

The Primary Prevention:

What's causing the rise in Type 1 diabetes—and can it be stopped?

by James Dinneen

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Submitted to the Program in Comparative Media Studies/Writing in Partial Fulfillment of the  
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ABSTRACT

Decades of research have failed to identify the environmental factors behind rising rates of Type 1 diabetes. However, the search has made Type 1 diabetes one of the best studied autoimmune diseases, with a network of clinics and laboratories dedicated to understanding the interplay of genetic and environmental factors behind the disease. This has enabled clinicians to begin testing treatments to prevent diabetes in high-risk patients at the “primary” phase when all there is to go on is genetic risk. This thesis discusses the search for environmental determinants of diabetes in the context of a primary prevention clinical trial underway at the Institute for Diabetes Research in Munich, Germany. The trial and others underway represent a possible answer for the millions of people at high genetic risk for developing Type 1 diabetes, and other associated autoimmune conditions like celiac disease and allergies. They also offer an early view into the promise and pitfalls of precision medicine.

Thesis Supervisor: Kim Tingley

## The Primary Prevention

*What's causing the rise in Type 1 diabetes—and can it be stopped?*

James Dinneen

Leo was a baby at risk. Both his parents, Haydn and Ada, a soft-spoken couple from Munich, Germany, had Type 1 diabetes. This fact alone gave Leo a much higher chance of developing the disease, which is caused when a person's immune system destroys the cells in their pancreas that produce insulin. (These names are pseudonyms to protect the medical privacy of the family.) Without insulin to transport sugar from the blood into cells, blood sugar rises. Unless insulin is injected regularly, that high blood sugar leads to serious complications and, eventually, death. In Germany, about one in every three hundred people develop the disease. With a first degree relative, the risk is around one in twenty.

Knowing this, Ada joined a Facebook group for diabetic mothers to seek advice. Type 1 was usually manageable for adult patients, but treatment was more onerous when it developed in a young child unable to manage their own insulin injections, or recognize dangerous swings in blood sugar. Until the child could deal with diabetes themselves, the onus fell on parents and caretakers, adding a life-threatening factor to everything else involved in raising a kid. Ada and Haydn hadn't dealt with diabetes as infants themselves—Ada was diagnosed in her early twenties, Haydn when he was seven-years-old—but both understood how the disease could disrupt regular life. “If he ever gets diabetes then he has two experts” to help him through it, said Haydn.

Shortly before Leo was born, Ada saw a post on the group about a study at the Institute for Diabetes Research in Munich to screen newborns for genetic risk for Type 1 diabetes. She signed up. While she knew any child of hers and Haydn's would likely be at higher risk, a genetic test could confirm it. For other families, it could identify high-risk children without a family history of Type 1 diabetes, who account for around 90 percent of cases. When Leo was born in February, his doctors pricked his heel for a few drops of blood along with a few drops

for his regular newborn screening panel. The blood was dabbed on a special slip of paper, then routed through the mail to a lab in Oxford, U.K. along with slips from hundreds of other babies born that week.

Days later, Ada got a call from a doctor at the Institute with bad, if not unexpected, news. Leo had a greater than 1 in 10 chance of developing Type 1 diabetes by his sixth birthday—a risk more than 30 times that of an average German child. After explaining how the risk score worked, the doctor asked if Ada and Haydn would consider enrolling Leo in a clinical trial just getting started at the Institute on a treatment to prevent Type 1 diabetes in high-risk children.

“We just talked about it and said that we want him to have a normal life,” said Ada. “And that’s the best thing that we can do.”

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Once known as “juvenile diabetes,” Type 1 diabetes is distinct from the much more common Type 2 diabetes. Both diseases involve high blood sugar, but have different causes. Type 2 diabetics are able to produce insulin, but for various reasons, their body resists the hormone. Type 1 diabetics are unable to produce insulin, their insulin-producing cells destroyed by an errant immune system. Without insulin to absorb sugars, the body responds as though it were starving, eventually poisoning the blood with toxic ketones. Before the advent of insulin therapy in 1921, a diagnosis of Type 1 diabetes was a death sentence. Today, it’s a different story. For people with access to care, synthetic insulin and other technology like wearable pumps and blood sugar sensors have made Type 1 diabetes a burdensome, but largely manageable chronic disease. Globally, about ten million people live with Type 1 diabetes; about 1.6 million people in the United States have the disease.

