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Decoding Destiny

Once a genetic test proved that she was likely to develop breast cancer, she had to confront one of contemporary medicine's scariest questions.

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Not long ago, Karen Belz made an appointment to see me in my office. I'd known her for years, as a family friend. She worked as an English teacher at a local high school, played in the same tennis league as my wife, had two school-age children, and was active in town politics. Always frank and direct in her dealings, she expected the same from others. Now she was telling me that she wanted to be tested for mutations in the so-called breast-cancer genes, BRCA1 and BRCA2. "I can't continue in this limbo," she said. "I have to know."

I wasn't surprised, because she wasn't the first member of the Belz family to visit my office. (For purposes of confidentiality, the names and certain identifying details have been altered.) Karen's mother, Eva, after a long struggle, had succumbed to breast cancer some three years ago. Five months earlier, Karen's sister Ruth, only two years older than she was, had developed the same malignancy, at age thirty-six. By the time Ruth's gynecologist detected the cancer on her routine surveillance mammogram, it had spread to her vertebrae and her lungs. I was currently treating her with intensive chemotherapy and radiation. Shortly after her tumor was diagnosed, Ruth had tested positive for a BRCA mutation linked to breast cancer and had pressed Karen to be tested as well.

Marek Belz, Karen and Ruth's father, was strongly opposed to his daughters' being tested, fearing that the result would one day be exploited to harm his family. He was familiar with the abuse of genetics. Marek had escaped from Poland a year before the Nazi invasion, with Eva. When she became ill, neither could tell me about the occurrence of cancer in close family members: every member of their own generation and every member of the generation before had perished in the Holocaust. Karen, however, was unmoved by her father's opposition: she told him she'd simply have to take the risk. Since Ruth's diagnosis—first of cancer and then of the aberrant gene—the anxiety of not knowing had dominated Karen's thoughts, preventing her from getting to sleep and then shocking her awake at 3 or 4 a.m. Her daydreams were penetrated by memories of her mother's slow death, and she had nightmares that Ruth would soon be lost as well. Not knowing seemed worse than knowing.

All participants in cancer-genetic-susceptibility programs are required to read and sign an informed-consent document before being tested. At Beth Israel Deaconess Medical Center in Boston, ours comes with some assurances. The patient can elect not to know the test result immediately but to wait until she is ready, or even change her mind and never know; the result is to be given only to her, in person and by her own physician; the fact that she has been tested, as well as the test's outcome, does not appear in her medical records but is stored in a locked research file, identified by a code number; the list connecting the code with her name is kept separate from the test results; and no insurance company, governmental agency, health worker, family member, or other party can obtain the test result without her written permission.

I informed Karen of the protocol, and read to her a section entitled "Potential Risks of Knowing Your Genetic Test Result," which states, "This information may cause you distress, sadness, depression, anxiety, or anger."

“I look forward to all of the above,” Karen said acidly.

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BRCA testing is one of the first fruits of the human-genome project. The project is vast and ambitious, and has enlisted the energies of scientists and clinicians around the globe. The goal is to decipher the code of all human DNA—our genetic blueprint—and then to use the information to understand how each gene contributes to health or to disease. The task should be completed within one or two decades.

The informed-consent document that Karen signed before being tested is specific for the genetic testing of BRCA1 and 2, two genes among the estimated hundred thousand genes contained within our forty-six chromosomes. All human beings carry two copies of each of their genes, one inherited from their mother and one from their father. Women who inherit a single defective copy of either BRCA1 or BRCA2 are at a significantly increased risk for breast and ovarian cancer over the course of their lives. Of some two hundred thousand new cases of these two cancers which will occur in the United States this year, between three and a half and seven per cent will be the result of inherited mutations in the BRCA genes. There is a particularly high incidence among Ashkenazi Jews, like the Belzes. This probably reflects the so-called founder effect: the Ashkenazi population arose from relatively few “founder” families, which migrated east into Poland, Lithuania, and Russia, with very little marrying outside the community, and thus conserved the mutation from generation to generation. The combined frequency of BRCA1 and 2 mutations among Ashkenazi Jews is greater than two per cent, a very high number in population genetics.

“Why would a gene that promotes deadly cancers be conserved during evolution?” Karen asked.

There is no exact answer, I told her, but we could extrapolate from Darwinian principles. Nature cares only about an organism's reaching the point of reproduction and nurturing the next generation. Since the mutated BRCA genes do not impair fertility, and generally wreak their havoc beyond the age at which children would be produced and reared, there is no apparent evolutionary pressure to select against the genes. Their perpetuation might even be a benefit to the population, by shortening the life span of adults who were taking precious food and water away from the younger generation.

