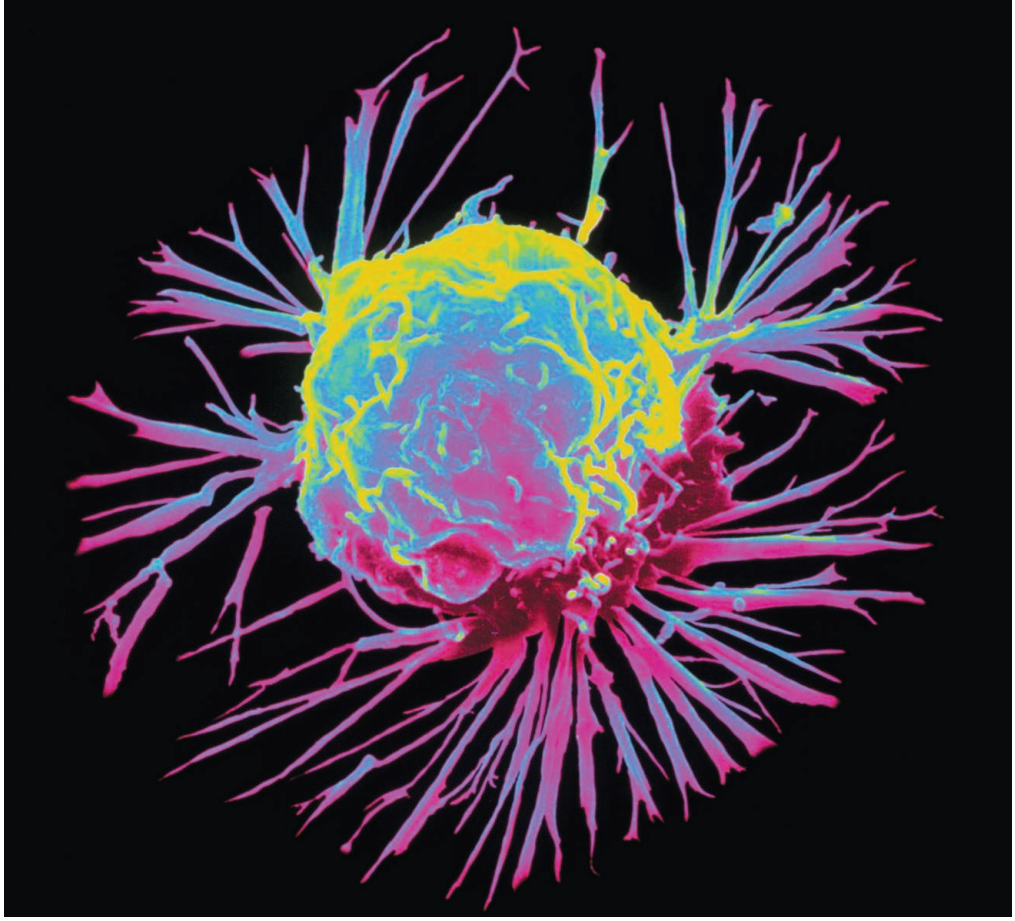

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The foe. What goes awry in a breast cancer cell (*left*) is becoming clearer, but scientists are still debating the role of different genes.

The 'Other' Breast Cancer Genes

Since the discovery of *BRCA1* and *BRCA2*, dozens more breast cancer genes have come to light. But what risk they pose—and what to tell women who carry them—remain quandaries

A quarter-century after the first breakthroughs in breast cancer genetics, scientists have a good grasp on the risks that come with mutations in *BRCA1* and *BRCA2*, the most prominent breast cancer genes. Frustratingly, though, just as the sky began clearing with the *BRCA*s, a whole flock of other genes has swept in and muddled the view.

BRCA1 and *BRCA2* dominated the breast cancer agenda for so long for good reason. *BRCA* cancers attack women early in life, they're aggressive and deadly, and they might hit three or four women in one family, a devastating legacy. On top of all that, they've been embroiled in political controversy, as the subject of a landmark Supreme Court case about the legality of patenting genes.

However infamous, though, the *BRCA*s account for only about 25% of breast cancers with a hereditary component. And with the rapid expansion of next-generation DNA sequencing, scientists have now unmasked dozens of other genes associated with breast cancer. *PALB2*, *ATM*, *CHEK2*, and others probably won't gain the notoriety of either *BRCA* gene, but they've already become important players. "We always knew we should [test for] 10 genes instead of two," says Charles Perou, a geneticist at the University of North Carolina (UNC), Chapel Hill, "but it wasn't technically feasible in the past. Now it's practical."