Despite these advances in treatment, clinicians remain without a way to prevent the disease from developing in the first place. This has been a goal for clinicians since they first recognized Type 1 diabetes was not just a hereditary disease, but that non-genetic, or

“environmental” factors also played a significant role in causing it. You couldn’t do anything about genetics, researchers reasoned, but environmental factors might be altered. A virus could be stopped with a vaccine. A deficiency in some vitamin could be corrected. Diets could change. It might even be a pretty simple adjustment.

The search for environmental factors was also motivated by the rising rates of Type 1 diabetes and other autoimmune disease researchers observed starting in the 1950s. Over the past three decades, global rates of Type 1 diabetes have risen even more rapidly, increasing 3 percent each year on average, with rates highest in Northern Europe, followed by the United States and Southern Europe. Though rates are significantly lower in much of the rest of the world, rapidly modernizing countries like China and the United Arab Emirates have also seen a rise. The speed of this rise, as well as its geographical and historical dimensions, could not be explained by genetics alone. Other evidence pointed to environmental factors as well. For instance, people who immigrated from regions with low rates of Type 1 diabetes—say, Bangladesh—to regions with high rates—say, Sweden—were found to be more likely to develop the disease than people who stayed home. What caused this difference, and could it be changed?

The search continues. Decades of research and hundreds of millions of dollars have not identified environmental factors capable of explaining the rise in Type 1 diabetes. Many things—from gut microbes to cow’s milk—have been linked with risk for developing the disease, but the links aren’t strong enough to explain the rise, let alone what to change to prevent it. Without clear guidance on how to prevent Type 1 diabetes, some parents of children with high genetic risk turn to the internet, where they find blogs touting unproven nutritional cocktails and dietary regimens.

However, the search has had other results. Type 1 diabetes is now one of the best studied autoimmune diseases, with a massive network of clinics and laboratories dedicated to understanding the subtle interplay of genetic and environmental factors behind the disease. This has enabled clinicians to test treatments to prevent diabetes in high-risk patients at the “primary” phase when all there is to go on is genetic risk—to treat the disease before it

begins. “Primary prevention will be possible if we find the right treatment,” said Anette Ziegler, who directs the Institute for Diabetes Research in Munich, where two such clinical trials are underway. One involves feeding thousands of at-risk infants insulin; the other involves feeding them a species of bacteria uniquely evolved to thrive in the human infant gut.

These and other trials represent a possible answer for the millions of people at high genetic risk for developing Type 1 diabetes and other associated autoimmune conditions like celiac disease and allergies. By relying on widespread genetic risk screening to enroll participants, they also offer an early view into the promise and pitfalls of what some see as the precision future of medicine, in which genomic and environmental data are used to treat patients with personalized interventions.

In Finland, which has the world’s highest rates of autoimmune disease, a new vaccine against a virus linked with developing Type 1 diabetes is completing a phase 1 trial. Other Finnish researchers are going lower-tech, testing whether exposing newborns to plain old dirt might be protective against the disease (researchers have shown Finns who grow up on farms are less likely to develop autoimmune disease). Furthest along, though, are the two trials being run out of the Institute for Diabetes Research in Munich, where on a sunny morning in March, Haydn and Ada arrived with Leo asleep in a carrier.

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The Institute is a four-story concrete structure set in a pleasant suburb of Munich across from an auto mechanic and a garden shop. It’s part of a larger institution called Helmholtz Zentrum München, itself a part of the eighteen centers of the Helmholtz Association, which is Germany’s largest scientific organization, and whose mission is to “solve the grand challenges of science, society, and industry.” In other Helmholtz centers the grand challenges are artificial intelligence and renewable energy. In Munich, the grand challenge is the environmental determinants of disease. Stretched across the third story window of the Institute is a large white and blue banner: World Without 1.

