Genomics, plain and simple

A Pennsylvania clinic working with Amish and Mennonite communities could be a model for personalized medicine.

In 2003, Leon and Linda Hoover embarked on a trying medical odyssey by horse and buggy. The Hoovers, of Lewisburg, Pennsylvania, are Mennonites, a religious group that mostly eschews cars, televisions and other modern conveniences. Along with the Amish communities that dwell in the region, they are the ‘Plain people’ whose handmade clothes and horse-drawn carriages are an iconic part of the landscape.

But modern medical technology was to become a large part of the Hoovers’ lives when they rode to the doctor with their six-week-old son, Raylon. He had been suffering from a deluge of infections — from croup to thrush to cytomegalovirus. After two months and consultations with various physicians, he received a tentative diagnosis: severe combined immunodeficiency (SCID), which describes a number of genetic disorders that leave children unable to fight infections. Although SCID can be treated by bone-marrow transplantation, refining the diagnosis and finding a matching donor require genetic testing. Physicians shipped blood samples to Duke University in Durham, North Carolina, and sent the Hoovers home to wait. But after three long weeks without results, Raylon’s health was worsening, and Leon was getting desperate.

He called the Clinic for Special Children in Strasburg, Pennsylvania, a timber-framed, slate-roofed structure housing an arsenal of modern genetic and genomics instrumentation. Hoover spoke for 45 minutes to Kevin Strauss, a paediatrician there. ‘You have a SCID baby, and you are at home?’ Strauss asked, incredulous. To speed things up, he referred the Hoovers to his colleague Nancy Bunin, now director of stem-cell transplantation at the Children’s Hospital of Philadelphia (CHOP) in Pennsylvania. She quickly arranged for genetic testing and a bone-marrow transplant. But it came too late. Raylon died at 6 months and 15 days.

Last September, when the Hoovers had another child, the story was very different. A Pennsylvania clinic working with Amish and Mennonite communities could be a model for personalized medicine.
test at birth revealed that their daughter, Kendra, had a dangerously low white-blood-cell count and probably had SCID. In tears, Hoover called Strauss on a Sunday at dawn. The paediatrician sprang into action. A midwife collected Kendra’s umbilical-cord blood and had it driven the 170 kilometres to his laboratory. Within 12 hours of Kendra’s birth, the lab team had detected a single letter change in her IL7R gene — the same mutation that had affected her brother.

The next morning, Strauss drove to the Hoover family’s sewing-machine shop. There, 16 relatives lined up to give blood in the hope that one could become Kendra’s bone-marrow donor. Testing at the clinic revealed that her sister, 11-year-old Ester Mae, was a match, and Kendra received the transplant at CHOP within 16 days of her birth. Kendra’s total medical bill was US$12,000 — compared with $500,000 for her brother. And she is doing well today.

“This is what genomic medicine is supposed to do,” Strauss says. “If you know which people are at risk, you can determine a diagnosis before a child is 24 hours old. You can come up with a treatment based on the genetics.”

THE MILLION-DOLLAR INTERPRETATION

The Clinic for Special Children, it seems, has found a way to apply the basic tools of genomics to save lives, money and resources. At the clinic, two paediatricians, a molecular geneticist and their staff have tools such as sequencers, microarrays and a LightScanner, which detects gene mutations. Using these tools, they nimbly stitch together the elements of basic science and clinical practice necessary to move from a blood sample to DNA analysis, all the way to diagnosis and treatment — sometimes in a matter of days.

By doing so, the clinic has achieved what many others in genomic medicine are struggling to do. Although genome sequencing is creeping into clinical care around the world, it has yet to become an integral part of every-day medical practice. “We’ve talked about the thousand-dollar genome and the million-dollar interpretation,” says Eric Topol, a genomicsist at the Scripps Research Institute in La Jolla, California. “The challenging bottleneck is the process of trying to nail down which DNA variation is the root cause.”

The team at the Clinic for Special Children can negotiate that bottleneck in part because of the unusual community with which it works. The Amish and Mennonites in Lancaster County are descended from a small founder population, have a remarkable knowledge of family history and tend to marry within the groups. This means that they have a high rate of particular genetic disorders, which makes it easier for researchers to trace the causes of such diseases.

But the clinic’s success also hinges on its combined clinical and laboratory facilities, and the close relationship that Strauss and his colleagues have built with the community.

The Amish and Mennonites shun technology to varying degrees — some even forbid zips on clothing — but they unambiguously support the clinic. If a technology draws people together in “fellowship”, says Mark Martin, a Mennonite and member of the clinic board, then the churches will indulge. The community even holds quilt and handicraft auctions to raise funds for the clinic, which last year netted $500,000 — about one-third of the clinic’s budget.

Holmes Morton, who started the clinic in 1988, says that it could serve as a model for personalized medicine in many other small populations with similar genetic histories. “Plain populations are interesting not because they are different,” he says. They are interesting because their genetics are the same as those of people everywhere, he says.

Morton, now 61, grew up in Fayetteville, West Virginia. He was a high-school dropout, who spent six years as a boilerman and engineer in the Merchant Marines and the Navy while taking a slew of correspondence courses. He used these to talk his way into Trinity College in Hartford, Connecticut, and from there went to Harvard Medical School in Boston, Massachusetts. The dean of admissions, Morton says, was intrigued by his unusual background.