In theory, women at high risk of breast cancer might benefit from such testing. They and any female relatives carrying a risky mutation could undergo screening more often, increasing the chances of catching tumors early. If the mutation looks especially risky, they might opt for prophylactic mastectomies, surgery to remove their ovaries, or sometimes both, because breast cancer and ovarian cancer share genetic risk factors. And if they do develop tumors, knowing the underlying genetic basis may help determine treatment.

But as Matthew Ellis, a geneticist at Washington University in St. Louis, puts it: "As the genetic diagnosis gets easier, the interpretation gets more difficult." Identifying a risky mutation in these other breast cancer genes has proved challenging. Geneticists simply don't know in many cases which mutations within a given gene will lead to cancer and which won't. A clearer picture will emerge only from long, involved trials to link mutations to clinical diagnoses.

This has led to a lot of handwringing among doctors and genetic counselors about what to do in the short term: when and whether to test the full panoply of other breast cancer genes in their patients, and how much to reveal to women who are tested. Some in the field even suggest not telling patients about certain mutations they harbor in their own DNA until geneticists can assess the risk more accurately, however long that takes.

Depending on what the tests turn up, most geneticists recommend that patients seek genetic counseling to help them understand the risks revealed by the tests. But not all women receive such counseling, especially in the United States, where testing companies can market directly to family physicians.

And even the best counseling can't alleviate the fundamental problem that the data continue to outpace the understanding. This has left doctors and patients alike in a bind, Ellis says. "You have to say ['I don't know'] a lot," he says, "and that's a pretty unsatisfactory answer."

Repair crew

Biologically, the role of the other breast cancer genes is becoming clearer. Like the *BRCA*s, most of them help repair broken DNA, says Mary-Claire King, who mapped *BRCA1* in 1990 and is a geneticist now at the University of Washington, Seattle.

Specifically, these genes help repair double-strand breaks. If a single strand of DNA's double helix breaks, cells can repair the flaw pretty easily by using the other, complementary strand as a template. Double-strand breaks are messier, and cells often have a tough time aligning the tattered fragments properly. Repair work therefore requires specialized machinery, and dozens of genes lend a hand.

If a woman inherits a mutation in one of

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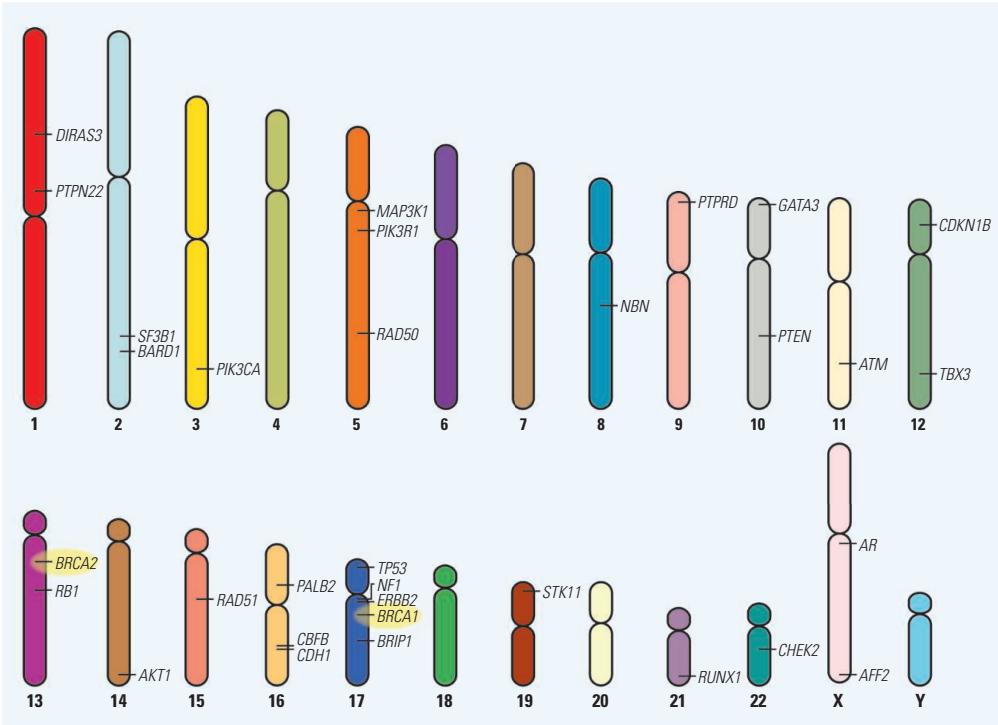
these genes, her cells can get along fine at first, because every cell has two copies of each gene, one on each chromosome. Problems arise only if the good copy gets disabled as well. Unfortunately, many genes involved in breast cancer have a high likelihood of getting shut down, King says, because they reside in "bad neighborhoods" on their chromosomes. For example, they might sit near a high concentration of *Alu*s, mobile genetic elements that have a nasty habit of inserting themselves into genes and disrupting function.