This is the slogan for a group of researchers called the Global Platform for the Prevention of Autoimmune Diabetes, or GPPAD, which has study centers in the U.K., Belgium, Sweden, Poland, and several cities in Germany; it is one of the leading groups for research on preventing Type 1 diabetes. The Institute in Munich serves as GPPAD's headquarters, coordinating the thousands of biological samples that whiz between clinics every week. By the time Leo's blood spots arrived at the lab in Oxford for genetic analysis, GPPAD programs had screened more than 300,000 other infants for genetic risk, and nearly one hundred thousand more for the autoantibodies that are telltale signs of the disease beginning its course. Partly responsible for these staggering numbers is a robot inside the Institute—named Robby by the lab workers—who spends his endless days churning through stacks of blood samples.

Anette Ziegler, who founded GPPAD in 2015 and directs the Institute, works out of a corner office on the top floor, a room over from Robby the Robot. Colleagues say she has been integral to GPPAD's sprawling research program, and central to the larger project of preventing Type 1 diabetes since the early days. "Anette has a very practical way of looking at things," said Ezio Bonifacio, who studies Type 1 diabetes at the GPPAD center at Technische Universität Dresden, and is married to Ziegler. "She can't handle things that don't happen." Her steady grey eyes, pant suits, and polite German-inflected English contribute to this no-nonsense image, though that is belied by a careful attention to other's wellbeing. In the middle of a long day speaking with researchers at the Institute, a granola bar arrived for me via Ziegler's assistant, who said Ziegler had become concerned I had missed lunch.

Ziegler got her start in the lab of the diabetes researcher George Eisenbarth at Harvard in the early 1980s. When she joined the lab, Eisenbarth had just completed a series of studies on identical twins with Type 1 diabetes that clarified the basic model of how the disease works. Preventing the disease was still a long way off at that point, Ziegler told me when we first met over Zoom in February. The focus then was simply understanding the progression of the disease, from a person with a normal insulin-producing pancreas to a patient in the emergency room with skyrocketing blood sugar. Researchers knew insulin-producing cells were destroyed by an autoimmune reaction, but when that happens, how long has the immune system waged its war with the pancreas? Is it a sudden betrayal followed by a rapid invasion?

Or is it a more subtle insurgency, with T-cell saboteurs harassing pancreatic cells over years? And what starts the conflict in the first place?

In animal models, and through the twin studies, Eisenbarth's group demonstrated that Type 1 diabetes is most often a cold war that ends in disaster. High blood sugar is only the final consequence of a series of stages that begins with genetic predisposition, followed by the gradual loss of all, or nearly-all, insulin-producing cells. This process is illustrated in Eisenbarth's original paper by a graph now famous among diabetologists for making sense of disparate findings on Type 1 diabetes. The graph shows the mass of insulin-producing cells depicted by a line, at first flat, then gradually falling through a series of stages as the confused immune system does progressively more damage. Above the inflection point where the line begins its decline, Eisenbarth wrote:

? Precipitating Event

In other words, what causes it? And implicitly: How does one stop that thing, whatever it is, from happening? For Ziegler, the question would define her career, and provide fodder for forty years of research. It would do the same for many other scientists as well. "It was a conceptualization of what we needed to do for the future," said Bonifacio, whose research turned to focus on Type 1 diabetes around the same time. Indeed, it was right around then that Ziegler and Bonifacio met in diabetes research circles. They were married after Ziegler returned to Germany to continue her research.

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So Type 1 diabetes had an environmental trigger. That much was clear. The problem with identifying what it might be, Ziegler and others soon realized, is that the "environment" includes pretty much everything. "Measuring environmental exposures is really, really tough," said William Hagopian, who studies the genetics and epidemiology of Type 1 diabetes at Pacific Northwest Diabetes Research Institute in Washington. "If you don't believe me, tell me what you had for lunch the day before yesterday."



Lunch is an environmental exposure. So is what you breathe, and where you breathe it. The dirt in your house, the chemicals used to clean it, and the dog that tracks it back in are part of the environment. The viruses that infect you, and the vaccines that protect you count. The bacteria on your toothbrush are included, as are the microbes—good and bad—that live in your gut. Exposures during the first year of life are especially important for training the immune system for the enemies it can expect to encounter later on. Indeed, where and how you were born, what you ate (and what your mother ate), and where you played are all potential environmental factors. Even the weather counts—people who live farther from the equator are more likely to develop Type 1 diabetes, possibly because, with less exposure to sun, they produce less vitamin D than people who live near the equator. The totality of exposures in an individual’s lifetime is sometimes called the “exposome.”

