BRIAN DONNELLY STUDIO

Erik Puffenberger, Kevin Strauss and Holmes Morton (from left to right) in front of the Clinic for Special Children, which treats those with inherited disorders.

Genomics, plain and simple

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

BY TRISHA GURA

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

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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 everyday medical practice. "We've talked about the thousand-dollar genome and the million-dollar interpretation," says Eric Topol, a genomicist 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 unanimously 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 1989, 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 engineman 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.

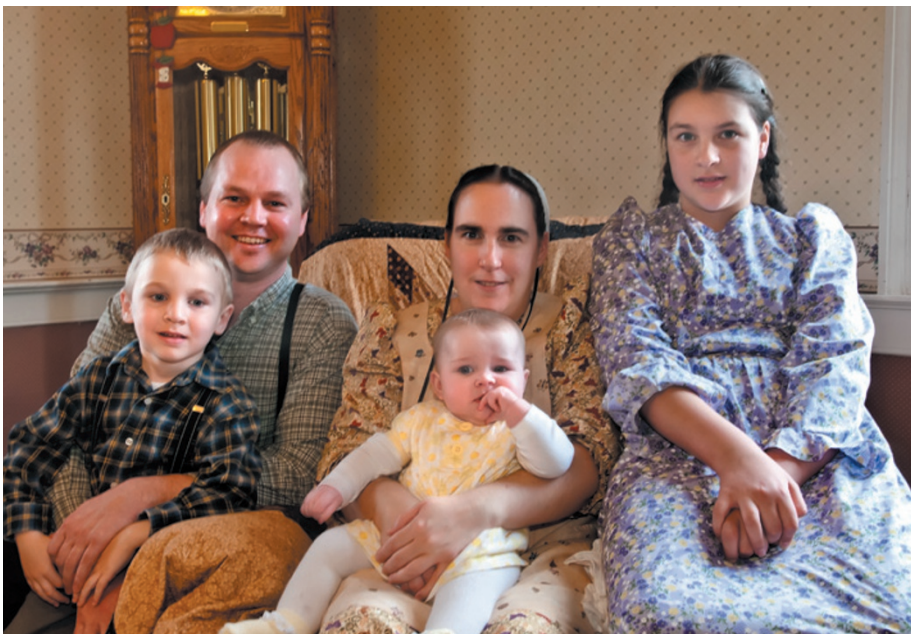
In 1988, while completing a medical fellowship in metabolic diseases at CHOP, Morton encountered his first Amish patient — a six-year-old boy with a strange form of cerebral palsy. Through a urine test, Morton diagnosed him with glutaric aciduria type 1 (GA-1), which is caused by a defect in a protein-digesting enzyme and can lead to brain damage, severe movement problems and early death unless strict dietary restrictions are observed from infancy[1]. (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 Caroline 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 quest[2]. 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 Stoltzfoos, an Amish farmer whose grandchildren 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



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Prompt genetic testing and treatment have given Kendra Hoover (front centre) a good prognosis.

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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 all the 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 proper cell division and seems to explain the condition[3].

> *"They have all these patients, but every one is treated like their own child."*

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 paediatrics 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 present in only a handful of people. About one-half to three-quarters will be treatable, he estimates, especially if detected early, as in the case of Kendra Hoover.

How applicable their approach is for other clinics that are currently adopting genomic tools is an open question, however. Some scientists are sceptical. "It's a pretty unique situation because they are dealing with a closed population," says Leslie Biesecker, chief and senior investigator of the genetic-disease research branch at the National Human Genome Research Institute in Bethesda, Maryland. By 'closed', he means that because of its small founder population and intermarriage, Plain people stand to inherit only a relatively small number of rare disorders.

Although conceding that disease genes are easier to identify among the Amish and Mennonites, Strauss argues that the criticism misses the mark. "If isolated populations make it so easy to do this work," he asserts, "why haven't other major academic centres nearby that see these patients made the genetic discoveries that we have?"

The answer, he says, is that other institutions keep the clinic separate from the research, which complicates genomic screening and makes it prohibitively expensive. By contrast, the clinic embeds its laboratory within its walls, certifies it and uses a blanket institutional review board approval from nearby Lancaster General Hospital. That allows Strauss or Morton to order, say, a microarray test to screen for a genetic mutation in a newborn in the same manner that other physicians might order a cholesterol test. The lab's integration, as much as the community structure, is key to surmounting the problem of million-dollar interpretation.

Puffenberger says that the advantages provided by such populations are shrinking. Many of the team's recent discoveries were — or could have been — determined by sequencing the exomes of just one patient and his or her immediate family, rather than reaching out to extended families for multiple affected individuals. As other medical centres begin to apply genome and exome sequencing, Strauss, Morton and Puffenberger hope that more will adopt the same sort of integrative style.

Even sceptics such as Biesecker concede that the idea of a general population as a well-mixed melting pot is inaccurate. Instead, the 'general population' is actually a mosaic of subpopulations, immigrating together and often living for decades in the same geographical location. In the United States, for example, there are pockets of high intermarriage in Appalachia. And Iceland has some 318,000 residents, who are largely descended from a small founder population. Genomics approaches similar to that used at the clinic are already at work for consanguineous populations in the Middle East and Ireland, says Stacey Gabriel, director of cancer and medical sequencing at the Broad Institute in Cambridge, Massachusetts.

"Founder populations are the history of the world," Morton says. "Whether they are located in a county in West Virginia or a region in Brazil, each population has a genetic make-up that can be studied and served." That, he adds, is where the model of the clinic becomes useful.

Moving forward, the team at the clinic hopes to streamline its approach to diagnosing new patients and the roughly 1,000 current patients in the area still without a molecular diagnosis.

For help in proving that the mutations they identify really do lie at the heart of disease, the team is collaborating with neuroscientist Rob Jinks of the Lancaster-based Franklin & Marshall College. With support from an education grant from the Howard Hughes Medical Institute, Jinks and a group of undergraduate students are working to determine the biological consequences of the mutations the clinic discovers.

But the clinic team is quick to note that scaling up genomic sleuthing is not the top priority. "We solve the problems for one child, one family at a time," Strauss says.

The Hoovers have experienced this first hand. Last October, Kendra Hoover lay in her mother's arms as a needle delivered human immunoglobulin into her scalp. These proteins would help protect Kendra from viral and bacterial infection while the cells transplanted from her sister began to take residence and give her a functioning immune system. Her prognosis is good, and her father, Leon, couldn't be happier.

"I don't know if I can put into words, how much they mean to us," he says. "They have all these patients. So many to take care of. But every one is treated like their own child." ■ SEE EDITORIAL P.5

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