Building on pioneering achievements, UChicago Medicine works to better understand and treat a disease that affects nearly one in 10 Americans.

It was a radical act. On Wednesday, August 23, 2006, six-year-old Lilly Jaffe disconnected her insulin pump. Diagnosed with type 1 diabetes soon after birth, Lilly was cutting her connection to the

hormone that had kept her alive since she was one month old.

For years, Lilly's parents had monitored her insulin levels—glucose checks every few hours plus three to five daily insulin injections before she got the pump at age five. Her mother analyzed every bite she ate. Despite their vigilance, Lilly had two nighttime seizures caused by low blood sugar.

But the growing capacity to detect and treat disorders at the molecular level gave Louis Philipson, PhD'83, MD'86, geneticist Graeme Bell, and their colleagues at the University of Chicago Kovler Diabetes Center reason to believe that Lilly could be weaned off insulin. They knew why Lilly's pancreas was not pumping out insulin, and they had been in close touch with a British group testing an established drug—designed to treat type 2 diabetes in adults—that they believed could fix it.

Lilly was born with a tiny mutation in a single gene that codes for a potassium channel, a tightly controlled passageway letting potassium ions in and out of the cell—part of the process regulating insulin secretion. Her case is a form of what is called neonatal or "monogenic" diabetes, caused not by the usual suspects, such as a misdirected immune system, but rather by specific genetic quirks.

Pleased with their initial victory, Lilly's care team wondered how to uncover more such cases. The Jaffes proved to be the answer. A Chicago Tribune reporter spoke with Lilly's mom, Laurie Jaffe, and convinced his editors to run their story on page one.

From a public health standpoint, diabetes has become "one of the most common and most serious medical conditions humankind has had to face," says diabetes specialist Kenneth Polonsky, dean of the Biological Sciences Division and the Pritzker School of Medicine.

Within weeks, other young patients with neonatal-onset diabetes were in the test-and-treat pipeline. Patient two came from Florida, followed by children from California and Alaska. To date, the UChicago team has worked with more than 100 young patients, and a few older ones, to wean them off insulin; worldwide, the figure reaches 500.

In the first year, the influx of patients helped the UChicago team to find new diabetes-causing gene irregularities—some treatable, some not—including 10 previously unknown defects in the insulin gene alone. Today that number is closer to 25.

Lilly was the fourth such case in the United States. It took careful consideration, and considerable gumption, for a family to enroll their child in such

an experiment.

It paid off. Lilly was admitted to the University of Chicago Medicine's Clinical Resource Center. Over five days, a life of constant monitoring and insulin therapy evaporated, replaced by a few inexpensive daily pills. Two weeks later she unhooked her pump. She's been healthy on just the pills ever since.

In 2009, the Illinois legislature passed Lilly's Law—requiring state health care providers to report children diagnosed with diabetes in the first year of life. Meanwhile, the University set up the first national web-based registry of patients with neonatal diabetes (those diagnosed before age one, most before six months). Expanded to include older patients known or suspected to have diabetes caused by a single genetic flaw, the neonatal-monogenic diabetes registry now includes more than 2,000 people with diabetes-related mutations and their close relatives. Such specific genetic diagnoses could lower treatment costs and improve outcomes.

FROM GENETICS TO SLEEP DEPRIVATION

Established in 2006 with a naming gift from the Kovler family—who for more than three decades have helped advance UChicago's breakthrough research in cancer, infectious diseases, and diabetes—the Kovler Diabetes Center continues a

rich history of diabetes-related research at the University.

Since the 1980s, rapid advances in genetics have sparked diabetes research, with UChicago at the forefront. At the Diabetes Research and Training Center, director Graeme Bell, the Louis Block Distinguished Service Professor of Medicine and Human Genetics—who helped clone and characterize many of the genes that regulate glucose metabolism—has worked with diabetes specialist Kenneth Polonsky, dean of the Biological Sciences Division and the Pritzker School of Medicine, and Nancy Cox, professor and chief of genetic medicine, to identify many novel genetic components. Among them are four of the six known genes associated with later onset forms of monogenic diabetes known as Maturity Onset Diabetes of the Young (MODY), including some that can be mistaken for type 1 diabetes.

Success in unraveling the genetics of such rare forms has encouraged UChicago researchers to apply a similar approach to the far more common type 2 diabetes. Accounting for 90 percent of cases, type 2 is usually triggered by lack of exercise and weight gain, and patients have a combination of impaired insulin secretion and insulin resistance.

90 PERCENT

OF DIABETES CASES ARE TYPE 2, WHICH IS ASSOCIATED WITH LACK OF EXERCISE AND WEIGHT GAIN.

