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## A Doctor for the Future

By [LISA BELKIN](#)

Dr. D. Holmes Morton stood at the front of the red-and-white-striped tent set up in a farm pasture in Lancaster County, Pa. Behind him were a horse and a buggy - his host's main mode of transportation - and a whitewashed barn and silo. To his left was a sunken barbecue pit, with 60 chickens cooking inside a homemade wire-mesh spit. Before him were seven families, upward of 50 people. The women wore bonnets and aprons, the men, long pants and long sleeves, in keeping with their Mennonite ways. Many of the youngest were in wheelchairs. One teenage girl had her left heel in her mouth. A boy was chewing on the handout Morton had distributed. It was two pages long and titled "Pretzel Syndrome."

The families had gathered here at the Weaver farm on this sticky July afternoon so that Morton could tell them what was wrong with their children. He could not give them a scientific name for their disease, because it did not have one yet. Morton and his team had discovered the existence of this illness only a few weeks earlier. Nor could he tell them how to cure it, or how to ease its symptoms, or what the future held for their kids - though he said he hoped that would come in time. All he could tell them then was why - why their children looked different, and had seizures, and could not speak, and died young. Why the youngsters' joints were so elastic that they could rest their feet behind their heads, their bodies twisted like pretzels. The cause, he could say with brand-new certainty, lay in their genes.

Morton, his gray hair blending with his faded jeans and herringbone jacket, his bow tie untied and draped around his neck, is a glimpse of the medicine of the future. And that future does not look the way we once thought it would. It has been five years since the first rough draft of the human-[genome](#) map was completed, five years since President Clinton predicted that "with this profound new knowledge, humankind is on the verge of gaining immense new power to heal." At the time, scientists told us they would soon be able to tinker with our DNA, repair our imperfect chromosomes and eliminate inherited disease. Gene therapy would be like penicillin, they said - a significant breakthrough, a complete cure.

That has not happened yet, and it is not likely to happen any time soon. "The enthusiasm has dimmed," says Dr. David Ginsburg, a professor of medical genetics at the University of Michigan. "Many in the field have been accused of overhyping it."

But while all eyes were fixed in recent years on the gene-therapy prize, a quieter transformation has been taking place. From a single drop of blood, scientists can now read our DNA - looking for which genes are present or missing, intact or broken, making diagnoses of disorders that were once either unheard-of, uncertain or misunderstood. From that they have been able to begin to decipher the consequences for a patient's life, longevity and health - a process some have taken to calling "genomic medicine." "This really is the future," says Edward R.B. McCabe, co-director of the University of California at Los Angeles Center for Society and Genetics. "Genomic medicine will be predictive, preventive and personalized," meaning that treatment will be shaped by, and tailored to, each patient's DNA. Perhaps doctors won't be able to fix genes, he says, but "it won't be enough to just diagnose" either. The time is past for knowledge for knowledge's sake, he says. "You have to use that information to help the patient."

Eventually doctors will be able to do that for all patients. Does [heart disease](#) run in your family? Your genes will one day reveal your personal risk in intricate detail. Is your genetic legacy [Alzheimer's](#)?

Diabetes? Stroke? We're nearing the day when a quick blood test can refine your odds and allow you to prevent or mitigate what's etched in your DNA.

At the moment, though, this genetic approach to medicine applies mostly to clusters of rare disorders, ones caused by a single gene, making them easier to identify and, because they occur in a limited population, easier to study. And no doctor in the country treats more of those than Holmes Morton. Among his 700 pediatric patients, there are more than 60 rare disorders, making his practice, in the farmlands of Pennsylvania, both a model and a test of medicine as it will eventually be. In time, all patients will come to understand genes as clearly as they now understand germs. Morton's patients already do. Someday soon, patients will expect that doctors will look into their genes as surely as they look down their throats. Morton's patients are used to that, too. Eventually new parents will assume that their babies will be given a battery of tests at birth, screening for every possible disorder. Morton's patients are almost there.

Medicine combined completely and seamlessly with genetics is so unformed at the moment that it doesn't really have a name. Some universities have departments of "human genetics" and "molecular medicine," though the former term implies research rather than treatment, and the latter connotes medicine on the cellular level, not the DNA level. Other schools use the term "medical genetics," which is the name of the board-certified specialty, but Dr. Victor A. McKusick, who is known as the father of the entire field for his studies dating back to the 1950's, says the description is obsolete. He prefers "genetic medicine," as in "the McKusickNathans Institute of Genetic Medicine at Johns Hopkins," which was named after him. "'Medical genetics' conjures up visions of rare diseases that are only of interest to a few people," he says. "'Genetic medicine' tells it the way it is. Genetics pervades all of medicine. It is starting with the rare conditions that Holmes is seeing. But it involves hypertension, it involves heart disease, it involves us all."