By the time Ziegler started her research in the 1980s, there was already a profusion of hypotheses about what in the exposome is relevant to Type 1 diabetes. Because of the timing and geography of the rise, any change to modern life since WWII was suspect: too much sugar, too much cow’s milk, not enough breast milk, gluten, air pollution. It’s something in the gut. It’s leaking in the gut. It’s leaking in the gut *because* of not enough breast milk. It’s viruses. It’s vaccines. It’s cleanliness itself (part of a wider theory of autoimmune disease known as the “hygiene hypothesis”). The list grew: C-sections, stress, obesity, omega-3’s, vitamin D3, and on. Many of these factors reasonably could influence the early development of the immune system. The hard part was proving there was a link between a given exposure and developing the disease, and then explaining precisely how that exposure caused the disease.

One of the first steps to narrow the field was to identify not which, but *when* environmental factors had the most influence, Ziegler explained. In Eisenbarth’s multi-stage model of Type 1 diabetes, when did the mysterious “precipitating event” tend to take place? Type 1 diabetes was most commonly diagnosed between age ten and fourteen. But the triggering exposure might have occurred years before diagnosis. Was it something that happened in the womb? Months after birth? Years? “One didn’t really know *when* to look for the cause,” Ziegler said.

In 1989, Ziegler led one of the first studies to take this question on. Called BABYDIAB, the study followed 1,353 German newborns with at least one parent with Type 1 diabetes until they developed autoantibodies, an early sign that full-blown diabetes was imminent. (At the time, genetic screening tests didn't exist, so risk was determined simply through family history.) Soon after BABYDIAB started, similar studies were conducted in Finland and in Colorado. A key finding from all three studies was that the earliest stage of autoimmunity most frequently begins when a child is just one or two years old. “That changed the search for environmental factors quite dramatically,” said Ziegler. The most significant triggers would have to occur in the womb or soon after birth. Likewise, any intervention that sought to preempt the trigger would have to happen immediately after birth.

Spurred on by results from those studies, and a sense that the culprit was out there if only they had more data, Ziegler and other clinicians planned a colossal study they believed would lead to definitive answers. Diabetes research centers that had been working separately—including in Finland, Germany, Sweden, the United States, and the U.K.—would combine their expertise to identify, and follow more than 8,000 high-risk patients from birth until they turned 15, capturing more detail on environmental exposures than any previous study, including dietary records harmonized across different countries, regular stool samples, water samples from the tap at home, even psychological data on stress at school. A name for the massive project came to Ziegler one night when her doorbell rang with a gift for her daughter sent by Eisenbarth. It was a teddy bear. The study, which began enrolling participants in 2004, was called The Environmental Determinants of Diabetes in the Young, or TEDDY.

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Getting TEDDY started was a major step, and running it a major undertaking, but waiting for results would take at least fifteen years. In the meantime, Ziegler, Bonifacio, and other GPPAD researchers considered ways to continue testing preventions, even if no “smoking gun” environmental factor had yet been identified. To do that in a robust way would involve conducting randomized, placebo-controlled trials—the gold standard for clinical research.

That meant enrolling trial participants, giving half of them a treatment, giving half a placebo, and then waiting for enough participants to develop diabetes to make statistically significant comparisons between the treatment group and the placebo group. (Think of the clinical trials on vaccines for COVID-19. Counterintuitively, Pfizer, Moderna, and others had to wait for enough trial participants to develop COVID-19 to prove their vaccines made a difference.)

The trouble with this approach for Type 1 diabetes is that the disease is relatively uncommon and takes a long time to develop. In Finland, with the world's highest rates, only about 1 in 100 people develop Type 1 diabetes. You'd have to follow 100,000 randomly selected Finns for years just to have one thousand cases of Type 1 diabetes against which to judge the effects of a prevention. Genetic risk screening could help—by identifying a higher-risk population, researchers would only have to keep track of around 1,000 participants, rather than 100,000—but even that was daunting. Such a trial would require screening hundreds of thousands of newborns.

“We needed to recruit a lot of babies,” said Bonifacio.