“What a wonderful Malthusian gift,” she said, with a grim smile.

Mutations often occur within our genes, for the enzymes that copy DNA when a cell grows and divides are imperfect and make random mistakes. Mutations in DNA also occur when we are exposed to radiation or to certain toxins in the environment. In most instances, these mutations don't really matter: either the changes are trivial and well tolerated by the cell or they're so damaging that the cell dies, with limited consequences. But some mutations are neither trivial nor lethal. These pervert the cell's behavior, causing it to proliferate wildly and assault vital organs. This is the pathological process we call cancer.

The normal BRCA2 gene is composed of 10,254 nucleotides, or DNA building blocks. The BRCA2 gene carried by the Belz family was missing nucleotide No. 6,174. This single omission results in a short and crippled form of the protein that BRCA2 codes for. At the time of the test, I had explained to Karen that the normal function of BRCA genes is understood only in general terms. The most recent research suggests that they somehow repair damaged DNA, rehabilitating nascent cancer cells like an interventional therapist. Why, when the genes malfunction, cancers arise only in breast and ovary, and not in other tissues, is still a mystery, but it suggests that sex hormones like estrogen somehow modulate its activities.

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Five weeks later, Karen and I sat again in my office. I had just given her the test result. “So I’m destined for cancer, just like my mother and sister,” she said. “Talk to me straight, Jerry. I should get rid of my breasts and ovaries, shouldn’t I?”

Karen’s style was to cut to the heart of the matter, but I worried that she was moving too fast. It wasn’t possible to say even that she was destined for cancer, let alone talk to her straight about what to do. I felt off balance, without a platform of established clinical data upon which to stand. It is a moment of inadequacy that every physician dreads, realizing that while current knowledge is severely limited, a course must be taken—a course that might prove fatally flawed in the future. I paused, studying Karen’s unflinching face: deep-set almond brown eyes, sculpted Slavic cheekbones, and determined chin.

I was tempted to hide behind the popular notion that patients alone are “empowered” to choose their therapy, and simply tell her that it was her decision. But wasn’t that a kind of cowardice—an easy out? The decision had to be hers; but that didn’t mean she had to make it alone. “Remember that our genes are just the starting point, far from the whole picture,” I cautioned. “Their program during life is modified by many factors. Despite having the same mutation in a BRCA gene, you are different from your mother and from Ruth.”

“But how different? That’s what I need to know. And you can’t really say, can you?”

“I can’t,” I admitted. I went on to explain that the BRCA2 gene was identified in 1995, just two years before, so the available data tell us mainly about the over-all susceptibility of the affected group to cancer and not about specific individual outcomes. One set of clinical data on BRCA mutations indicates that the age at which tumors first occur is highly variable. Although recent surveys of Ashkenazi Jews indicate that the risk for breast cancer with a BRCA mutation is about

sixty per cent, in families with several closely related cases of the disease the risk is higher, on the order of between seventy-five and ninety per cent. Still significant, but somewhat lower, is the risk for ovarian cancer, about twenty per cent. “Keep in mind that these odds are actuarial—projections over the course of a person’s lifetime, culled from a handful of preliminary studies in the United States and Israel,” I told her. “Nonetheless, I think one can accept them as accurate approximations.”

I stopped speaking, in part to give Karen a chance to ask questions, in part because I didn’t like the way I sounded. It was important to provide her with all the available information on the mutation, but I had heard my language becoming increasingly remote and clinical.

Karen’s face had turned into a mask, and I feared that she was numb from having learned her test result, that the swirl of uncertain numbers had passed by her in a blur. When I asked if everything was clear, however, Karen said it was. She had already garnered most of this information from the Internet. She was waiting for me to get to her question.

“Should you have your breasts and ovaries removed?” The question hung suspended between us for a long moment. “To answer most helpfully, I’d have to be sitting where you are, rather than on my side of the desk, and be a thirty-four-year-old woman, with two children and a solid marriage. So I’m limited on these counts. But if I had a genetic mutation analogous to yours, carrying as much as a ninety-per-cent risk of, say, testicular cancer, and a twenty-per-cent risk of prostate cancer, and my father had died from it, and my brother now had it, despite close medical surveillance—regular physical and radiological examinations, biopsies, and blood tests—and he was undergoing intensive chemotherapy and radiation treatments for metastases, with all their toxicities and an uncertain chance of cure, what would I do?” I wanted, as I spoke, to spark

intuition, hers and mine. “And I faced two unsatisfactory choices: one conservative, waiting under surveillance, and one radical, undergoing surgery, with no real middle ground—”

“Is there actually nothing more than that?” Karen interrupted. “I accept that there’s no simple solution. But you feel desperate when you hear that that’s all there is. You want to do something for yourself, something proactive, and not just live under surveillance. It seems like passively waiting in the ghetto to be selected.”