McCabe, at U.C.L.A., is among those who think that even the newer term "genetic medicine" is too limited in that it is used to describe genetic counseling and prenatal testing. Prediction (testing carriers, testing embryos), with its labyrinth of ethical dilemmas, is a different realm than treatment, so this label is lacking, too. McCabe uses the term "genomic medicine" to describe the implied promise of treatment in the mapped genome.

Whatever it is called, it is taking root in Lancaster County, home to one of the nation's largest populations of Old Order Amish and Mennonites. Genetically these are two separate groups with some shared culture and beliefs whom history brought to the same place. To outsiders, the Amish are the men with the beards and the Mennonites are the men without. Both separate themselves from the modern world, which they call "the English," shunning technology, taking their children out of school after eighth grade, never becoming doctors or scientists, rather farmers and craftsmen.

At first, the juxtaposition seems a paradox - this simple culture being treated at Morton's high-tech clinic, which sits literally in the middle of an alfalfa field in Strasburg, Pa. But look more closely, and it makes perfect sense. These groups, known collectively as the Plain People, have long been entwined with genetic research in the United States. Because members keep to themselves and marry within their communities, they rarely get to shuffle their genetic decks, and they are afflicted with a wide variety of rare diseases in far greater frequency than the population as a whole. For more than 30 years, genetic researchers have flocked here to study them, identifying the mutations that cause dozens of disorders by using samples of Amish and Mennonite blood. (McKusick's groundbreaking book, "Medical Genetic Studies of the Amish," was published back in 1978.) Most researchers, though, swoop in from their universities, collect their samples, then return to their labs. Morton is the first who has stayed, not just researching but also treating - taking tomorrow's health care to a world that lives in yesterday.

"Think of the rest of medicine trying to catch up with people in a horse and buggy," says G. Terry Sharrer, a curator of health sciences for the Smithsonian Institution, who has spent time studying

Morton's clinic. "We think of molecular medicine as being far off in the future. Well, molecular medicine is being practiced in an alfalfa field in Strasburg."

Friends and colleagues describe him as a cross between Albert Einstein, Albert Schweitzer and the doctor in a Norman Rockwell painting, but back in his teens, Holmes Morton was a high-school dropout who wanted to be a writer. Born 55 years ago in Fayetteville, W.Va., then a town of 2,000 people, he figured he would have more to write about if he saw the world, so he spent six years as a boilerman and engineman in the Merchant Marines and the Navy. He read voraciously during those years, then talked his way into Trinity College and went on to Harvard Medical School. (When he won the prestigious Albert Schweitzer Prize for Humanitarianism for his work in Lancaster County, in 1993, his high school awarded him an honorary diploma.) Gravitating toward the care of children, he did his [pediatrics](#) residency at Children's Hospital in Boston, followed by research work at Children's Hospital of Philadelphia.

He does not consider himself a geneticist. He considers himself a pediatrician. He stumbled onto the crossroads between the two worlds one night in 1988 when he was working in a hospital lab in Philadelphia and was asked to analyze a urine sample from a 6-year-old Amish boy named Danny Lapp. The child had the signs of [cerebral palsy](#), but his parents insisted that he had been perfectly healthy for more than a year after he was born, whereas C.P. tends to make itself known much earlier. Morton ran a test and found glutaric acid in the boy's urine, the unmistakable sign of glutaric aciduria Type 1, known as GA1. It was a disease so rarely diagnosed as to be thought almost nonexistent. There were only seven or eight reported cases in the medical literature when Morton made his diagnosis, and not one of those was in Lancaster County.

Intrigued, Morton drove his old brown Honda to Amish country for the very first time. "None of us had ever seen a case," he says. "I came mostly out of curiosity." Danny's parents, John and Ida, told him how the boy had been crawling and babbling until he was 14 months old. Then he came down with a simple stomach [virus](#) and within a few hours became paralyzed and unable to speak. His uninsured farm family had amassed tens of thousands of dollars in bills trying to figure out what was wrong with him.

It was Morton's introduction to the Amish view of medicine. Although they keep their distance from most technology, they have developed a trust in doctors because they suffer from so much disease. It was also an introduction to their ways of paying for health care. The Old Order Amish do not accept government assistance, and therefore they do not get Medicaid. They also don't carry private insurance but rather rely on the community to cover bills that individuals cannot cover themselves. The system worked well for decades, back when medicine was simpler, but it was already struggling with the rising costs of treatment by the time Morton first arrived.