After a smaller pilot study to prove their screening process could work, GPPAD started enrolling families in its first randomized, placebo-controlled primary prevention trial for Type 1 diabetes in 2018, with results expected in 2025. (The only previous study to do this was a trial in Finland testing whether delaying exposure to complex proteins in milk prevented Type 1 diabetes; it didn't.) Called POInT, the GPPAD trial follows more than 1,050 at-risk children to test whether feeding them insulin has a preventative effect; when eaten, rather than injected, insulin does not affect blood sugar.

Bonifacio explained POInT was inspired by research showing peanut allergies could be mitigated or avoided by feeding a child peanut protein at 5 months of age. The first autoantibody to emerge in Type 1 diabetes is often against the insulin molecule itself. Perhaps early exposure to lots of insulin—like early exposure to peanut protein—would help train a person's immune system to recognize insulin and leave it be.

With POInT underway, GPPAD considered the next project. “Recruitment was wonderful,” said Bonifacio. “What’s next?”

They considered Vitamin D supplements—results from TEDDY showed higher Vitamin D during childhood slightly decreased risk for Type 1 diabetes—but decided against it. Vitamin D was easy to get, so researchers would be unable to prevent study participants from procuring supplements on their own, creating an unreliable placebo group. They considered a vaccine targeting a type of virus—called coxsackievirus B—linked to risk for Type 1 diabetes, but decided the vaccine wouldn’t be ready soon enough. “Then there had been this interest in the microbiome,” said Bonifacio, referring to the trillions of microbes that populate the human body. Several studies, including TEDDY, had found associations between imbalances in the gut microbiome and risk for Type 1 diabetes. “And we said, Ok. Let’s explore it.”

After speaking with everyone they could think of about different methods to influence the microbiome, the GPPAD group decided to test a probiotic—essentially a packet of live bacteria—made by a California-based company called Evolve Biosystems. The bacteria used in the probiotic are called *Bifidobacterium longnum infantis*, often shortened to *B. infantis*, or more fondly, just “bif.”

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*B. infantis* makes its home exclusively in the human infant gut. The microbe has reason to like it there. Unlike most other bacteria, *B. infantis* is able to feed on complex sugars in breast milk called human milk oligosaccharides, or HMOs. Infants themselves aren’t able to digest the sugars. Rather, explained Steven Frese, a microbiologist at the University of Nevada, Reno who helped develop the probiotic, the sugars feed *B. infantis*. In return, the bacteria appear to play an important role in the crowded ecology of the infant gut, keeping populations of other microbes in check, and transforming indigestible sugars into compounds the body can use. If the infant gut microbiome is like a vacant hotel, “*B. infantis* renovates the hotel,” said Frese.

*B. infantis* is commonly found in infants in developing countries, said Frese. In developed countries, however, it's "really, really rare," possibly contributing to widespread imbalances, or dysbioses, in the gut microbiome. Dysbiosis is often unrelated to *B. infantis*, but a study by Evolve Biosystems researchers found American infants with dysbiosis often lack *B. infantis*, in particular strains able to metabolize human milk oligosaccharides. Such dysbioses can lead to gut inflammation, which could influence the early development of the immune system, and in turn risk for autoimmune disease. Ziegler's original birth cohort study BABYDIAB, as well as TEDDY and the two other large birth cohort studies in Finland and Colorado, found a link between dysbiosis and risk for Type 1 diabetes. "I thought that was quite convincing," said Ziegler. "You have multi-study evidence in multiple countries for an environmental factor."

It is notoriously difficult to measure particular types of bacteria among the teeming microbes within the gut, but one clue *B. infantis* (and other types of *Bifidobacteria*) specifically might be linked to Type 1 diabetes came from an oft-cited study conducted between 2008 and 2016 in Finland, Estonia, and the Russian Karelia, a forested, castle-dotted region bordering Finland. Despite a similar climate and genetically similar populations, rates of autoimmune disease in Finland and Estonia are around six times higher than in the Russian Karelia, creating a kind of living laboratory for studying environmental determinants of Type 1 diabetes. Called DIABIMMUNE, the study compared the gut microbiomes of 74 at-risk infants from each region.

