CASE PRESENTATION

Testing for Genetic Risk: The Angelina Jolie Effect

In May 2013, the actress and director Angelina Jolie made a highly publicized announcement about a personal medical decision. Writing in the *New York Times*, she described her decision to have a preventive double mastectomy earlier that year. It turned out that Jolie had tested positive for a dangerous defect in the BRCA1 gene, a rare mutation that gives women, on average, a 60 percent risk of developing breast cancer. Due to the specific form of Jolie's BRCA1 mutation, her physicians estimated that she actually had an 87 percent chance of developing breast cancer and a 50 percent chance of developing ovarian cancer. Jolie's decision to undergo preemptive surgery was also influenced by the fact that her mother had died of ovarian cancer at age 56 and her aunt had died of breast cancer.

"Once I knew that this was my reality, I decided to be proactive and to minimize the risk as much as I could," Jolie wrote. She said she was making her surgery public to help other women fight the sense of powerlessness often associated with cancer. As a result of her surgery, Jolie's estimated chance of developing breast cancer fell below 5 percent, and she said that she could now confidently assure her children that they would not lose her to the disease. While acknowledging that only a fraction of cancers are caused by inherited genetic mutations, Jolie expressed hope that more women would get genetic testing, as a way to "take on and take control" of the challenges posed by serious illness.

In the weeks and months after Jolie's high-profile announcement, genetic counselors and testing centers around the world reported sharply increased demand for their services. The influential medical writer and cardiologist Eric Topol went so far as to call Jolie's announcement a "tipping point in medicine" that would inspire patients to take charge of their health care decisions through direct-to-consumer genetic testing. A resurgence of this "Jolie effect" was widely expected following the actress's subsequent announcement, in March 2015, that she had her ovaries and fallopian tubes surgically removed, as a further step to address her genetically elevated risk of developing ovarian cancer.

It may be tempting to dismiss the public's response to these announcements as little more than "recreational genetics" driven by prurient interest in the private life of a celebrity. Certainly, some of the public's increased interest in genetic disease risks appeared to be based on misconceptions about BRCA mutations and genetic testing in general. But two retrospective studies of the "Jolie effect" found that it had roughly doubled the number of referrals for women who were genuinely at high risk for hereditary breast cancer. It also appeared to have decreased stigma associated with prophylactic surgery.

Despite its Hollywood backdrop, the story of Angelina Jolie Pitt (as she is now known) exemplifies many of the challenges faced by those who choose to be tested for genetic disease risks. As Jolie Pitt discovered, such testing can provide patients with empowering knowledge that allows them to take decisive action to protect their health. But it can also present patients with difficult life-and-death choices, which must be made on the basis of probabilities and limited information. Making sense of genetic testing results can be even more challenging if they are obtained through a direct-to-consumer testing service such as 23andMe, which do not provide face-to-face genetic counseling. As these services offer an increasing number of FDA-approved medical tests, it is more important than ever for patients and physicians to take stock of what genetic testing can and cannot tell us about our risk of disease.

Genetic Disease: A Blurred Concept?

Since the 1990s, the discovery of hundreds of disease-predisposing genes has been accompanied by the development of dozens of new genetic tests. Given the increasing sophistication of biotechnology, tests that were complex and expensive just a few years ago have become simple and cheap. Automated processes using intricate arrays of genetic probes can efficiently test a saliva or blood sample for the presence of hundreds of genetic variations.

Researchers have identified an expanding catalogue of genetic anomalies and associated diseases, but the concept of a genetic disease is not as clear-cut as it may seem. Although single-gene disorders such as sickle-cell anemia, cystic fibrosis, and Huntington's disease have been at the focus of much research, they account for only about 2 percent of genetically influenced disorders. Most diseases result from a multiplicity of conditions, including (1) the particular form of a gene (many genes can have hundreds, even thousands, of potential mutations); (2) the simultaneous presence or absence of other specific genes; and (3) the presence or absence of specific environmental factors. These complications can raise a number of challenging questions about the benefits and drawbacks of genetic testing.