Morton tends to listen more than he talks, and only after the Lapps had told their story did he take his turn. GA1 works like that, he explained. It devastates swiftly and suddenly. GA1 patients lack an enzyme that fully breaks down protein. As a result, excess amounts of glutaric acid, a protein byproduct, accumulate in the brain and other organs. What happens next was unclear when Morton met the Lapps and remains fuzzy. But somehow the stress of what would normally be a mild childhood illness - chickenpox, diarrhea, a simple cold - can trigger a strokelike episode. Once the brain is "injured," Morton said, the damage is irreversible.

Having read McKusick's work on Amish genetics, Morton theorized that if there was one patient with a rare genetic disorder in this contained population, there were likely to be others. (GA1, like nearly everything else Morton treats, is a recessive disorder - to get it, a child must have a copy of the defective gene from each parent; if only one parent is a carrier, the couple will not produce a child with the disease, and if both parents are carriers, each of their children has a 25 percent chance of having the disease and a 50 percent chance of being a carrier.) When Morton asked Danny's parents if they knew of any other

children like their son, they sent him to a neighboring family of seven children, two of whom had died, it appeared, of whatever had damaged Danny, and three of whom were still living but physically devastated. The gene for GA1 had not yet been found - that would not happen for four more years - but the biochemical urine tests Morton ran showed that these children, too, had glutaric aciduria. By the end of the summer, he had found 20 more cases among the Amish, some of whom had been told that their children had cerebral palsy, while others had never received a diagnosis.

And GA1 was not all he found. Every family knew someone with a child who was "not right," and the list of rare disorders living behind the walls of the simple Lancaster County farms steadily grew. Many were metabolic disorders, which arise from the inability to fully break down proteins, fats or sugars, putting patients at risk for the sudden strokelike episodes. The isolation of these families, both physical and cultural, meant that their children could not quickly get the care they needed. The local pediatricians were not familiar with such obscure ailments. The nearest hospital was miles away, a trip the Amish make by horse and buggy or, if necessary, in a hired car or van. If help were closer and more attuned to their unique needs, Morton thought, these diseases might not be death sentences.

Against the advice of his mentors - who believed he was throwing away a prestigious academic career - he decided to open a clinic in Amish country. His goal, at first, had nothing to do with reading genes but was simply to treat disease. He kept his day job in the laboratory where he had diagnosed Danny Lapp's illness and also his night job in the newborn I.C.U. at a hospital near his suburban Philadelphia home. Once a week he would drive out to Lancaster County and make house calls on his growing list of Amish patients.

He did this for a year, while he applied for grant money, the traditional way of financing medical projects. He needed enough for some office space in Lancaster, a computer and a mass spectrometer, which cost about \$80,000 at the time, to analyze urine and blood samples, as he had done with Danny Lapp. His wife, Caroline, would be his executive director. He would be the sole practitioner available to patients around the clock.

He did not get the grant, as his mentors warned, because as a junior clinician he was not good grant material. And most government and academic institutions prefer to finance pure research. He and Caroline were about to take a second mortgage on their house when *The Wall Street Journal* wrote about his struggle. Readers sent several hundred thousand dollars, Hewlett-Packard donated equipment and he was able to set up his clinic.

Today the Clinic for Special Children is probably the only place in the country with a mass spectrometer inside and a hitching post outside. The building itself was "raised" by a team of Amish and Mennonite carpenters, in the traditional post-and-beam style: it is held together by pegs, not nails. The two and a half acres of land on which it sits are in the middle of a field owned by the grandparents of some of the first children whose illnesses Morton diagnosed and who sold it to him at less than half the market price. As his office manager, Morton hired Rebecca Smoker, an Old Order Amish woman and aunt to the three children he met through the Lapps. Smoker greets patients wearing her traditional bonnet and apron and speaks to them in familiar Pennsylvania Dutch.

Ask Morton how his practice is different from every other medical office anywhere else in the country, and he will not start with the buggies and the bonnets and the clash of cultures. Nor will he begin with the fact that he no longer applies for research grants, because "they take too much time to fill out, time I'd rather spend with patients," or that he raises most of his \$1.2 million budget through the nominal fees he charges his patients and four annual auctions, organized entirely by the community, extravaganzas of handmade quilts, furniture and crafts.

What he will tell you is that he gets the rare chance to watch disease up close. Time was, he says, when all doctors treated genetic illness, though they didn't yet think of themselves as geneticists. "We've been

treating genetic disorders ever since the onset of the practice of medicine," he says. "If your dad went [deaf](#) young and your granddad went deaf young, then odds were that you would go deaf young, and that was genetic, but we couldn't find the gene or see the gene or know about the gene, so it was simply called medicine."