In 1988, while completing a medical fellowship in metabolic diseases at CHOP, Morton encountered his first Amish patient — a six-year-old boy with a strange form of cerebral palsy. Through a urine test, Morton diagnosed him with glucaric aciduria type 1 (GA-1), which is caused by a defect in a protein-digesting enzyme and can lead to brain damage, severe movement problems and early death unless strict dietary restrictions are observed from infancy1. (Morton and Strauss later developed a formula to meet those restrictions.)

Morton knew that there were more Amish children with GA-1 and other treatable genetic conditions who were not receiving care, either because centres were too far away or tests were too expensive. So he decided to open a clinic that could meet the needs of the community. This meant bringing in diagnostic equipment to provide cheap, in-house testing, factoring in physician time for home visits and, most importantly, setting up shop in the heart of the community — within driving distance for a horse and buggy.

BREAKING GROUND

Morton applied for federal funding to cover office space, a computer and a mass spectrometer, but was denied. So he and his wife Carol line decided to take out a second mortgage on their house. Just before they did so, a reporter from the The Wall Street Journal wrote about Morton’s quest2. Within a week, readers had sent in several hundred thousand dollars and Hewlett-Packard had donated equipment. In the grand barn-raising tradition of the Plain people, Amish and Mennonites came together to build the clinic on a plot of land donated by Jake Stoltzfus, an Amish farmer whose grandparents Morton had treated. It is probably the only medical centre today with both a hitching post and an Ion Torrent DNA sequencer.

Despite the technology available, Strauss says, one of the clinic’s most important tools is “institutional memory”. An Old Order Mennonite family came to visit Strauss in 2006, for example. Their six-month-old daughter, Rosalyn, had a cluster of developmental problems. Unable to diagnose her, Strauss, who would eventually take over as medical director of the clinic, wandered downstairs to talk to his lab...
director Erik Puffenberger, a molecular geneticist. “I’ve got a girl with a small head and vision problems,” Strauss said. “Does that ring a bell?”

It did. Puffenberger recalled a Mennonite family he had met in the late 1980s when he was working with Victor McKusick, a renowned geneticist and author of Medical Genetic Studies of the Amish. The family had six children: all blind, with abnormally small heads. Puffenberger and Strauss tracked down the family to the same cinder-block residence they had occupied all their lives. The mother was in her eighties, still caring for her five surviving children, by then in their fifties and sixties. Strauss collected blood samples and Puffenberger analysed them, using gene-expression analysis and sequencing the entire known protein-coding regions of the genome, known as the exome. Puffenberger and his colleagues identified a novel mutation in a gene called TUBGCP6, which encodes a protein necessary for normal cell division and seems to explain the condition.

Although the disease cannot be cured, Rosalyn's vision problem, which involved the retina detaching from the eye, was treated with surgery to prevent otherwise inevitable blindness. Strauss’s team has since caught the same disorder, before the onset of symptoms, in two of her siblings through newborn screening. One has already received surgery and the other, still an infant, is scheduled to undergo surgery soon.

In addition to those within the Lancaster community, Morton and Strauss examine patients from communities in 27 other states and a handful of other countries. Like any paediatricians practice, the physicians send out some samples for routine testing, but can perform almost any genetic and biochemical test in their own basement laboratory. They now know and can test for the molecular basis of 121 heritable genetic diseases common among the populations they serve. If a patient has none of these — the case for nearly half the children they see — the basic research starts.

Strauss estimates that, in the Lancaster populations, his team will uncover the roots of between 5 and 15 new genetic diseases a year for at least the next decade. Many of those will be detected within the 1,000 families served each year. If a patient has none of these — the case for nearly half the children they see — the basic research starts.

When Marginet and his colleagues identified a novel mutation in a gene called TUBGCP6, which encodes a protein necessary for proper cell division and seems to explain the condition.

Although the disease cannot be cured, Rosalyn's vision problem, which involved the retina detaching from the eye, was treated with surgery to prevent otherwise inevitable blindness. Strauss’s team has since caught the same disorder, before the onset of symptoms, in two of her siblings through newborn screening. One has already received surgery and the other, still an infant, is scheduled to undergo surgery soon.

In addition to those within the Lancaster community, Morton and Strauss examine patients from communities in 27 other states and a handful of other countries. Like any paediatricians practice, the physicians send out some samples for routine testing, but can perform almost any genetic and biochemical test in their own basement laboratory. They now know and can test for the molecular basis of 121 heritable genetic diseases common among the populations they serve. If a patient has none of these — the case for nearly half the children they see — the basic research starts.

Although the disease cannot be cured, Rosalyn's vision problem, which involved the retina detaching from the eye, was treated with surgery to prevent otherwise inevitable blindness. Strauss’s team has since caught the same disorder, before the onset of symptoms, in two of her siblings through newborn screening. One has already received surgery and the other, still an infant, is scheduled to undergo surgery soon.

In addition to those within the Lancaster community, Morton and Strauss examine patients from communities in 27 other states and a handful of other countries. Like any paediatricians practice, the physicians send out some samples for routine testing, but can perform almost any genetic and biochemical test in their own basement laboratory. They now know and can test for the molecular basis of 121 heritable genetic diseases common among the populations they serve. If a patient has none of these — the case for nearly half the children they see — the basic research starts.

Although the disease cannot be cured, Rosalyn's vision problem, which involved the retina detaching from the eye, was treated with surgery to prevent otherwise inevitable blindness. Strauss’s team has since caught the same disorder, before the onset of symptoms, in two of her siblings through newborn screening. One has already received surgery and the other, still an infant, is scheduled to undergo surgery soon.