Among other differences, the study found the Russian babies—at low-risk of developing Type 1 diabetes—were more likely than the high-risk Finnish and Estonian babies to have populations of *Bifidobacteria* in their gut; the Finnish and Estonian babies had an abundance of another type of bacteria, called *Bacteroides*. Any causal chain between *Bifidobacteria* and risk for Type 1 diabetes is poorly understood, but Tommi Vatanen, a Finnish researcher involved in the DIABIMMUNE study, explained it could have to do with how *Bifidobacteria* affect how the developing immune system learns to distinguish self from invader. Part of this "training" process involves encounters between the immune system and different types of bacteria in the gut. A lack of *Bifidobacteria*, and ensuing overabundance of other types,

“might mask the immune training from the other bacteria,” said Vatanen. An alternative, or additional explanation is *Bifidobacteria*'s ability to transform the sugars in breast milk into fatty acids that help feed the cells lining the gut, preventing leakage.

Precise mechanism aside, it's certainly plausible that dynamics of the infant gut microbiome are connected to autoimmune disease, said Frese. “That first 100 days of life, the immune system is expanding and developing in a way that's really unique. The direction that those immune cells take is what puts you on a path of being at risk for developing atopic dermatitis, or asthma, or food allergy, or Type 1 diabetes.”

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That, in somewhat greater detail, is what families learn when they come to the Institute for Diabetes Research in Munich to enroll in the trial, called “Supplementation with *B. infantis* for Mitigation of Type 1 Diabetes Autoimmunity,” or SINT1A. A poster hung at the Institute is covered with colorful footprints from babies who enroll in the trial. Their larger footprints will be added when they age out years from now, some with Type 1 diabetes, some without.

The day I visited, the clinical engine was revving to identify and enroll the 1,144 at-risk infants needed for SINT1A, which got started in April, 2021. Ziegler first met me in her office where she made sure I understood everyone in the lab was extremely busy, and had little time to talk, before proceeding to introduce me to nearly everyone in the building. This included an impressive array of staff involved in running several large clinical trials in parallel across a continent, handling everything from regulatory matters (Brexit continued to create headaches shipping study samples to the U.K.), to finance (most funding flows from an American nonprofit called the Helmsley Charitable Trust), to logistics (supplies of a key medication were running low, which if not remedied could lead to unacceptable gaps in treatment).

On the fourth floor, Ziegler introduce me to Christiane Winkler, a study doctor who has worked closely with Ziegler for the past eighteen years. She was at work going over the genetic risk scores of the 1,365 newborns screened in GPPAD study centers just that week.

Like Leo's, these babies' heels had been pricked in the hospital, then portions of their DNA had been sequenced in Oxford. Winkler was double-checking the results to make sure the algorithm had not misidentified any patients as at-risk or missed any who were. "Sometimes there are quite weird things," she said. In such cases, she said it's good to have humans in the loop.

The scores appeared as letters in a spreadsheet—CT, CC, TC—each column representing a single point in a baby's DNA linked with developing diabetes. Identifying these variations among the billions of letters in the human genome had required comparing the DNA of thousands of patients who developed Type 1 diabetes in search of similarities. The points—called single nucleotide polymorphisms, or SNPs, pronounced "snips"—were central to the trial. Without them, Winkler explained, it would be impossible to find enough patients who would ultimately develop the disease to study treatments that might prevent it.

Where older genetic risk tests looked at just two SNPs associated with risk for diabetes, the most recent version of the test used 51, some of which increased risk and others of which reduced it. Added together, they gave patients a risk score with unprecedented predictive power, capable of identifying newborns with a greater than 10 percent chance of developing diabetes by the time they turned six; more than twice as good as previous tests. (An important limitation is that the test is likely less predictive for populations outside Europe, said Bonifacio, especially for people of non-European descent.)

Even with the more powerful test, the numbers of people needed for SINT1A were intimidating. After nearly a year's effort, just 293 families out of the 1,144 required were enrolled. And more at-risk babies weren't easy to come by. Of the more than one thousand newborns Winkler reviewed that week, only about 13 were at high enough risk to be eligible for the trial, and only a few of their families would likely be interested in participating.

Adding to the enrollment challenge, each at-risk baby represented a ticking clock. The nature of the *B. infantis* probiotic required it be administered as soon as possible after birth, when the immune system is first learning to behave and the gut microbiome taking shape—at the latest,

six weeks. By the time Winkler reviewed the scores, a week had already passed since birth. That left only five weeks for one of several study doctors to get in touch with the family, give them time to digest the bad news, then try to explain why they should come to Munich to enroll their newborn child in an experimental trial for a disease the child did not have.