If both copies of a DNA-repair gene end up disabled, the cell can lose the ability to repair double-strand breaks. At that point, King says, "all kinds of hell breaks loose" and breast cancer will likely result.

But geneticists still struggle to say which mutations in these new genes are important risk factors in cancer. Marc Tischkowitz, a geneticist at the University of Cambridge in the United Kingdom, sums up the difficulty succinctly: There is no *BRCA3*, he says. That is, no other single gene, when mutated, can explain a large number of breast cancer cases.



The "others." Scattered across the chromosomes, dozens of genes (a sampling shown here) have now been implicated in hereditary breast cancer, but how much each contributes to a woman's risk is unknown.

Consider *PALB2*, which interacts with *BRCA2* in repairing double-strand breaks. *PALB2* mutations cause a two- to threefold increased risk of cancer, a significant jump. (For comparison, harmful *BRCA1* mutations increase the risk of cancer by about fivefold; harmful *BRCA2* mutations increase it by about fourfold.) But *PALB2* mutations appear so rarely that they probably don't explain more than a tiny percentage of tumors. They're so rare, in fact, that Tischkowitz had to organize an international consortium to study the gene, because no one country had enough cases. So while *PALB2* and other risky but rarely mutated genes contribute to our understanding of breast cancer, they explain few cases of breast cancer overall.

Adding to the difficulties, some mutations in the newly identified genes have incomplete penetrance. That means they only sometimes lead to cancer, making them tricky to interpret. If a woman has two or three low-penetrance mutations spread among a few different genes, scientists also don't know in most cases whether the risks add up in a straightforward way.

Some mutations are clearly worse than others, King says. As examples, she mentions mutations that lead to premature stop codons during protein production, as well as insertions or deletions that lead to frameshift mutations. "Critical mutations" like these, she says, "whack the gene completely."

Unfortunately, most mutations are more ambiguous. A point mutation near a functional domain, for instance, or a mutation in a noncoding region might well hamper a gene—but then again might not. Equally daunting, geneticists see huge numbers of different mutations in the population at large, each of which requires independent evaluation. In a phrase that

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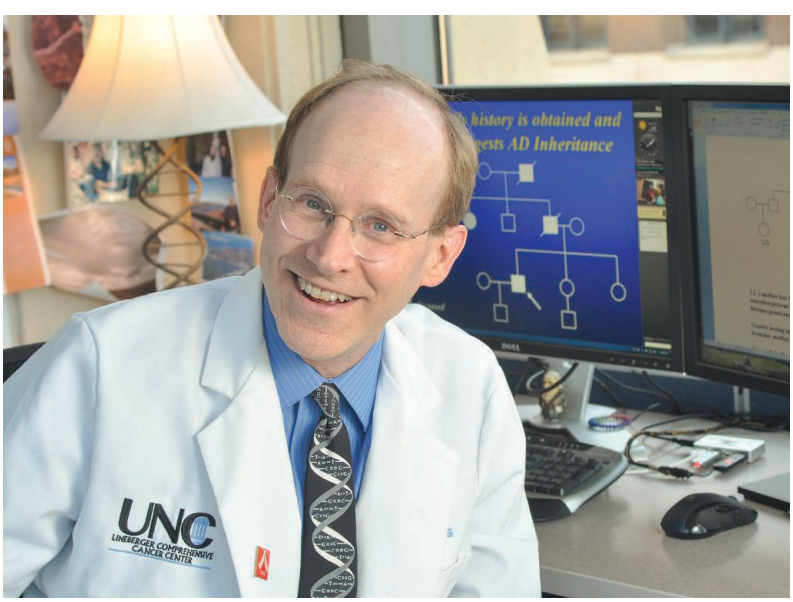
—James Evans, University of North Carolina, Chapel Hill



CREDITS (TOP TO BOTTOM): K. ENGMAN/*SCIENCE*; COURTESY OF THE UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL

pops up over and over—it's practically a mantra in breast cancer research—geneticists refer to these ambiguous mutations as "variants of uncertain significance."

