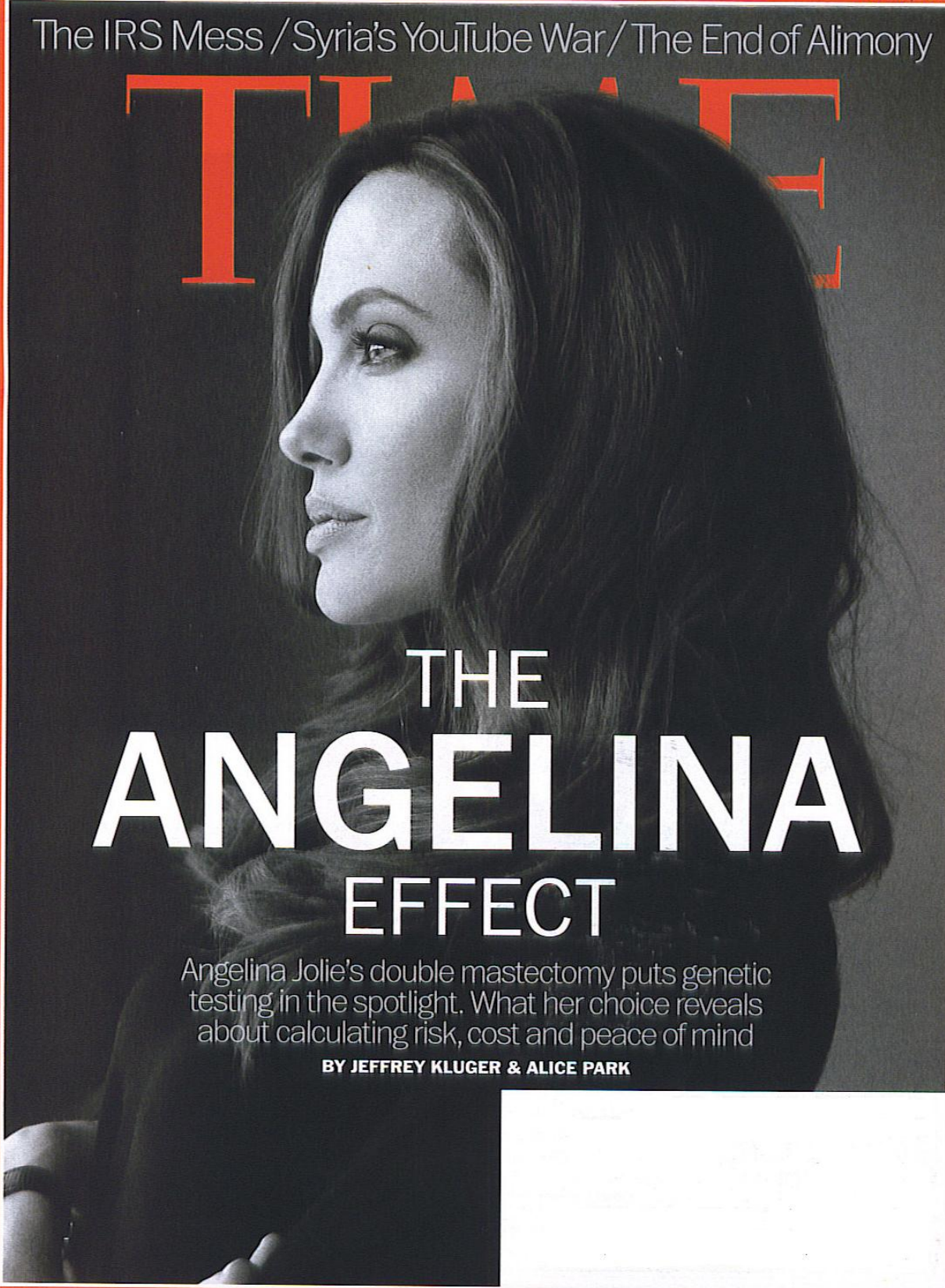


MAY 27, 2013

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TIME



THE
ANGELINA
EFFECT

Angelina Jolie's double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind

BY JEFFREY KLUGER & ALICE PARK

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THERE'S A CHILLY ARITHMETIC TO THE way we all get sick. At the end of any year, a fixed and knowable number of us will have developed heart disease, and another number won't have. There will be a different entry in the ledger for cancer, another for lung disease, another for Parkinson's or dementia or HIV. The people who study those mortal metrics—the actuaries, the epidemiologists—don't give too much thought to the individuals behind the numbers, and the truth is, they can't. It's no good sentimentalizing math—not if you want to get anything useful out of it.