The modern era, he says, has brought knowledge, yes, but also a separation between those who study genetic roots of disease and those who treat that disease. "We've trained a whole generation of people who, because they are in the lab, don't get very close to patients," he says. "Funding has gone to lab-based research that doesn't require the individuals doing the research to know, meet or shake hands with the people who have the disease."

In part that is because most geneticists study rare disorders, and the few patients who suffer from those disorders are scattered far from the research lab. So the researcher sees them only as bits of DNA collected on a field visit or sent by another doctor through the mail. On the flip side, the actual treating physician might see only one or two cases of a rare disorder in a career and will have to refer care to the experts in far-off research centers. Morton, in contrast, has a large percentage of existing GA1 cases in the country living right outside his clinic door, so he can research and treat at the same time. If an era of genomic medicine is to take root, he says, more doctors are going to have to learn how to combine the two. Separation of research and treatment might have worked during the intense discovery period of the last two decades, he says, but it will not work as genetic knowledge is more regularly integrated with patient care.

Which is not to say that he does not understand the value of traditional distance - of keeping some analytical breathing space between doctor and patient. He has not, for instance, "gone Amish." He lives in Strasburg, about a mile away from the clinic, in a house with electricity within and two cars outside. He and Caroline have three college-age children, who went to nearby public schools. True, they spent more time than the average child playing in barns with Amish friends. And there was the year they surprised their parents by bidding on and winning a pony and cart at one of the clinic fund-raising auctions. Soon after, the children could be seen riding the back roads between the clinic and their home in their own version of a horse and buggy.

But while Morton is not of the community he treats, he is immersed in it, and he says that the proximity has taught him volumes. "We have struggled to take care of them over the years," he says, thinking of those he has lost, like Danny Lapp, who died a couple of years after the clinic opened. "We've learned a lot."

It is a process he compares to playing the cello. He took up the instrument five years ago, when he was 50. He was a lover of classical string music and often listened to J.S. Bach's Suites for Cello, which in their entirety take more than two hours to play. The Suite V in C minor Sarabande contains 107 notes, and he set out to master those. He has played them every day for the past five years and still finds them difficult, still finds the unexpected. That, he says, is the way to study disease as well. "Over 15 years, I have spent more than 10,000 hours learning about GA," he says. "Many days, I have worked 18 hours or more trying to keep a child alive and limit the injury the disease causes the brain. I study the cello just as I study medicine. I am not looking for skills and information. I want insight, understanding."

Through immersion he has come to understand that the devastation of metabolic disorders like GA1 is not inevitable, as had once been thought. If you can keep the child healthy for the first 24 months of life, the time of the greatest brain development, Morton has learned, you can probably keep him healthy for life. Strict monitoring from birth of the ingestion of protein can keep glutaric acid from accumulating and becoming toxic. But even if the child does go "into crisis," does get a cold or [flu](#), etc., Morton has also learned to take immediate action to limit the transformation from healthy to helpless. "We've developed strategies for rescuing children when they get sick," he says, including immediate infusions of sugar to keep patients from losing oxygen, and an amino-acid derivative, carnitine, that helps the brain reverse the

buildup of excess glutaric acid. The clinic has taken to giving parties for 2-year-old GA1 patients because "it truly is a new birth day," Morton says. He does not get every patient past the danger zone, but he certainly saves more lives than before. When he first arrived in Lancaster, 95 percent of the GA1 children he treated were physically and cognitively devastated. Now only 25 percent are.

While he was fine-tuning clinical treatment, Morton was also filling in genetic informational gaps. During the 1990's, scientists throughout the world identified a variety of different mutations, or genetic glitches, that can cause GA1. In 1996, by comparing the DNA of his affected patients with the range of possible mutations found to cause the disease, Morton determined which mutation all his patients shared. Now known as "the Amish mutation," it is also found in patients in areas of Europe where the ancestors of his patients once lived. Morton has come to know the genes that cause other Plain People diseases too. Some he discovered himself - like the gene for one cause of [sudden infant death syndrome](#) common in the Amish. Others he did not discover but narrowed down - like the gene for maple syrup urine disease, which got its name because sugars thrown off by the body give patients' urine a distinctly sweet smell. M.S.U.D. is effectively the Mennonite version of GA1 - similar symptoms, similar inability to digest certain proteins, but found among Mennonites rather than the Amish. It can be caused by a variety of genes and mutations, and in 1994 Morton determined which of these specifically afflicted his Mennonite patients.