When Ruth became ill, Karen told me, well-meaning friends had bombarded them both with suggestions: eat strictly organic, take megavitamins, avoid all alcohol and fats, try special herbal tonics and Eastern healing techniques. Karen and I now talked about such suggestions. Many of these nostrums were harmless, and some, for all anyone knew, might even be helpful, but they remained unproved and could not be relied on to prevent breast or ovarian cancer in a woman who was genetically predisposed. Prophylactic studies of estrogen antagonists like tamoxifen are just being organized and will take years to yield data on risk and benefit.

As we spoke, I could see her brow fall and her eyes become heavy. I knew that what I had to say would be even more unnerving and had best be delivered quickly.

“If surgery were to give me a full guarantee against cancer, I’d probably sacrifice intimate parts of my body in exchange for it, with all that that means regarding sex and self-image,” I said. “But no one really knows how much protection is gained by such mutilating surgery, because the data are scant.” No one had had the opportunity to follow women with BRCA1 or BRCA2 mutations who chose surveillance instead of having their breasts and ovaries removed. There were only extrapolations from the past, when healthy women who had strong family histories of these cancers chose surgery. But this was a heterogeneous group, not genetically defined, and had come

into being before the era of high-quality mammograms, pelvic ultrasonography, and blood tests, which could identify tumors at their onset. “Unfortunately,” I added, “it’s all we have to go on.”

“And?” Karen put in.

“And removing both breasts is roughly estimated to reduce your risk of cancer by ninety per cent but not to zero,” I said. Even the most meticulous mastectomy, I explained, leaves some cells behind that can later transform and become malignant. Oophorectomy—removing the ovaries—would be likely to reduce her risk of cancer, but, again, not to zero. There are often microscopic islands of ovarian cells growing outside the ovaries. These islands stud the peritoneum, the lining of the abdomen, and are too small to be found and cut out by the surgeon during the operation. They can provide the seeds of cancer after the ovaries are excised.

“And the success of intensive surveillance in finding the cancer early, before it spreads, like Ruthie’s?” Karen pressed.

“Unknown over the long term,” I replied.

I paused, then told her that nonetheless most women I care for, and presumably most women nationwide, currently elect this conservative approach of surveillance rather than the radical surgery.

In the shared silence, Karen gathered herself into a tightly held coil, as if she were a child chilled to the bone and were trying to protect her body’s ebbing warmth: head bowed, arms crossed over her chest, legs tightly drawn together. “I can’t do it,” she said, finally. “I can’t get rid of my breasts and my ovaries.”

I was taken aback. As we talked I had been imagining Karen as my wife, Pam, and the Belz family as my in-laws, and I had convinced myself that I would want Pam to have the operation—that the physical alteration of her body would not change who she was or the substance of our

relationship. And Karen was a friend as well as a patient. I had mourned the death of her mother and was now afraid that Ruth would soon succumb as well. Above all, I wanted Karen to be saved. Surely that imperative overrode the loss of breasts and ovaries, of self-image and libido. But I hadn't understood her as well as I thought I had.

"The final decision shouldn't be made today," I said, giving us both more time. "Just as we didn't immediately go ahead with the test. It's best to think more before committing to a course." I watched her carefully. She exhaled heavily and nodded.

We agreed to meet in a week to talk again about the options. I stated that afterward I would refer her to the clinical psychologist in the cancer program, to give her the opportunity to explore her decision with another professional, and perhaps from a different perspective.

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And maybe I needed a different perspective myself. After Karen left, I tried to organize my thoughts by recording a summary of our conversation in her medical chart. But I was stopped by the realization of something that neither of us had brought up. What of her children? Her daughter was thirteen and her son eleven, both at an age where explanations are required. When and how should they learn about the BRCA2 gene?