But sometimes it's impossible not to: sometimes the person who is sick has a very recognizable face. So it was in 1985, when Rock Hudson, Hollywood heart-throb of an earlier era, died of complications from AIDS and a country that thought it could fence off a disease suddenly realized we were in this together. So it was in 1995, when Christopher Reeve, a man best known for playing a character utterly immune to injury, was thrown from a horse and suddenly could do nothing at all without help—and with that, the spinal-injury community had a point man a lot more powerful than Superman.

And so it was again when Angelina Jolie, the most beautiful woman in the world by a lot of people's lights, stepped forward and announced in an op-ed in the *New York Times* that she had undergone a double mastectomy, an operation she decided to have after learning that she carried a genetic mu-

tation that in her case increased the odds of developing breast cancer to a terrible 87% and ovarian cancer to 50%. She decided to get tested because her mother died of ovarian cancer at age 56. Jolie herself has no current signs of either disease.

She explained her treatment decision with a simple clarity: "Once I knew that this was my reality, I decided to be proactive and minimize the risk as much as I could." She explained it with an eye toward the 12% of all women who will one day develop breast cancer and the 100% who worry about it: "I hope that other women can benefit from my experience. Cancer is still a word that strikes fear in people's hearts." And she explained it in a way that went straight to what many were thinking, when a woman whose very name signals beauty and whose profession depends on it makes such a dramatic choice. "On a personal note," she wrote, "I do not feel any less of a woman. I feel empowered that I made a strong choice that in no way diminishes my femininity." Jolie, like many other women who have undergone mastectomy, has had successful reconstructive surgery. But as with those other women too—especially the ones who were not yet sick—it took a lot of courage to get to that point in the first place. "It's such an emotional and personal decision," says Sarah Hawley, associate professor of general medicine at the University of Michigan, "particularly because it's the woman's choice."

Jolie, according to most experts who have weighed in publicly, made a smart choice for her case. "It's one of the truly unique situations where most medical professionals would say if a woman chose to have both breasts removed, it's a pretty reasonable thing to do," says Dr. Eric Winer of the Dana-Farber Cancer Institute. Exceedingly reasonable, judging by the numbers. Jolie's doctor estimates that her cancer risk fell from its 87% high to just 5%.

But the seeming straightforwardness of Jolie's case masks a much murkier reality, one that involves science, policy and probabilities, not to mention Americans'—indeed everyone's—tendency to observe what the famous do and then conclude that we should do the same. When Katie Couric underwent a televised colonoscopy in 2000, demand for the procedure jumped—a phenomenon that was

promptly dubbed "the Couric Effect." In that case, many lives were likely saved by the raised awareness. This trendsetting power is exponentially greater in the case of Jolie, a megawatt star. She gave birth to a girl in 2008 and named her Vivienne, and in 2009 that name cracked the top 1,000 in popularity for newborn girls for the first time in the U.S. since 1930. It is now trading at a high of No. 322. Something similar happened with the names of her children Maddox and Shiloh. It's one thing when you model your fashions after Jolie's; it's another thing to model your kids.

If form holds, the 250,000 women each year who undergo the same genetic testing Jolie had will be joined by thousands more; but the mutation that was detected in her, in what's known as the BRCA1 gene, is present in only 0.24% of the population and accounts for no more than 10% of all cases of breast cancer. Still, form does appear to be holding. "I think we will see an increase over the next months for sure in genetic testing for breast cancer," says Rebecca Nagy, a genetic counselor at Ohio State University's medical center and president of the National Society of Genetic Counselors. "What's important to know is that it's not appropriate to test everybody."

And therein lies the problem. In the case of the BRCA genes, a mutation can mean a significant increase in risk. But Otis Brawley, chief medical officer for the American Cancer Society, recalls a woman with no family history of breast cancer who insisted on getting screened for the BRCA gene anyway. The test revealed a mutation of "unknown significance." She nonetheless had a double mastectomy—and the mutation that her test detected has since been shown not to be associated with a higher risk of breast cancer. A growing number of women who discover cancer in one breast are electing to have both breasts removed protectively, even without evidence that they are at genetic risk of having the disease spread. That kind of overreaction, Brawley argues, reflects "the pinking of America," the high-profile campaigns to raise awareness about the risk of breast cancer: "We have overemphasized and scared people too much."