Individual Choice

Recent studies have indicated that roughly 60 percent of Americans say they would be interested in genetic testing to determine if they or their children are at risk for serious diseases. While this figure reflects an increase over polls from two decades ago, which showed an even split on the question, many Americans are clearly still ambivalent about testing for genetic predispositions, particularly if they feel there is nothing they can do about the results. Patients such as Angelina Jolie Pitt, by contrast, believe that "knowledge is power" and argue that "it is possible to take control and tackle head-on any health issue" by learning about the options and making "choices that are right for you."

There is no question that information about genetic disease predispositions can be powerfully beneficial. It can prompt patients to seek medical evaluation so that they can receive appropriate and early treatment for a disease, should it develop. Further, such information can help patients avoid environmental factors that may trigger the expression of a genetic condition. For example, those with the genetic mutation that causes xeroderma pigmentosum are extremely sensitive to ultraviolet radiation, and exposure to it is likely to lead to a form of skin cancer (melanoma) that is often incurable. However, if those with the gene avoid prolonged exposure to sunlight, they have a better chance of avoiding melanoma.

By contrast, in the case of some single-gene diseases such as Huntington's, the knowledge that one is a carrier of the gene opens up few options for altering the outcome of the disease. Huntington's is currently not preventable and treatment options are limited to the temporary mitigation of symptoms. Although some patients might want to know whether they are carriers of the gene in order to make informed plans about such matters as childbearing, marriage, and careers, others might prefer to live their lives without knowing. (See Case Presentation: Huntington's Disease in this chapter.)

Even the dangerous genetic mutation that prompted Jolie Pitt's prophylactic surgeries can leave patients uncertain about what course of action to take—a problem that is exacerbated by the complexity of the treatment options and underlying genetics.

The mutated gene BRCA1, located on chromosome 17, was identified in 1994 as responsible for breast and ovarian cancer susceptibility in families with multiple incidences of those diseases. A second gene, BRCA2, located on chromosome 13, was identified in 1995 as causing increased susceptibility to breast cancer and was later also linked to ovarian cancer.

When functioning properly, the BRCA1 and BRCA2 genes produce tumor suppressor proteins that repair damaged DNA. But when parts of these genes are mutated or deleted in such a way that they fail to produce effective proteins, DNA damage can run rampant in cells. While thousands of mutations have been identified on BRCA genes, many of which have no negative effects, researchers have identified a number of mutations, particularly those on BRCA1, which are strongly associated with cancer in younger women. Some studies have indicated that women who carry these mutated BRCA1 genes are estimated to have an 85 percent chance of developing breast cancer and a 60 percent chance of developing ovarian cancer by age 65. (This may account for the 87 percent risk of breast cancer estimated by Jolie Pitt's physicians.)

While BRCA mutations are likely responsible for the majority of hereditary breast and ovarian cancers, they do not appear to play a role in the 85 to 90 percent of these cancers that are "sporadic," with no known link to inherited susceptibilities. In addition, even the most dangerous BRCA mutations do not guarantee that a

A Sample of DNA Tests Currently Available

Disease	Description
Huntington's disease	Progressive neurological disorder, onset in forties or fifties
Polycystic kidney disease	Multiple kidney cysts leading to loss of kidney function
Cystic fibrosis	Mucus clogs lungs and pancreas; death in thirties is common
Sickle-cell disease	Hemoglobin defect; anemia, strokes, and heart damage
Familial adenomatous polyposis	Colon polyps by age thirty-five, often leading to cancer
Muscular dystrophy	Progressive muscle deterioration
Hemophilia	Blood fails to clot properly
Tay-Sachs disease	Lipid metabolism disorder causing death in first one to four years of life
Phenylketonuria	Enzyme deficiency producing mental disabilities
Retinitis pigmentosa	Progressive retinal degeneration leading to blindness
Hereditary breast and ovarian cancer (HBOC)	10 to 15 percent of breast and ovarian cancers
Familial hypercholesterolemiaboc	High levels of cholesterol leading to early heart disease
Spinocerebellar ataxia	Neurological disorder producing lack of muscle control

patient will develop cancer. Other factors, including diet, exercise, alcohol consumption, and other bodily systems may play a significant role in whether above-average odds translate into disease.

Nevertheless, about a third of women diagnosed with dangerous BRCA1 mutations opt for prophylactic double mastectomies and even more start with surgery to remove their ovaries and fallopian tubes. As Jolie Pitt has noted, these surgical interventions have been shown to bring cancer risks for women with BRCA mutations back into the single digits—close to average levels of risk. But they also come with serious consequences and side effects.