Such knowledge fortified his treatment arsenal. All of Morton's Mennonite M.S.U.D. patients have the same mutation for the disease, and theirs is the most lethal version possible; their bodies do not produce any of the enzyme required to break down proteins properly. But not all his M.S.U.D. patients are Mennonite. About 15 percent of his practice consists of non-Plain families who have traveled to Lancaster from 27 states and more than a dozen countries, learning of his work through the word-of-mouth and Web-based communities that grow up around any disease. These patients often have less-lethal versions of the mutation, a fact that is verifiable only once you can read their genes. Morton recently began treating a 14-year-old girl whose family is not Mennonite but was originally from Puerto Rico and who has a milder form of M.S.U.D. in that her body produces some of the critical enzyme. The girl can eat three times as much protein as the Mennonite children, which makes a world of difference to her every day.

For a brief moment, Morton thought he could cure at least some of his patients. The year was 1999, and the disease was Crigler-Najjar syndrome, a liver-enzyme deficiency that allows a lethal buildup of bilirubin in the blood. It was first discovered in 1952 by Dr. Victor Najjar and Dr. John Crigler, who was a professor of Morton's at Harvard Medical School. Crigler-Najjar children become severely jaundiced and must sleep under hot, bright, blue-toned lights to break down the bilirubin. Eventually, though, even the lights don't work, and the condition causes brain damage or death. There are about 90 known cases in the country, and 25 of those are Amish or Mennonite. Nearly all of those are Morton's patients.

The field of gene therapy had existed for only a decade when, in June 1999, Morton invited many of those patients to a conference at a local inn. There the families learned of a new delivery system for genetic repair. Until that point, scientists had been experimenting with a method using viruses to transport DNA into the body, hoping that the viruses would insert themselves into cell structure and that the replacement DNA would correct the gene mutation. The new theory introduced at the 1999 meeting was called chimeraplasty, and rather than relying on viruses, it used a molecule called a chimeraplast - a manufactured mix of DNA and RNA - to trigger the system's cells to repair themselves.

The most notable moment came when Morton announced that the first human trials of the new approach would be on three of his Crigler-Najjar patients. The company that had developed the chimera technology would ask the F.D.A. for permission to test it on humans in the fall. "I really thought we would start treatment in six months," he says now. "I believed it would happen."

What happened instead was that two months after the conference, in September 1999, an 18-year-old Arizonan named Jesse Gelsinger died during a gene-therapy trial at the University of Pennsylvania. Gelsinger was not a Crigler-Najjar patient, and the trial in question used viruses, not chimeraplasts, but the field came to a complete halt for several years and has still not recovered. The company that was to conduct the Crigler-Najjar trials was sold to a French firm, and the scientists who had brought hope to Morton's patients moved on to other things.

The disappointment changed the lens on Morton's view of medicine. It made him look not at what science might someday be but rather at what was already possible. It solidified his conviction that genetics is not a separate realm but a part of everyday care. He had been waiting for the start of genomic medicine. When his gene-therapy trials fell through, he realized that genomic medicine was what he was already practicing. +

Crigler-Najjar patients, he knew, would benefit from [liver transplants](#), but transplants are invasive and expensive, and he had been delaying the procedure for a number of children, hoping to stall until gene therapy was available. He stopped stalling, and four of his patients have had those transplants since then. Similarly, he concluded that the best available hope for GA1 patients was diagnosing their disease at birth, before they are nursed or given protein-rich formula. So he turned new attention to the subject of newborn testing.

To that end, he hired Erik Puffenberger, who has a Ph.D. in human genetics. Puffenberger now oversees the hundreds of thousands of dollars of instrumentation at the clinic - a single room that is as well equipped as most university labs. There is the mass spectrometer that Morton started with 17 years ago. (Although the original has been replaced with a newer model.) There is also a gene sequencer, an amino-acid analyzer and a gas chromatograph, which allows scientists to separate and identify organic acids in a sample of blood or urine.

Morton began screening newborns before he even opened the clinic, starting by collecting urine-soaked diapers from local midwives and testing them for GA1 and M.S.U.D. Now, under Puffenberger, the clinic does onsite tests for about 40 disorders, and while some of those tests can be done during [pregnancy](#), they rarely are, because for the Amish and Mennonites terminating a pregnancy is not an option. Testing immediately before birth, however, raises no such ethical issues, and patients have come to expect that when labor begins and water breaks, a midwife will send a sample of amniotic fluid to the clinic via courier, and the analysis will be done within hours, sometimes even before the baby is born. Some are biochemical tests - looking for chemicals in blood or urine that are the warning signs of a disease. Some are genetic tests - actually looking into a patient's DNA to either confirm a preliminary biological test or find evidence of a disorder that cannot be confirmed by other means. But whichever the mechanism, the disorders found are all caused by defective genes.