More challenging for doctors trying to guide patients through their choices is the fact that many cancer-screening tests, especially nongenetic ones, do not



JOLIE LOST HER MOTHER MARCHELINE BERTRAND TO OVARIAN CANCER IN 2007, WHEN BERTRAND WAS 56. IN THE U.S., 36% OF WOMEN WHO, LIKE JOLIE, CARRY THE BRCA GENE MUTATION, HAVE PREVENTIVE DOUBLE MASTECTOMIES

yield clear treatment options. For some common tests, what looks like trouble may be nothing—or little—of the kind. Thyroid-cancer diagnoses are triple what they were in 1975 simply because doctors are checking more closely for any trace of the disease, but the mortality rate in all those years has not budged. In the past year, experts have begun recommending that men stop getting routine PSA screening tests for prostate cancer, or at least get them less frequently, since the elevated enzyme levels that may indicate the presence of the disease can also be a result of inflammation, infection or simply riding a bicycle. Even when the cancer is real, in many cases it grows so slowly that, as doctors say, the patient would have died with it, not of it. For every 1,000 men in the 55-to-70 age group who undergo annual PSA testing over the course of 10 years, a single life will be saved. Meantime, up to 200 will undergo a biopsy, and up to 100 will have their prostate removed unnecessarily.

The problem, of course, is that when it comes to life and death, we don't think about statistical significance and sample groups of 1,000, we think of sample groups of one—and we're the only member. The U.S. may indeed be home to some of the world's best medical technology, but the final decisions about what to do with all that wondrous know-how still rest with the least rational, most capricious part of the whole system: us. Jolie, to all appearances, made a sober and well-thought-through choice. But every patient is different, and the gravitational pull of a superstar role model has a way of distorting what needs to be a highly individual decision.

The Blueprint of Disease

THE BRCA1 GENE THAT SITS AT THE CENTER of Jolie's case was discovered in 1994 by a team of researchers at the University of Utah and elsewhere. It produces a protein that helps stabilize DNA. A lot of proteins do this kind of housekeeping chore in a

lot of tissues, but BRCA1 is expressed at higher levels in breast tissue, and when it can't do its job, it leaves a lot of room for some of the most defective and destructive cells of all: cancer cells.

Just a year after the BRCA1 gene was discovered, a team of researchers unearthed the BRCA2 gene, which produces a different protein but does basically the same work. Both belong to the group known as tumor-suppressor genes, and certain defects in each can increase the risk of other cancers too, including ovarian and pancreatic and, in men, testicular, prostate and the rarer male form of breast cancer.

Family history plays a role in breast cancer too, though in ways that aren't entirely clear. According to the American Cancer Society, a woman who has one first-degree relative—a sister, mother or daughter—with breast cancer is at twice the risk of developing the disease herself and three times the risk if she has two such relatives. Much of this data collection was done before widespread testing for the BRCA gene, and thus all cases of the disease—among women who had the BRCA mutation and those who didn't—were considered to be in one undifferentiated group.

Once BRCA screening became available, you'd have thought the variations in breast-cancer risk would have gotten immediately clearer, but the opposite turned out to be true. A 2007 study found that women whose close relatives tested positive for the BRCA mutation were at up to five times the average risk of developing breast cancer themselves, even if they tested negative for the BRCA mutation. A 2011 study, however, overturned that research, finding flaws in the methodology. When those errors were corrected and a different sample group was studied, women without the BRCA mutation who are relatives to women who do have it were at no significantly greater risk of breast cancer than the general population. That points to the dangers of reading too much into even a peer-reviewed study, much less the case of just one woman.

Overlearning the Lesson

WHETHER A DOUBLE MASTECTOMY WAS IN fact necessary in Jolie's case will almost certainly never be known. If she remains cancer free, it will be easy to infer a cause

and effect, but that doesn't mean that even a woman whose case seems identical to hers would not have other viable options. The anticancer drug tamoxifen, taken prophylactically, may cut cancer risk by 40% to 50%, according to recent studies. That, coupled with regular MRI screenings to detect the earliest signs of a tumor, may bring the danger down even further. In the case of an actual malignancy, partial breast removal may suffice as well. "The survival rate for women with early-stage breast cancer who get unilateral mastectomy or lumpectomy with radiation is equivalent," says Hawley.

