DNA dilemma – a potentially life-changing test

By Bonnie Rochman, Time

Know your enemy, we tell ourselves; knowledge is power. Laurie Hunter wanted to know what disease was attacking her daughter Amanda, who by the age of 2 months was not developing normally. Her muscle tone was low. She wasn't lifting her head. She was slow to talk, and she didn't walk until she was 2.

"As a mother, you know that everything that happens to your child is not your fault, yet you still feel responsible," says Hunter, 42, a high school English teacher who lives in Jackson, N.J. "We turned to genetic testing because I wanted answers." The first tests, done at the Children's Hospital of Philadelphia (CHOP) when Amanda was 4, came back normal. So did another round when she was 9. Doctors could not figure out what was making Amanda weak—even as she got weaker and slower and stopped being able even to blow her nose. "It's like her muscles are getting tighter and not moving in the way they should," Hunter said. But the doctors held out hope. Genetic testing grows more sophisticated every day, they said, allowing researchers to explore a child's health down to every last typo on a chromosome.

In March, a third round of tests found seven genes missing from Amanda's first chromosome. At last, Hunter thought, when the genetic counselor called and asked to see her. "It felt like finally I might have an answer." But it was not the answer she was looking for. The small deletion, the counselor said, did not explain Amanda's condition. That was still a mystery. And now a whole new threat appeared.

One of the seven deletions has been linked to very rare

tumors. The geneticists wanted Amanda, who is 14, to be screened by an oncologist. “It was like, Oh, my God, now we are adding cancer to the mix,” Hunter says. “Never in a million years did I think this would be an issue.”

She was even more surprised when a counselor called after her own tests came back. “I know you’re going to be upset,” the counselor said, “but we found that you have the same deletion.” And so might her other two children.

This is the world we are heading into: one with powerful new weapons against age-old diseases and a host of questions about how to use them wisely and not turn them on ourselves. Imperfect knowledge can make us crazy—or bankrupt—chasing down threats that may never materialize. The human genome is an exquisitely complex blueprint. Geneticists hunting for answers to mysterious symptoms invariably trip over incidental findings, genetic twists they were not even looking for that might signal a risk of cancer or Alzheimer’s or Parkinson’s in the near or distant future. But do doctors have to tell patients everything they learn, even about the risk of diseases for which there are not yet cures? Do parents have to tell their children what might await them as adults? And who will pay for all this? “Everyone at this point is flying by the seat of their pants,” says Dr. James Evans, a medical geneticist at the University of North Carolina School of Medicine. “The technology is outpacing us.”

From labs to living rooms

The mapping of the human genome, completed in 2003, cost $2.7 billion. Now the cost for an individual’s whole-genome sequencing (WGS) is $7,500 and falling fast. One day WGS could be as easy to get as a pregnancy test at the drugstore. To do the testing, lab technicians need less than a teaspoon of blood, which is chemically treated to burst open the cells so the DNA inside them can be collected. Those microscopic strands are then fed into sophisticated machines that read

each of the 3 billion bits of information, called base pairs, that make up a person's genetic alphabet. Computers scan the data for the equivalent of spelling mistakes. Some mistakes cause disease; others don't. And in between is a vast gray area where scientists just don't know what the changes mean.

In an ideal world, genetic analysis could save money by catching diseases early, offering targeted treatments and identifying the most effective preventive measures. Dr. Katrina Armstrong, a professor at the University of Pennsylvania School of Medicine, notes that testing 21 genes could reveal which breast-cancer patients are unlikely to benefit from a particular chemotherapy—knowledge that could spare women the treatment and save $400 million each year. "If genomics can help us understand who will get the most benefit and who will get little or no benefit from an intervention," Armstrong says, "it will take us a long way toward improving patient outcomes and saving money."

But a majority of doctors in a recent survey predicted that more testing will trigger higher costs, as patients with ambiguous results begin to seek frequent screenings—and potentially unnecessary procedures—for diseases they might never develop. "If we open the door to a test that has no clear, well-defined purpose, that is a recipe for unnecessary medical care," says Dr. Wylie Burke, a geneticist who chairs the department of bioethics and humanities at the University of Washington. "Instead, we could say, Here are the 1,000 mutations we should check in everyone." The American College of Medical Genetics and Genomics is already working on that, painstakingly assembling a list of a few dozen conditions that it says should be routinely looked for during genome sequencing. The hope is that focusing on certain hot spots—contenders include several syndromes that increase the risk of various cancers—will lead to improved analysis and, with it, better patient outcomes.