Mastectomies, as Jolie Pitt has noted, are usually long and complicated surgeries, particularly when they involve techniques aimed at artificially reconstructing the breasts. But the long-term physical and mental side effects are relatively minor. Breasts serve no biological function apart from breastfeeding, and most women who get mastectomies report high satisfaction with the decision years later. By contrast, *oophorectomies*, or removal of the ovaries, are now relatively simple laparoscopic procedures, but can come with substantial side effects. In addition to eliminating the capacity to conceive children, oophorectomy forces a woman's body into menopause. The abrupt shift can increase risk of heart disease, high blood pressure, and stroke, while interfering with sleep, cognition, and libido. While these side effects can be mitigated by hormone treatments, they should not be taken lightly.

Getting tested for BRCA mutations can thus present women with a set of complicated dilemmas. If they test positive for one of the riskier mutations, their best treatment option may involve a surgery that causes sterility and long-term side effects. If they decide to forego surgery, they may have to live with decades of expensive, ambiguous, and anxiety-provoking tests aimed at detecting early onset cancers. Thus, even though the CDC recommends that women with a strong family history of breast and ovarian cancer be tested for BRCA1 and BRCA2, some may choose not to. The high cost of BRCA screening may also pose an obstacle for these patients. (See Case Presentation: Genae Girard and Gene Patents for more on this topic.)

Other women, such as Jolie Pitt, see the knowledge that comes with genetic screening as inherently useful and empowering. Even if they have ruled out surgery, what they learn from the test can help them make informed choices about career, family, and lifestyle—something which they see as

valuable in its own right. If they test negative for BRCA defects, knowing that they are no more likely than other women to develop breast or ovarian cancer can provide peace of mind and a chance to focus on standard cancer prevention strategies. If they test positive, they are in a position to reevaluate the full range of aggressive prevention procedures and screening protocols.

Direct-to-Consumer Genetic Testing

Patients such as Angelina Jolie Pitt believe that "knowledge is power" when it comes to obtaining and taking action based on genetic information. Some proponents of patient-driven medicine see direct-to-consumer genetic testing companies as the ultimate way of empowering patients, allowing them access to their genetic information without interference from (potentially paternalistic) gatekeepers such as physicians and insurers.

From the time of their rollout in the mid-2000s, however, direct-to-consumer genetic testing companies such as 23andMe, deCODE Genetics, and Navigenics faced questions about their scientific accuracy and legality. The companies typically provided non-disease-related genetic analysis of ancestry and paternity, along with characteristics such as male-pattern baldness, "supertasting" ability, and ear wax consistency. But they also claimed to provide information about genetic "risk factors" for diseases, which brought charges from state and federal regulators that they were providing medical advice without meeting the standards required for clinical laboratories. Their methods of assessing disease risk were also challenged by scientists.

SNPs and Risks. Unlike the genetic test that revealed Jolie Pitt's BRCA1 defect, most direct-to-consumer genetic tests have not generally tested for individual genes, nor sequenced the billions of DNA base pairs in an individual's entire genome—a more expensive process typically carried out in academic laboratories. Instead, direct-to-consumer tests have often focused on the hundreds of thousands of segments of DNA known as *single-nucleotide polymorphisms*, or *SNPs* (pronounced "snips").

PERSONAL GENOMICS AT BERKELEY

The University of California, Berkeley, announced in 2010 that it will mail a DNA-collecting kit, consisting of a cotton swab and a plastic tube, to all members of incoming freshmen classes.

Returning the DNA sample is voluntary, but those returned will be tested for three genetic markers associated with the ability to metabolize alcohol, lactose, and folates. The three genes were selected because the students who test positive for them could use the information to live healthier lives by consuming less alcohol, avoiding dairy products, and eating more leafy green vegetables. The privacy of students will be protected using an anonymous bar code system.

Jasper Rine, the geneticist heading the project, sees it as an opportunity for students to learn about personalized medicine and their own genetic traits. "The history of genetics is the history of finding bad things," he is quoted as saying. "But in the future, nutritional genetics is probably going to be the sweet spot."