Women who do opt for prophylactic surgery may choose an oophorectomy—removal of the ovaries, something Jolie

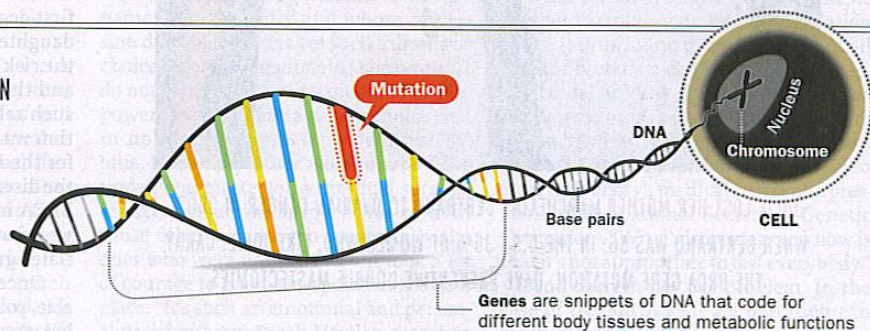
considered before deciding to start with breast removal, since that surgery is less complex and her risk of breast cancer was higher than her risk of ovarian cancer. But ovarian cancer is also deadlier, mostly because it's harder to detect, and once it does show itself, it's often too far along to be curable. There is also good evidence that removal of the ovaries, which produce the estrogen that helps fuel some cancers, can reduce the risk of breast cancer. A 2002 study led by Dr. Kenneth Offit, chief of clinical genetics at Memorial Sloan-Kettering Cancer Center and the discoverer of the most common BRCA2 gene mutation, found that 3% of women undergoing oophorectomy developed breast cancer after about two years, com-

pared with 11% of women who did not have the surgery. Removal of the breasts does seem to reduce the incidence of ovarian cancer—by 89%, according to one 2010 study—but the mechanism is unclear, and the findings are mixed.

"We don't have good screening strategies for ovarian cancer, so it makes sense to try to be aggressive in preventing the development of the disease," says Dr. Isabelle Bedrosian, associate professor of surgical oncology at MD Anderson Cancer Center.

Up and down the disease spectrum, holes in our detection screens make these kinds of judgment calls necessary, even when, as with BRCA, we have culpable genes in hand. A study published last year in the *American Journal of Human Genetics*

GENETIC TESTING IS BECOMING AN IMPORTANT PART OF DIAGNOSING AND TREATING DISEASE. MORE THAN 2,500 GENETIC TESTS CAN NOW DETECT THE RISK OF AILMENTS, AND ONE-FIFTH OF THOSE ARE TREATABLE



How it helps breast-cancer patients

1 EXPLORING INHERITED RISK

Inheriting abnormal versions of the BRCA1 and BRCA2 genes can increase the risk of breast cancer by 40% to 90% and ovarian cancer by more than 50%



Removal

Some women decide to remove both breasts or their ovaries before cancer appears



Observation

Regular breast screening with MRI can detect the smallest tumors so they can be treated



Drugs

The anticancer drug tamoxifen can lower the risk of breast cancer by up to 50%

2 GUIDING TREATMENT DECISIONS

Sequencing a tumor's DNA can reveal how likely a cancer is to recur and which chemotherapy drugs will be most effective

How others can benefit

CURRENTLY AVAILABLE

These genetic tests pick up inherited DNA mutations

Lou Gehrig's disease (ALS)