Some genetic testing has already moved out of the lab and into

the living room. Companies like 23andMe offer DNA analysis directly to consumers—no doctor required. Since 23andMe's founding in 2006, more than 180,000 people have been tested as the price has fallen from $999 for information on 14 specific traits and health risks to $99 for more than 200. The promise boils down to "forewarned is forearmed." If parents learn that their child carries a gene called ApoE4, indicating a higher risk of Alzheimer's, they might discourage the child from playing youth hockey or football, since research has linked traumatic brain injuries with a greater likelihood of brain disease in people who test positive for ApoE4.

"I do believe at some point in time everyone will be genotyped at birth," says 23andMe co-founder and CEO Anne Wojcicki. Her husband, Google co-founder Sergey Brin, has a genetic mutation that increases the risk of Parkinson's disease up to 80 percent; she has already tested their two children. Wojcicki's grandmother had macular degeneration; when testing revealed that some of Wojcicki's nieces and nephews are at increased risk for it, she bought them high-quality sunglasses. If her kids were predisposed to developing diabetes, she says, she'd encourage healthier eating. "I want to do everything I can to potentially enable my children to be disease-free."

But having more-detailed genetic information does not always point to a clear path. Dr. Ian Krantz and Nancy Spinner, a husband-and-wife team at CHOP, are working with an $8.8 million federal grant to understand what genomic information patients and parents want to know. Most parents go in looking for the cause of a mystery illness. "If you tell parents their child also has an increased risk for colon cancer or breast cancer," says Krantz, a pediatrician who oversees medical-genetics training at CHOP, "that's a whole different level of stress."

If you want to start an argument, ask doctors and patients what they think doctors should do when they discover genetic results they weren't looking for. It can be an emotional

blow—and a lifelong burden—if a mom learns that her baby girl carries a mutation that increases her risk of ovarian cancer or a dad finds out that his aspiring linebacker is genetically predisposed to developing Alzheimer's. In focus groups that are part of Krantz and Spinner's study, nearly all the parents said they would want to know about every disease risk, even if there's no treatment available. But in groups of bioethicists, lab directors, geneticists, pediatricians and genetic counselors, the majority said only results that could be immediately acted on should be shared with families.

This year, the lab Spinner runs tested a baby with a mysterious illness and found a completely unrelated mutation that indicated that dementia would likely set in at around age 40. Endless discussions followed: Should they tell the baby's parents that their child would probably develop a progressive neurologic disease marked by incontinence, blurred vision and confusion? There is no current treatment or cure. Telling them would all but guarantee that their child would never be able to get disability or long-term-care insurance. "We came around to the realization that we could not divulge that information," says Spinner, who is a genetics professor at Penn's medical school. "One of the basic principles of medicine is to do no harm."

At about the same time, her lab discovered that a 2-year-old with kidney disease carried a genetic risk for a kind of colon cancer. In some cases, polyps have been known to develop as early as age 7. With this patient, withholding the information would have seemed unethical. "We feel good about that one," says Spinner. "Proper screening can make a huge difference."

Genome sequencing isn't the first medical development that has forced doctors to grapple with the question of how much to tell patients. There have been cases of physicians' choosing to keep quiet when a test revealed a child's father was not his or her biological father. In years past, doctors have agreed not to share news of a terminal illness with an elderly

patient if the consensus was that the knowledge would cause too much anxiety.

But genomes are vastly more complicated. “If you fall off your bike and get an X-ray looking for a fractured rib, the radiologist scans the entire X-ray and automatically reports back to your doctor if something else is going on,” says Dr. Robert Green, a geneticist at Harvard Medical School. “More than a few cancers have been picked up this way. The problem with genomics is that everyone could have incidental findings.”

Perhaps nowhere is the risk of overreacting to murky results greater than in the field of prenatal testing. This year two groups of researchers announced that they had each sequenced a fetus’ DNA from cells gathered from the mother’s blood, leading to concerns that in the not-too-distant future, women might abort a pregnancy if they learn their unborn baby has an increased risk for cancer. “Great, we can sequence the genome of a fetus. What the hell does it tell us?” says bioethicist Tom Murray, a visiting scholar at Yale. “Much less than most people probably believe. Probabilities are not the same as guarantees.”