Getting at type 2's genetic roots has proved difficult. Bell and Cox headed the first multinational, genome-wide study to focus on the disease. The results, published in 1996, pointed to regions of the genome that appeared to contain several potential disease-causing genes. But follow-up studies showed many genes that, in concert with other susceptibility genes, raise the risk of type 2 diabetes.

To tease out each contributor's small role requires analyzing huge sets of data. One of Bell and Cox's studies, involving 75 scientists at 27 institutions, "has generated data on a scale that has not been possible for any individual group to perform," Cox says. The data set includes entire exomes—all coding sequences—from 13,000 samples.

"With enormous computing power and huge data sets," Cox says, "we can now completely interrogate not just individual genes but also combinations of genes. What we are finding is that

common diseases, like type 2 diabetes, are associated with common gene variations."

The problem is the multiplicity of common variations. More than 70 variants that raise the risk of type 2 diabetes have been identified, but together they account for only about 10 percent of the heritability of the disease. "There will be hundreds, perhaps thousands, more variants," says Cox, "with similar and even smaller effect sizes." Often, these involve changes not in the protein but in gene expression. "So the gene itself is normal," Cox explains. "It's the mechanisms that regulate it that alter risk."

To complicate matters further, there are tradeoffs. Some variants may increase risk for type 2 diabetes yet lower risk for something else, like cancer: "What we have learned so far is that we have much to learn."

Graeme Bell (shown) and Nancy Cox headed the first multinational, genome-wide study to focus on type 2 diabetes. Since the first results were published in 1996, follow-up studies showed many genes that, together with other susceptibility genes, raise the risk of type 2 diabetes. Testing each contributor's role requires analyzing huge sets of data.

In the case of type 2 diabetes, modern lifestyles play a major role. Diet, lack of exercise, and obesity

have long been associated with the disease, but researchers at the Sleep, Metabolism, and Health Center were the first to implicate a new factor: sleep deprivation. In 1999, professor of medicine Eve Van Cauter, who directs the center, and her team showed that chronic partial sleep deprivation —the growing tendency to get far less than the recommended seven to eight hours a night—can trigger profound metabolic and hormonal changes.

Sleep deprivation acts in multiple ways, demonstrated in a series of UChicago studies. Sleep loss changes circulating levels of the hormones leptin and ghrelin in ways that boost appetite, especially for sweet, calorie-dense foods. Short or poor sleep links with decreased blood-sugar control in people with diabetes. Suppressing deep sleep in healthy young adults lowers their ability to regulate blood-sugar levels.

In 2012, Van Cauter's team worked with associate professor of medicine Matthew Brady, PhD'94, a specialist in adipocyte biology, to demonstrate how losing sleep damages fat cells, where extra energy sources such as glucose are stored. Short sleep decreased the cells' ability to take up glucose when exposed to insulin by 30 percent.

A 2014 study showed that episodes of obstructive sleep apnea during rapid-eye-movement (REM) sleep—a sleep stage first described in 1953 by UChicago's Nathaniel Kleitman, PhD'23, and

Eugene Aserinsky, PhD'53—can worsen type 2 diabetes more than apneas in non-REM sleep. Because patients tend to use an apnea-preventing device only for the first half of the night, and most REM sleep occurs late in the sleep cycle, the researchers suggest wearing the device all night to get the full antidiabetic benefit.

THE PUBLIC COST OF DIABETES

The World Health Organization estimates that one in 10 people on the planet aged 25 or older has diabetes. In China, almost 12 percent of adults have diabetes, and one in two shows signs of prediabetes. Last November, Eli Lilly announced a $350 million factory expansion in Suzhou, China, "to manufacture more insulin," according to a press release, "for people there with diabetes."

Dean Polonsky summed up the problem in a 2012 essay in the New England Journal of Medicine. From a public health standpoint, he wrote, "We are arguably worse off now than we were in 1812." Although huge advances like the discovery of insulin have prolonged the lives of patients with type 1 diabetes, for those with type 2, "little progress has been made in reducing the burden of diabetes in the last two centuries." Instead, diabetes has become "one of the most common and most serious medical conditions humankind has had to face."

"If we don't change our diet and exercise habits or find new, more effective, and less expensive ways to prevent and treat diabetes," Huang says, "we will find ourselves in a lot of trouble as a population." Without major changes in public or private strategies, this population and cost growth will "add a significant strain to an overburdened health care system."

"The public policy implications are enormous," agrees study coauthor Michael O'Grady, senior fellow at the National Opinion Research Center at the University of Chicago. "The cost of doing nothing is an increase in the pain and suffering of America's population."

9.3 PERCENT

OF THE US POPULATION IS AFFECTED BY DIABETES—A FIGURE THAT DOES NOT APPLY EVENLY ACROSS SOCIOECONOMIC GROUPS.