Huntington's disease

Cystic fibrosis

Breast cancer

Hemophilia A and B

COMING SOON

Researchers are looking for by-products of genes that signal these conditions

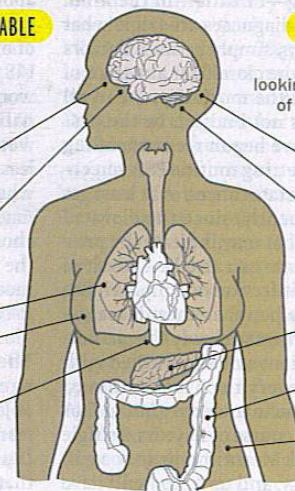
Early-onset Alzheimer's disease

Autism

Diabetes

Colon cancer

Obesity



found that in the case of Type 2 diabetes and rheumatoid arthritis, which have been tied to 31 different gene variants each, lifestyle factors such as smoking and obesity and, in the case of rheumatoid arthritis, a history of breast-feeding did as good a job of predicting the diseases as reading the genetic tea leaves. Other research has turned up similar results for heart disease. A new genetic screening test of the tissue in prostate-cancer tumors can help distinguish between aggressive and less severe cases, which may clarify treatment options once the disease has taken hold—but that still leaves the value of PSA testing open to question. Genes are a factor, sometimes a critical one, in diagnosing and treating disease, but they're by no means the only one.

The Map of Health

JUST HOW PROACTIVE ANY ONE PATIENT will be in the face of any one set of risk factors can have as much to do with geography as genealogy. In the U.S., about 36% of BRCA-mutation-positive women opt for preventive double mastectomies; in different parts of Europe, the numbers go in entirely different directions. "If you go to Paris and the Institut Curie and you have a BRCA mutation," says Offit, "the chances of having preventive breast surgery are almost zero. Whereas in northern Europe, the rate is close to 100%."

The fact that Americans are so proactive in seeking preventive treatment doesn't mean patients can demand any test they might have heard about and think they need. A BRCA-screening test, which can cost up to \$3,000, requires a referral, and that's something most doctors—sensibly—don't give out to just anyone who asks. False positives and unclear results can lead to the kind of premature surgery Brawley cites. Even if a doctor does agree that a test is warranted, there's currently no guarantee that a woman's insurance company will pay for it.

Insurers instead place women on a coverage continuum, relying in part on guidelines established by the National Comprehensive Cancer Network (NCCN), an advisory panel made up of some 30 physicians, genetic counselors and other experts. Likeliest to have a BRCA test covered are women with early-onset breast cancer and a close



OF HER FAMILY JOLIE SAYS, "I CAN TELL MY CHILDREN THAT THEY DON'T NEED TO FEAR THEY WILL LOSE ME TO BREAST CANCER ... THEY KNOW THAT I LOVE THEM AND WILL DO ANYTHING TO BE WITH THEM AS LONG AS I CAN."

family member who is BRCA-mutation-positive. In the middle are women who do not have cancer but have a family member who tested positive. At the low end is someone who does not have cancer and has no close relatives known to be BRCA-mutation-positive.

But the test is only the first part of the process. Also critical is genetic counseling, which isn't free either. Then there's the cost of any surgery that follows and the reconstruction that may come after that. Depending on individual policies, every one of those stages could represent a separate insurance tollgate, and that leads some experts to wonder if it's even fair to start a patient down that road if she doesn't have the financial means to follow it all the way. "You almost wonder, Should I get someone tested if they can't use that information?" says Dr. Mary Daly, NCCN's chair of the genetic/familial high-risk assessment panel for breast and ovarian cancers. "It's kind of like doing free mammograms when you don't have a surgeon."

Even after full implementation of Obamacare, the language that guides insurance companies will be vague. Women will be covered for BRCA testing and genetic counseling "if appropriate" and when their "family history is associated with an increased risk for delete-

rious mutations." The policy vagueness regarding testing and treatment may reflect persistent conflict over health care priorities. But the scientific uncertainty is unavoidable. Genetic screening, if not in its infancy, is barely out of childhood. And the battle against all disease—especially cancer—is one we've been waging for millennia. The wisdom gained in the lab needs to be matched by the wisdom of both caregivers and patients, and that requires hard thinking and reasoned discussion.

Jolie's role in all of this adds one more important dimension. She has long been a symbol of the feminine ideal—which in its shorthand sense has meant feminine beauty. Her body has been a key dimension of her fame; now it may be an even bigger dimension of her influence. The loveliest and most resonant passages in her op-ed piece come during her brief description of her breast reconstruction: "The results can be beautiful," she reassured, adding that her children can see the small scars but that other than that, "everything else is just Mommy." With that, the most stunning woman in the world redefined beauty. That made us all a little smarter. —WITH REPORTING BY KATE PICKERT, SUSANNA SCHROBSDORFF, ALEXANDRA SIFFERLIN AND LILY ROTHMAN/NEW YORK ■

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