The clinic tests vigorously because all the rest of the doctors' knowledge - how to manage patients, and adjust their protein intake, and recognize their early danger signs - is worthless if they don't know which patients to treat. "It makes no sense to identify a child with a genetic disease only after that child has been injured," Puffenberger says. "The only way you can even think of treating that child is to identify them before they get sick and then figuring out how to keep them healthy."

For more than a decade, Morton has been part of a rising chorus of voices around the country arguing that every state should test for a wide array of genetic disorders from birth - including GA1. That, Morton says, is the best current use of genetic knowledge. It is an idea that is slowly gaining traction. Just this year, the March of Dimes recommended that babies should be screened for 29 disorders, including GA1. But at the moment, the country is still a procedural patchwork. The tests a newborn receives depend on where a mother gives birth. According to the National Newborn Screening and Genetics Resource Center, Mississippi tests for 51 disorders, while miles away in Louisiana newborns are tested for only 9. Massachusetts tests for 16, Texas for 8. New York began testing for 50 over the past year, but before that

tested for only 11.

Each added test has the potential to save lives, Morton preaches. Donna Upchurch, who has never met Morton, is not of Amish descent but is a believer. When her daughter Alli was born three years ago in a very modern suburb of Atlanta, Donna and her husband decided to bank her cord blood as a potential treatment for her mother-in-law, who had [leukemia](#). In the package that came with the collection vial was an expanded newborn screening kit, one that looked for 25 disorders that Georgia does not routinely screen for. Donna took that kit to her daughter's one-week checkup. The test came back positive for GA1, the first known case in the state.

And yet GA1 is still not included in Georgia's mandated screening panel, and the standard argument against adding any difficult and rare disease goes something like this: "They say, 'We're not sure we want to screen for it because we don't know how to treat it,'" Caroline Morton says. "Well, it's not like the disease goes away if you don't screen it. At best you learn more with each diagnosis until you can treat it, and at worst you give the families some early idea of what their future might hold."

A related mission of the clinic, therefore, is improving methods of treatment for rare syndromes as a way of breaking the cycle of objections to screening. If a disorder can be treated, then testing for it becomes less controversial. To this end, Morton invited Kevin Strauss, a young Harvard-trained pediatrician, to join the clinic, the first time a second doctor has taken full responsibility for patients. In part, Morton brought Strauss aboard because he wanted someone in the clinic whose training is more up-to-date than his own. And in part he is there to give Morton time to share the clinic's knowledge with the rest of the medical world. Until Strauss arrived, Morton had written very little of what he knew about GA1 treatment for publication in scientific journals. And that has caused some in medical circles to think of him as a maverick and an outsider, because serious scientists validate what they know through publication and peer review.

Morton agrees that he does not publish enough, and that talking to doctors who track him down when they are confronted with a case of GA1 is not the best way to disseminate medical information. "In 15 minutes over the telephone, we can't tell them what it took 15 years to learn," he says. In the four years since Strauss joined the practice, Morton has published two articles in the respected *American Journal of Medical Genetics*, summarizing the accumulated knowledge of years of GA1 and maple syrup urine disease treatments. "We want to publish, we intend to publish," he says, "but we also have patients to treat."

Every year, Morton travels back to West Virginia to talk at the National Youth Science Camp, which invites outstanding students to come explore nature and science for several weeks. He does this in part to remind himself of where he expected life would take him and where he is now. He begins by playing the Suite V Sarabande, and then he tells the high schoolers, among other things, that "the course of my life, my current work as a doctor, the questions that I have asked and answered were unimaginable when" he was their age. "Technology and information, upon which I depend every day, has changed in remarkable and unpredictable ways over the past 40 years. The very language of questions and answers that are fundamental to my current professional life didn't exist" when he was in high school.

What is true of Morton's life is true of medicine in general. It is not what scientists expected it to be, and the road it has taken was not even constructed when most of today's physicians and geneticists began their training. It is also true of individual research journeys. Morton has begun with many a routine assumption and wound up with an unusual, unforeseen conclusion.

Such was the case with Shawn Weaver, a Mennonite boy Morton examined at a few weeks of age in 1998. Shawn's mother, Dorothy, described a difficult pregnancy, with far too much amniotic fluid and a premature birth. From the beginning, Shawn had difficulty breathing and nursing and growing. Years ago

a baby this sick would probably not have survived, which may be why the Weavers had no known history of any genetic disorders in their families.