Scientists can now explain the genetic roots of about half of all family clusters of breast cancer, Tischkowitz says. "About a quarter of them will have mutations in *BRCA1* and *-2*, and a quarter of them will have a combination of common, lower penetrance variants. But about half of them are still unexplained. Which is a puzzle for us."

And things may get worse before they get better. Perou says that preliminary research has identified on the order of 100 other genes that might—or might not—also contribute to breast cancer. Sorting out the rogues from the pretenders, though, "is going to take some time," he acknowledges. "It's much easier to make a discovery than to show that that discovery has clinical utility."

CREDIT: SID HASTINGS/WASHINGTON UNIVERSITY IN ST. LOUIS

> "There's a moral hazard here. Just adding genetic information doesn't necessarily lead to better clinical management. A bad test can be as bad as a bad drug."
>
> —Matthew Ellis, Washington University in St. Louis

In the clinic

Current tests for breast cancer reflect this uncertainty. "Six years ago, when we had our *BRCA1* and *-2* results in hand, for most intents and purposes, we were done," says James Evans, a professor of genetics and a genetic counselor at UNC Chapel Hill. But particularly in the past year, so-called expanded panels have come onto the market. These genetic tests scour for mutations in a dozen or more breast cancer genes. As a result, Evans says, especially with women whose families have a history of breast cancer, "we are now faced, daily, with decisions about whether to expand our reach in testing."

Adding to the challenge, the panels differ from company to company, sometimes greatly, and the information they provide is not always helpful, he notes. He stresses that panels do have their use. "But the field has not settled on consistent, evidence-based guidelines," he says, "that tell us when we should use an expanded panel, when we shouldn't, and even what genes should be on that expanded panel."

To compound the problem, some genetic variants that predispose, say, Caucasian women to breast cancer might not predispose black or Hispanic women, and vice versa. So in addition to the general clinical trials necessary to link variants to an increased risk of cancer, scientists might also need to conduct separate clinical trials on different ethnic groups to sort out which mutations pose the worst risks for each.

Given all the uncertainty, geneticists and genetic counselors disagree about how often to use expanded panels, and especially about how much information they should pass along to patients. They do generally tell patients about unambiguously harmful mutations, and advise them to step up surveillance for early-stage tumors. But many geneticists hesitate to pass information about ambiguous mutations to patients. "I think it's probably better for them not to hear that," Perou says. "It's confusing to me, it's confusing to them, and to be accurate, you would have to report a million variants for every person. That's completely not helpful."

Ellis agrees. "There's a moral hazard here. Just adding genetic information doesn't necessarily lead to better clinical management." He adds, "A bad test can be as bad as a bad drug."

Faulty testing can also affect family members. In the 1990s, Tischkowitz says, preliminary studies strongly linked *CHEK2* to breast cancer; later studies reduced the risk substantially. But imagine that a geneticist had told a woman that a *CHEK2* mutation probably explained her family's history of cancer. Some of her sisters or daughters could easily test positive for the mutation as well.

In cases like this, Evans says, "you've just assigned a whole bunch of people in the family to screening and procedures that they didn't need." Perhaps worse, other family members, who tested negative for the mutation, might believe themselves off the hook. "You've given them false reassurance," Evans says, "and they haven't gotten the extra surveillance that they would benefit from."

Above all, geneticists and counselors worry about inadvertently pushing patients to take drastic steps. "Patients will go to the end of the earth to protect themselves from breast cancer," Ellis says, including prophylactic surgery. Mastectomies are still vastly more common among women with *BRCA* mutations, but a small percentage do elect for the surgery because of non-*BRCA* mutations.

So far, these cases seem limited to mutations with *PALB2* and other genes with rare but clearly harmful variants. Still, geneticists worry that, as more and more genes are linked to breast cancer, women might opt for mastectomies based on faulty or incomplete information, like the early *CHEK2* studies.

"One can imagine the headlines of people having unnecessary preventative surgery, when later on it's discovered that the risk of these genes may not be as strong," Tischkowitz says. He adds, "Maybe we'll look back in time and think we were overcautious, but I'd rather it be that way than the other way around." **–SAM KEAN**

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Editor's Summary