My focus was drawn to the pictures of my family arrayed on my desk. There were Pam and I dancing at our wedding, joined by a white handkerchief, in traditional Ashkenazi style. Pam's family had a history of breast cancer, and this past year my mother had developed it. Beside the wedding photograph was a picture of Emmy, my five-year-old daughter, on a swing, caught by the camera in a moment of fearless glee. What terrible aberrations hid in the fabric of her DNA, waiting for age and hormones and the myriad triggers of the environment to unleash them? Would the effort to unravel DNA condemn Emmy to the twilight terror that Karen had just entered? Perhaps

it was best for all of us to remain ignorant, so that life could progress naturally, without the burden of deadly prophecies. It sometimes seemed as if the decoding of our genome would cause a fundamental change in how we perceive time—as if we would come to ponder not the infinite time of an expanding universe but the sharply limited span of our existence. Like Karen, all of us will face the choice of learning our probabilities of illness. In addition to those in BRCA1 and 2, genetic mutations that predispose people to Alzheimer’s disease, colon cancer, Huntington’s disease, endocrine tumors, and melanoma have been identified. The list will grow until it encompasses all our potential pathologies. We might try to shrug off the knowledge, or run from it, but when we had quiet moments during the day or woke in the middle of the night we would be forced to accept it as our constant companion, because we could see its features in our very being.

And then it struck me that these new genetic terrors were like the ones I had come to know in my years of clinical and scientific work on AIDS. People with H.I.V. permanently acquire the destructive genes of this virus. They, too, live with a genetic time bomb. Vociferous debates racked the at-risk communities, particularly those of gay men and hemophiliacs: Should you be tested? Could the results be used to deny you insurance or opportunity in the workplace? What could you do for yourself to stave off the disease? Why did medical science seem powerless to find a cure?

A few years back, I had faced the decision of whether or not to be tested for H.I.V. All health-care workers were encouraged to have themselves screened, and so were researchers who, like me, had worked with H.I.V. in their laboratories. I knew I was at especially great risk of having been exposed to the virus. Before gloves and other precautions were instituted in hospitals, my hands had been soiled directly by infected blood and secretions, and I’d once pricked my finger deeply with a contaminated needle after performing a bone-marrow biopsy on an AIDS patient. I

had also received multiple blood transfusions during spine surgery in 1980, a time before blood products were screened for H.I.V.

For months, I avoided scheduling the test, finding excuses in the demands of work and travel. But finally I went ahead, feeling, like Karen, that I had to know. I also accepted the fact that the result could change my plans for work and family. Even after obtaining the negative result, I was still visited by the nightmares I had experienced while waiting, and found myself wondering whether I might be one of those rare people whose infection was not detected by the test.

Though I observed the anguish among those who learned that they had tested positive, I was also struck by the way the awareness could catalyze beneficial changes. It led many people to take better care of themselves—stop smoking, end drug use, improve diet, take up exercise, seek stress reduction. On a community level, activist movements forced the F.D.A., universities, and pharmaceutical companies to accelerate the process of drug research and development. Above all, the knowledge that one carried H.I.V. and was mortal gave many young people a precocious sense of maturity and wisdom.

The advances that had been made in developing safer and more effective treatments for H.I.V. could not have occurred without testing people with the virus at different stages of the illness. The most important breakthrough—the creation of the protease inhibitors—grew from an intimate understanding of the genes of H.I.V. and of how they functioned in an infected host. If we had not used our molecular tools to test for the virus and assess the range and the patterns of its growth in people, we would not have developed these potent drugs.

Testing also revealed that some people never became infected despite extensive exposure to H.I.V. Many of them had a mutation in a host gene which conferred resistance to H.I.V. Such people are serendipitously resistant to the virus, because H.I.V. is unable to get a grip on their

blood cells and penetrate them. The inherited mutation causes no apparent harm: these fortunate individuals seem completely healthy.

Such findings provide the intellectual framework for the design of therapies that mimic the serendipitous mutation and confer protection against the virus. Again, if people had not agreed to be tested and offered themselves as subjects for study, with no apparent benefit other than knowing they were contributing to scientific investigation, we could never have obtained this information. Commuting the death sentence of AIDS will be realized only if testing continues and more clinical data are obtained.

The ferment around breast cancer recalls the early days of AIDS: acute public awareness, increasing political pressure, the marshalling of research prowess and resources. It may take years or decades for researchers to come to understand the complex genetic underpinnings of breast cancer and to use this knowledge to design targeted ways of preventing or curing it. But that moment will arrive. And it will do so only as a result of the exploitation of clinical material: patients' blood cells and tissue biopsies and DNA.

So this was one reply to Karen's question of what she could do for herself—and, indeed, for her children, if they, too, had inherited the gene. I planned to encourage her to be an active participant in the fight by using her political skills to push society harder and faster to address her needs. I would ask her to enter our ongoing study of the clinical and psychological condition of women who have tested positive, allowing us to collect data on her medical course and on her functioning in the home and in the workplace. Studies on women like Ruth—those who have a BRCA2 mutation and a family history of breast cancer—will be vital to understanding the origins of the disease. Just as important are the insights that can be gained from the exceptions to the rule, as we determine why at least one in ten women with a BRCA mutation does not progress to cancer.