Dorothy and her husband, Mark, had taken their eldest son to the clinic because the boy would not stop screaming. Morton saw the problem for himself when Shawn cried for three hours. "We put him in the hospital for a few days just to give his family a break and so I could have a chance to figure out what was wrong with him," Morton says. He first suspected reflux, but treatment didn't keep the boy from crying.

When Shawn was 5 months old, he had his first seizure. Dorothy was nursing him when he became rigid and his eyes rolled up in his head. A few hours later he had another one. Morton prescribed anticonvulsant medication, which seemed to reduce the severity but not the number of seizures; soon the boy was suffering through as many as 20 episodes a day. Despite every test Morton and Puffenberger could think of, they had no idea what disease Shawn had.

"The only thing I knew is that I didn't know what it was," Morton says. "That's an important kind of knowledge. You keep looking." As all the tests continued to come back negative, Dorothy remembers thinking, "Well, at least it's not something genetic, because we wanted to have more children." When Shawn turned 5, the tests stopped. "We gave up on having a diagnosis," Dorothy says. "We assumed we would never know."

Shawn's little sister was born, healthy, in 2001 and his baby brother, healthy too, arrived in 2004. Shawn, in the meantime, repeatedly missed developmental milestones. Though he could understand what was said to him, he could not form words. Nor could he walk or control his hands. What he could do was rest the soles of his feet up against his ears.

Shawn was hospitalized at Lancaster General 15 times during the first five years of his life. It was during one of those visits, in spring 2004, that Morton asked Dorothy the same question he asked the Lapps 16 years before: Do you know any other children like your son? By that time the genome had been mapped, and there were new genetic techniques that made it simpler to find gene mutations working with a small sample size of affected patients, he told her. Whereas just a few years earlier it took hundreds of samples to screen for one mutant gene, new methods, more precise and quicker, made it possible to use as few as two or three. If they found a few more children, Morton said, the clinic could try to find the underlying genetic cause.

As it happened, Dorothy did know, indirectly, of two other Mennonite children. The first was a boy born five months before Shawn who lived in Illinois. Shawn's great-aunt knew this boy's family through her church conference and said she thought that the two children resembled each other, so Dorothy wrote to the family a few years earlier, describing Shawn, and struck up a long-distance friendship. The second child used to come with his mother into the grocery store that Dorothy's parents own nearby. Dorothy's mother often talked about the boy who looked just like Shawn. Both of the other boys had died by the time Morton asked his pivotal question. But their families, who each had another affected child, agreed to participate in research. Deciding, as Morton had years earlier, that where there were two there must be more, Dorothy set out to find them, searching the interwoven Mennonite pockets spread across the country.

The culture of Plain People is a patchwork of practice and belief. Among the Mennonites there are those, like the Weavers, who are strict constructionists, though even they bend the rules to adapt to the times. A phone in the house is prohibited, for instance, but they can keep one out in a shack in the field for urgent matters and farm business. Some of the families Dorothy called from her shack phone spoke to her from their own shacks, others from within their homes, a few on their cellphones. Some ban radio and television from their lives, a few have computers, but just for business use, others searched the Web regularly. But despite these differences, the stories they told were almost identical, hinting at their shared roots. All their children had been born early, all their pregnancies involved extra amniotic fluid, all had

seizures and hyperelastic limbs. And none of their doctors could figure out what was wrong.

In summer 2004, four of these families met at the clinic so Erik Puffenberger could take blood from the parents and children; three other families sent samples by air courier. Analyzing the DNA would require a cutting-edge Affymetrix GeneChip scanner, which Puffenberger did not have. Instead, he sent the collected blood off to the Translational Genomics Research Institute, a biotech company based in Phoenix. It owned the \$250,000 machine and offered to run the samples free of charge, for the sake of research. (A few months later, Affymetrix donated a new scanner to the clinic and trained Puffenberger to use it.)

The data the machine generated was a computerized array of letters and numbers that represent clusters of genes. He ran programs that analyzed the data, as he had done in the past with samples of as few as two or three. But this time nothing jumped out of the computer. Then Puffenberger began scrolling through the 84,000 genetic markers (12,000 from each patient), trying to find the mutation - the piece of DNA that had been scrambled - that all seven children had in common.

Puffenberger spent hours, days, weeks staring at the screen, waking up in the middle of the night, pacing the clinic hallways. At one point, he began to doubt the accuracy of his samples, thinking that maybe all seven children didn't have the same syndrome after all. "Are you sure all these kids have pretzel syndrome?" he asked Morton, using the nickname the staff had given the disease. Assured that they all had the same symptoms and appeared to have the same disorder, Puffenberger came back at the data from another direction. It was then that he noticed not the presence of something but the absence. All seven children showed a "no call" for the same marker on Chromosome 17. A piece of DNA was missing from each, resulting in a partial deletion of a gene. After that it was a simple step to develop an in-house test to identify the mutation in patients who might have it and parents who might carry it. A few weeks later they used that test for the first time to diagnose pretzel syndrome in a new patient.