In the United States, diabetes has accelerated so quickly that it has been difficult to project, or

budget for. Each new study provides a more distressing prediction. In 2009, a UChicago team led by Elbert Huang, associate professor of medicine and director of the Center for Translational and Policy Research of Chronic Diseases, calculated that the number of Americans with diabetes will rise from 23.7 million to 44.1 million by 2034. Those estimates were confirmed by June 2014 projections from the US Centers for Disease Control and Prevention. The CDC estimates that, with 9.3 percent of the US population affected, direct medical costs of diabetes are already more than $176 billion. Even with no increase in obesity, Huang predicted, spending will reach $336 billion by 2034.

That pain and suffering is not equally distributed. According to the CDC, 7.6 percent of the nation's non-Hispanic whites had diabetes in 2012, compared to 12.8 percent of Hispanics and 13.2 percent of non-Hispanic blacks. In Chicago's African American neighborhoods, the rate balloons to nearly 20 percent, and complications from diabetes—foot or leg amputations, kidney failure, blindness, and heart disease—are five times higher than in primarily white neighborhoods.

A study by CDC and Emory University researchers, published in April 2014, offered discouraging results, but with a major silver lining. Between 1990 and 2010, as the US adult population grew less than 30 percent, the number of adults

reporting a diagnosis of diabetes rose more than 300 percent. Although there were many more cases, complication rates for adults with diabetes declined significantly. But that silver lining had its own cloud: the drop in complication rates did not apply evenly across all socioeconomic groups.

HELPING POPULATIONS AT RISK

While patients with cancer tend to place life in the hands of their doctors, Lou Philipson says, "with diabetes you have to do it yourself—take your medicines, eat right, exercise." Kovler's diabetes clinic has a psychologist on duty five days a week, helping patients cope with the considerable burden of living with diabetes and testing ways to improve self care. The clinic's new James C. Tyree Diabetes Education Library provides instant access to carefully screened information, and the ability to order clinical devices such as insulin pumps—and is accessible to anyone via the internet.

Help is essential because diabetes is notoriously difficult to manage. Along with being told to regulate one's diet and exercise daily, a typical patient is asked to take two or three pills on a rigid schedule to control blood-sugar levels, several more to lower cholesterol, others to reduce blood pressure, and aspirin to prevent blood clots. As the disease progresses, the drugs increase, often including insulin shots.

10+ PERCENT

SAID THEY WOULD PREFER TO FACE COMPLICATIONS OR EVEN TO SACRIFICE SEVERAL YEARS OF LIFE TO END THE CONSTANT MONITORING AND MEDICATION.

A survey by Huang found that, after 10 or more years on an ever-more complicated regimen, one in five patients found the inconvenience no longer worth the trouble. When asked, more than 10 percent said they would prefer to face complications or even to sacrifice several years of healthy life to end the constant monitoring and medication.

Socioeconomic, psychosocial, and communications barriers can make coping with diabetes even harder. Overcoming such frustration, and the serious complications that can follow when treatment is discontinued, is one mission of Finding Answers: Disparities Research for Change, a national program, funded by the Robert Wood Johnson Foundation through a grant to the University and NORC, that works to reduce racial

and ethnic differences in health care, particularly diabetes. "Previous efforts we have seen haven't been powerful enough," says Marshall Chin, the Richard Parrillo Family Professor in Healthcare Ethics, who leads the program. "Diabetes is a huge problem. It hurts a lot of people and takes up a ton of resources. People on the South Side sometimes feel overwhelmed by the challenges."

With Monica Peek, assistant professor of medicine and associate director of the Chicago Center for Diabetes Translational Research, Chin is testing new ways to help disadvantaged people with diabetes through such pathways as the UChicago Medicine's Improving Diabetes Care and Outcomes on the South Side of Chicago project.

As associate director of the Chicago Center for Diabetes Translational Research, Monica Peek tests new ways to help disadvantaged people with diabetes—from grocery store tours led by nutritionists who point out healthful and inexpensive foods to partnering with local groups to help and inspire patients to move toward a healthy lifestyle.

Helping disadvantaged people with diabetes means supplementing visits to the doctor with educational and motivational add-ons, such as grocery store tours led by nutritionists who point out healthful and inexpensive foods. It means exercise instruction, through culturally tailored group sessions that include persons with limited

mobility. It means partnering with local groups to help and inspire patients to move toward a healthy lifestyle.

Community caregivers stress how difficult it can be to bridge the gaps between doctors and some low-income inner-city patients. Even the doctor's standard opening line, "What brings you here today?" can be heard as hostile. The physician may be asking, "How can I help you?" But the patient might be hearing, "Why are you sitting in front of me when I'm so busy?"