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For a week, I anxiously anticipated Karen's return appointment. I had not been trained in medical school or during my clinical residency to handle the issues that confronted me. I had not been instructed by a senior attending physician in how to speak and listen, how to decide which questions are appropriate and which taboo, or how to make one's case for the best option.

Karen arrived promptly for her mid-day appointment. It came during the school lunch hour, and I noticed her sitting in the waiting room, grading papers and recording the scores in a large ledger she balanced on her lap. She greeted my secretary warmly, and entered my office with a polite smile.

Karen spoke first, evenly and strongly. "I'm going to have my breasts and ovaries removed."

I was stunned by the reversal.

"No, I'm not losing it, Jerry. And I will see a psychologist to explain my decision. The shrink will find me *compos mentis*."

"What changed your mind?"

"Not 'what'—'who' should be your question."

Karen explained that when she returned home and told her husband, Sam, of our discussion, he couldn't believe she hadn't decided to have the surgery. He said that he loved her deeply, that she would remain desirable, and that their marriage was resilient. Even so, she was undeterred. "He was speaking theoretically, the way you were last week about your facing what I am," Karen continued. "I know that both of you were trying your best to help and comfort. But neither of you can really see yourself in my place."

I agreed, and then I saw who could. "Ruth," I said.

Karen nodded. I recalled telling her that she was different from Ruth. “How different?” had been Karen’s reply. Now Karen said, “She called me several times after the appointment, but I repeatedly put her off. I couldn’t bring myself to discuss it. She was always the big sister, scouting out danger and steering me away. This time, I thought I had to deal with it myself, without her. But Ruthie wouldn’t let it go.”

Ruth came to the house Sunday morning, Karen said, and Sam took the kids out to McDonald’s. The two sisters sat at the kitchen table over untouched cups of black coffee, and they talked.

“Ruth said that I was one of the lucky ones,” Karen went on, her eyes moist. “I had been given advance warning, by our mother and by her. That my relationship with Sam could survive any changes in my body, as hers had with her husband, despite the cancer and chemotherapy. And that I would never stop being who I am.” Karen paused, and I reached out to grip her trembling hand. “Ruth said she wished someone had told her to have a mastectomy. Not just in hindsight, not just because now she has cancer. But because she would know that she had done everything possible to try to prevent it, and wouldn’t live with regret.” Almost in a whisper, Karen added, “I want so much to see my kids grow up. Ruthie doesn’t think she’ll see hers.”

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Karen and Ruth both entered clinical and epidemiological studies in 1997—studies that will help us understand how to use the genetic information we have. But clinical testing and observation are only part of the solution. The laboratory is where the tools to disarm mutant BRCA genes in the next century will ultimately be developed.

Such research could eventually permit us to use genes like drugs, as a form of therapy. This concept of gene therapy has great appeal: it is targeted to the fundamental cause of the cancer, in

contrast with what is brutally termed “slash, burn, and poison,” meaning surgery, radiation, and chemotherapy. If the issue is a mutant gene, then block it and substitute its normal counterpart. There are still many formidable obstacles to achieving this goal—obstacles that will take years to overcome. No technology exists yet to deliver the healthy gene throughout the breast tissue and the ovarian tissue, to switch off the aberrant BRCA gene and make sure that the healthy one functions properly. But recent successes in locally bypassing blocked arteries in atherosclerosis and restoring immune function in inherited immune deficiencies by the use of gene therapy indicate that one day the technology will be developed to help families like the Belzes.

One last thought came to mind as I contemplated the uncertainties that patients like Karen would be facing. It had to do not with science or society in the future but with wisdom from the past. Karen began each school year discussing Greek mythology, Bible stories, and fairy tales, showing how they contained enduring themes that were to be the subjects of her course in modern literature. Within the legend of King David was a parable concerning his desire to know about himself. After learning everything that was within his ken, David had beseeched God to reveal to him the date of his death, so he could plan his life accordingly. God had answered that no man can know the time of his passing. David was to live with an acute awareness of his mortality, and in this way more wisely fulfill his life.

I had taken this tale at face value for many years, assuming that it spoke of God’s omniscience as hidden from man, and on the fixed limits we face in trying to learn life’s secrets. But recently I had been wondering whether there was another interpretation. Perhaps God did not inform David because God did not know; perhaps the date and circumstances of David’s end were not determined. The hope that sustains us comes from the belief that our future is yet to be created, and is created in part by us.