Morton, Puffenberger and Strauss are now creating a portrait of the disease - information they say they eventually hope to publish in a medical journal, along with the exact location of the gene, so that other scientists can critique their work. For the moment, their rough sketch of the disorder shows patients with fewer nerve cells in their brains, which probably leads to their seizures and might explain why known seizure medications don't really help them. They have an increased likelihood of heart problems, in the form of a "hole in the heart," and also of kidney problems, resulting in constant thirst and urination, known as diabetes insipidus. (It is this constant thirst that Morton hypothesizes might have caused Shawn to cry nonstop as a baby.) Their skeletons are abnormally shaped, their mental development is significantly slowed, the connective tissue of their joints is malformed and at least one of the children developed leukemia. They will probably die young. As far as Morton and his colleagues know, there is no available cure.

It was early spring of this year when Morton told Dorothy and Mark Weaver that he thought his team had found the pretzel syndrome gene. A week later their son died. "It didn't come in time to help Shawn, but it did help us," Dorothy says. She and the other mothers had started a "circle letter," in which the first in the chain writes a page and mails it to the second, who adds her own page and sends it farther down the line. That's what she uses to spread medical news from Morton.

When genomic medicine is at its best, it works as it does for GA1. A look into a patient's genes gives doctors something specific and practical to use to protect the patient. Diseases like GA1 are the easiest to do this with because they are not only single-gene disorders - disorders that are caused by a mutation of just one gene - but they are also metabolic, meaning that the cascade of damage can be prevented with early intervention. That they are simple in their genetics and straightforward in their mechanics makes these disorders easier to find and to mitigate.

More difficult are complex traits, caused by the interaction of several genes at once - things like high blood pressure or [arthritis](#) or osteoporosis. These are harder to find and more complicated to mitigate, though the chances brightened recently with the announcement that a follow-up of the Human Genome Project is now complete. It is effectively a "map" that identifies "neighborhoods," in which genes likely to cause related diseases tend to cluster, perhaps making it easier to find the source of common conditions. Odds are that even after doctors learn to read the genetic roots of these disorders, and tell us that we are at risk, it will be a long while before they can tell us exactly how to fix things.

Pretzel syndrome is a single-gene disorder, but it is complex in its mechanics, and in that way it is the more telling example of the implications of genomic medicine for most of us. All Morton can offer the pretzel syndrome patients at the moment is information. Which leads to the question, What is the value of knowing if that knowledge does not come with a cure? It's a question the families in the study wrestled with last July when the Weavers invited them all to their farm for barbecued chicken and an update from Morton.

Mary Lou Martin, whose teenage daughter, Jennifer, is afflicted with the disorder, spent a long time that day talking with Kendra Zimmerman, who was there with 7-year-old Alana. Mary Lou had been hearing about Alana for years, as mutual friends would regularly tell her about the little girl whose behavior and movements were just like her own daughter's. Long before Dorothy Weaver called to invite her into the study, Mary Lou suspected that Jennifer and Alana had the same disease, but she was unsure about approaching the younger mother to tell her. To do so, she knew, would be to rob Kendra of denial and possibility. "Alana was still young," she says. "I don't know how I would have felt back when Jennifer was little if somebody who had a child eight years older had come and said their child, who had so many problems, seemed just like mine. When they are still a baby, you are still thinking it might get better."

But at the picnic, Kendra told Mary Lou that she had been wanting to talk over the years, too. Sitting together, Mary Lou says, the harsh truths she had been trying to spare a stranger walloped both of them full force. Seeing other children with the same disorder meant facing the reality that the damage was lasting. "You see all these children in one place and you realize, This is the way it's going to be," she says. "They will always be in diapers, in wheelchairs. We got some knowledge, but at the same time we gave up some hope."

Alana died last month. And still, both women say that they would rather have answers than uncertainty. That is Morton's conclusion too. His entire career was changed the day he told Danny Lapp's family that he knew what was wrong with their son. Then he set about learning how to cure it. He says he hopes, one day, to be able to soften the blows that pretzel syndrome deals his patients too. But even if that isn't possible, he says, "at least they have a name for what's wrong. We can tell them it's not their fault, it's nothing they did wrong. It's in their genes. That gives us a place to start."

Lisa Belkin, a contributing writer for the magazine, last wrote about whether strep infection can cause obsessive-compulsive disorder in children.