"It was eye-opening," Peek says, to learn that the seemingly compassionate ways that medical students are taught to reach out to their patients can actually alienate those who most need help.

So Finding Answers developed a six-step roadmap that helps patients, clinicians, and health care organizations to achieve high-quality care. The roadmap includes guidance to aid specific racial or ethnic groups who have an elevated risk of diabetes. Projects supported by Finding Answers include telephone-based care management delivered by a nurse, and a circuit-rider team with a certified diabetes educator nurse, dietician, and pharmacist rotating among rural clinics.

Arshiya Baig, assistant professor of medicine, is testing a similar approach, using hyperlocal support networks, especially churches, to help

Latinos in Chicago's Little Village neighborhood cope with the daily challenges of diabetes. One popular component of the eight weekly sessions is an exercise her team calls "photovoice." Participants use disposable cameras to document life with diabetes. The photos help jumpstart discussions about where to find and how to cook healthy foods. "Photovoice made it easy to convey emotions, experiences, losses, gains, without having to verbalize it," one observer says. These very personal images bring "context and depth to the conversation."

Can preventive care also save money? With Shantanu Nundy, MBA'13, clinical instructor of medicine, Chin and Peek tested an inexpensive intervention: texting. The care team contacted 348 diabetes patients, all UChicago Medicine employees covered by the institution's health plan. Using automated text-messaging software, the doctors sent about half of the participants three or four daily texts: advice about self care, reminders to take or refill medications, and prompts to complete particular tasks, such as foot care—a big challenge for diabetics.

After six months, those receiving the texts had small but real improvements, including eating habits, taking their meds, glucose monitoring, and foot care, compared to those who did not receive texts. Their A1c levels—a measure of long-term blood sugar control—dropped from 7.9 to 7.2. (The

typical goal for patients with diabetes is less than 7.) Results for employees who did not receive texts were unchanged.

8.8 PERCENT

WAS THE NET COST SAVINGS—FEWER DOCTOR VISITS, ER VISITS, AND HOSPITAL ADMISSIONS—FOR THOSE GETTING TEXTS ON PREVENTATIVE CARE.

The grabber for this small, short-term study, published in the February 2014 Health Affairs, was the drop in health care costs. The group receiving texts had fewer doctor visits, ER visits, and hospital admissions—for a net cost savings of 8.8 percent. Next step: a larger follow-up study.

And the next steps for patients like Lilly? The initial target audience, the estimated 2,000 people in the United States who had Lilly's mutation and could switch from shots to pills, has expanded. The Kovler team now estimates that between 100,000 and 300,000 Americans have neither type 1 nor type 2 diabetes but some inherited form of the

disease caused by one of many genetic defects.

"For most individuals, a genetic diagnosis is transformative," Philipson told patients and their families from as far away as Argentina and Australia at a July 2013 conference organized by Kovler. "Many we don't have cures for, but we're trying. Some have what Lilly has, and we can help. And some patients, who have been treated aggressively their whole lives, don't actually need treatment at all, just a physician who knows the fine points and can guide them through the system."

"For most individuals, a genetic diagnosis is transformative," says Kovler Diabetes Center director Louis Philipson. "Many we don't have cures for, but we're trying. Some have what Lilly has, and we can help. And some patients... don't actually need treatment at all, just a physician who knows the fine points and can guide them through the system."

Lilly Jaffe, now 14, is doing very well. Her insulin secretion is perfectly normal. She rarely checks her blood-sugar levels, and her A1c levels are optimal. "She's a normal teenager," according to assistant professor of pediatrics and endocrinology Siri Greeley. "Diabetes is the least of her concerns."

And Laurie Jaffe, Lilly's mom, is a normal mother, still paying close attention to her child's health. She and a cluster of other parents of patients in

the neonatal monogenic diabetes registry have introduced a new research tool: the Mom scan. After meeting at lectures or the conference, many parents of neonatal patients, mostly mothers, formed an internet chat group. It also includes several of their caregivers, who monitor discussions and weigh in as needed. Whenever a mother—and there may be no more focused instrument for observation—notices something unusual about her child, she mentions it to the group.

This network has uncovered some subtle, previously unrecognized issues. Some of the children have difficulty tracking rapid movements with their eyes. Some have reading or learning problems. Several years ago Laurie Jaffe wondered online if any of the other children had trouble sleeping. Within hours, 20 other moms confirmed the observation. So the Kovler team sent out devices, worn on the wrist overnight, to monitor their patients' activity during sleep.

The moms were right. Many of the children with Lilly's mutation had sleep problems. Several had impaired visual scanning, important for reading. Other families mentioned subtle neurodevelopmental problems. Now the team has to figure out why.