Faced with a growing need for protocols, the medical community is trying to hammer out some guidelines. This spring, the American College of Obstetricians and Gynecologists stated that though personalized gene profiles may be promising, they are “not ready for prime time” and should be discouraged. The American Academy of Pediatrics advises against genetic testing for children unless there is clear evidence of beneficial treatment or effective prevention strategies.

The challenge doctors face in determining how much to tell patients—or their parents—is complicated by a steady stream of new discoveries. Test results that are indecipherable today could be lifesaving in 2025. But waiting years to share sequencing information is a logistical nightmare, particularly

considering that patients may not remain under that geneticist's care and may change addresses many times over. Genomic transcripts are also so massive—labs typically FedEx a hard drive because there's too much data to transmit digitally—that the information is often relegated to a hospital's archives, if it's saved at all.

One possible solution to the problem of what to do with the deluge of data is a new Web-based venture called My46. Named for the number of chromosomes in human DNA, the nonprofit will allow people to store their sequencing results online and choose what they want to know and when. For example, parents of a baby who gets sequenced could opt to learn right away any findings about childhood diseases and put everything else—from unclear results to increased risks of adult-onset diseases—in the digital equivalent of a locked drawer, where it can be stored forever and accessed whenever they want to open it.

"Right now, it's not unusual for researchers to say that they're not returning results because there's no good way to do it," says Dr. Michael Bamshad, chief of pediatric genetics at the University of Washington, who works with Burke and is helping develop My46. Eventually, he predicts, "everyone will have their genome stored in a cloud."

Living with the results

For Laurie hunter, the news of her own cancer risk was not actually a shock. The disease runs in her family. Her mother and aunt had breast cancer, and her brother died of testicular cancer when he was 27. "I'd resigned myself that it was part of my reality, but I didn't think about it being part of my kids' reality—not this young, anyway," she says. One of the genes she's missing increases her risk of extra-adrenal tumors, which can pop up in the head, neck, chest and abdomen. The average age of onset is 30. Hunter is 42. So she scheduled blood tests and a full-body MRI to see if any tumors had started growing. She was thinking not just of herself and

Amanda but also of her son Ryan, 4, who has always been healthy, and of her youngest child Kailyn, who was born with a rare genetic disorder unrelated to Amanda's, called Wolf-Hirschhorn syndrome. At 2, she cannot talk and can barely sit up. "I have two girls, one of whom will never speak, and they need to be cared for by somebody," she says. "I worry about, if something happens to me, who will take care of them." And then there is Ryan. What if she had passed the cancer risk on to him?

"I have shed more than a few tears since I learned about this gene deletion," Hunter says. "I love all my children equally, but I have reconciled myself that neither daughter will ever drive, go to college, get married or live on her own. The hardest part is thinking about my son. I have this one child in whom all my hopes and dreams lie, and now he may have this deletion too."

She considered not testing him. Maybe ignorance would be better than knowing the worst. "But I thought, God forbid, what if he was one of the ones who develops tumors at 10 years old and I didn't know. I'd be consumed with guilt."

Ryan was tested in the last week of September. The waiting was a kind of torment. "We got the results back the other day," Hunter says. "He does not have the deletion. I feel like I can breathe again."

But because of Amanda's increased risk, she is being closely monitored. An MRI found a spot on her neck that turned out to be an enlarged lymph node. The doctors still don't know what is causing her other health problems.

"If all three of my children were healthy and had no issues, I don't know if I'd want to know about those seven missing genes," says Hunter, whose own MRI detected a lesion above her diaphragm. She's waiting to learn whether it's a tumor. "Sometimes what you don't know is easier. I feel completely

overwhelmed with information. Now it just feels like a waiting game.”

This is often how medicine works. Our powers outpace our principles and protocols, so that we wake up one day to headlines that a sheep has been successfully cloned and have to figure out what that means for the future of reproduction. In the case of genetic testing, there is little doubt that greater knowledge will bring many blessings, but it comes with costs, literal and emotional, and patients entering this territory with imperfect maps need to reckon with the odds of getting lost.