Critics worry that because genetic information can be cause distress, it ought to be provided only by physicians and in a setting in which counseling is offered. Defenders consider such a view paternalistic and argue that people should be able to learn about their own genes.

SNPs are variations in nucleotides (the adenine, cytosine, guanine, or tyrosine on a DNA strand) that occur together in a genome. (For a more detailed discussion, see Social Context: The Human Genome Project.) These variations may be harmless, simply reflecting ancestral and regional differences. But because SNPs can be identified in gene mutations (as well as in nongene segments of DNA), they also have been associated with problems in gene expression—such as the failure to produce certain enzymes or proteins.

In this sense, SNPs have been said to function as genetic markers. Whether or not they are responsible for a disease or trait, particular SNPs have been shown to be associated with diseases like breast cancer, asthma, bipolar disorder, macular

degeneration, cluster headaches, Crohn's disease, amyotrophic lateral sclerosis (ALS), diabetes, and colon cancer.

To make use of these associations between specific SNPs and specific diseases, direct-to-consumer companies have typically used biochips programmed to detect common SNP variations along a DNA strand. The chip creates, in effect, a catalogue of an individual's SNPs, which are then compared with those in a database linking particular SNPs with particular diseases. (The same process is used to associate SNPs with particular traits, such as hair color and lactose intolerance.) Combining the accumulated disease risk associated with multiple SNPs, the companies then typically provided customers with a risk percentage for specific diseases—such as a 65 percent chance of developing arteriosclerosis before age seventy.

One problem with this procedure is that there were wide variations in the databases different companies use to make SNP–disease associations, as well as in the methods different companies use to calculate risk. Based on these variations, two different companies sometimes offered different—or even diametrically opposed—estimates of specific disease risks for the same individual. A deeper problem is that many scientists question the reliability of SNPs as disease predictors, since they often appear in nongene or "junk" sections of a person's DNA, which are not expressed. The correlation between certain diseases and certain SNPs may not reflect a causal (or even a particularly reliable) relationship. While a few of the companies offered some form of counseling to help customers make sense of these complexities, experts generally dismissed them as an inadequate substitute for the advice of a personal physician.

Regulation and Renewal. Based on these and other concerns, state and federal regulators began to crack down on direct-to-consumer genetic testing companies. New York and California sent letters to dozens of the companies in 2008, warning them that they must obtain state licenses or conform to federal standards for laboratory tests, which were henceforth to be considered a form of medical advice. But little changed until 2013, when the FDA sent out a strongly worded warning to the companies that any health-related testing would require the agency's approval before they could be marketed.

Partly in response to the threat of being put out of business by federal and state regulation, the major genetic-testing companies agreed to stop performing disease-risk assessments. They also made a commitment to develop their own industry-wide standards and shared guidelines to reduce the inconsistency in their results. In February of 2015, 23andMe received approval from the FDA to market its first medical test since 2013, for a rare genetic condition called Bloom syndrome, which causes short stature, red skin, and cancer susceptibility. Unlike its previous "risk factor" screening, the 23andMe Bloom syndrome test is a "carrier test" that seeks to identify the presence of an abnormal gene in prospective parents. In this it resembles other medically established carrier tests for cystic fibrosis and sickle-cell disease. But it does constitute the first FDA approval of a genetic test to be directly marketed to consumers, and thus suggests a new direction for the industry.

Genetic Knowledge and Patient Autonomy

To the extent that direct-to-consumer genetic testing adopts the more rigorous standards of "brick and mortar" clinical laboratories, it may help support the type of informed and empowered patient championed by Angelina Jolie Pitt and others. Being able to access quick, affordable, and reliable information about genetic disease predispositions might prove highly appealing to Jolie Pitt's model patient who can "take control and tackle head-on any health issue."

But other patients will likely see little point in going outside traditional medical avenues of genetic testing, particularly now that GINA (Genetic Information Nondiscrimination Act) and the ACA (Affordable Care Act) have banned genetic discrimination by employers and most health insurers. Indeed many wonder if direct-to-consumer genetic testing will survive now that patients have much less reason to hide genetic information from their physicians. Another group of patients will look at the treatment and prevention options for genetically conditioned diseases and simply decide that it is better not to know.