Even the rush for six weeks might not be fast enough. Vatanen, whose work on the Finland-Estonia-Russia study helped to identify *B. infantis* as a possible environmental factor, said he thinks the trial is promising, but the relevant interaction between the immune system and gut microbiome might happen before six weeks. In that case, the probiotic could arrive too late to matter.

This time pressure was most evident in the Institute's lab, where Marlon Scholz, the fast-talking biobank manager, took me through a whirlwind tour. Amid humming centrifuges and burbling machines, a brigade of young, lab-coated workers prepared blood samples for tests to identify the autoantibodies that indicate the first stages of Type 1 diabetes have begun (the appearance of autoantibodies is the primary outcome for the GPPAD trials; waiting for participants to develop full-blown diabetes would take too long). Speeding things up further was Robby the Robot. Scholz showed me how Robby—a metal box about the size of a vending machine—is “fed” blue plastic trays of blood plasma, which are subjected to lasers. Positive samples return an ominous glow.

Across from Robby was a large stack of blood-spotted papers in a cardboard box direct from various Bavarian birth clinics. With quick expert clicks, Sholtz hole-punched several blood spots into a bar-coded tray. He raised the tray, peering at the blood-soaked chads. “Here we have many babies,” he said.

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The newest of these was Leo. When I met him, he was asleep on Haydn's chest wearing a grey woolen onesie with a red stripe across the middle, doing his best to ignore the adults'



dull conversation about his future. Over the course of an hour, two study doctors took the family step by step through everything they needed to know to participate in the SINT1A trial.

They explained the logic behind the genetic testing that had brought Leo there. They explained how genetic risk combines with environmental factors to cause Type 1 diabetes, and that clinicians believe imbalances in the gut microbiome may have something to do with that. (Ada and Haydn, being Type 1 diabetics, didn't need the details about how diabetes itself works.) *B. infantis* was simply described as "a good microbe." The treatment itself was set on the table in a white cardboard cube filled with packets resembling pouches of yeast.

Once a day for the next twelve months, Leo needed to be fed one packet, the powdered contents mixed with breast milk or water, which he could suck from a finger or a bottle. In addition to feeding Leo the probiotic, the family was responsible for collecting stool samples, filling out diet surveys, and attending twice annual visits to the Institute for the next six years. And there was, of course, a fifty-fifty chance that, after all that effort, Leo was in the group receiving a placebo.

It still seemed worth it to the family.

"We wanted to participate in the study to prevent him [from developing diabetes], of course," said Haydn.

"And to develop something to prevent it for other children," added Ada.

Leo interjected with a disgruntled *aaaaah* without opening his eyes.

"Every day it's going to be better," said Ada, while Haydn hushed the baby. "The treatment. The prevention. They're working for it."

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Embedded in the floor of the Center for Regenerative Therapies in Dresden is a large granite disk which makes a single rotation each year. Bonifacio, who works out of the center, said the installation helps remind him clinical research is often a maddeningly slow process, and that progress can be difficult to see, but is happening nonetheless. “[It] takes a long time to come around to something and then it goes exactly to where it was one year ago,” said Bonifacio. “I think it's perfect.” The search for the environmental determinants of Type 1 diabetes has certainly required such patience.

After nearly twenty years and hundreds of millions of dollars, TEDDY, the mammoth study meant to reach a definitive answer on environmental triggers for the disease, is now reaching its conclusion as participants start aging-out at fifteen. Researchers have learned a lot about Type 1 diabetes from the project. For instance, they’ve learned there are different types of Type 1 diabetes depending on which autoantibodies appear first, and they’ve ruled out a few potential environmental factors—maternal Vitamin D deficiency, for instance, does not increase risk. TEDDY data has also enabled the powerful genetic tests behind GPPAD’s primary prevention trials. “We have so much data,” said Haller, the Florida endocrinologist who works on TEDDY. “We collected insane amounts of data on every exposure under the sun.”

What TEDDY hasn’t revealed is what researchers most hoped to find out: What causes it? “It was supposed to be the hugest study in the world,” said Hagopian, a TEDDY principal investigator. “And it is the greatest study in the world. But it falls short.” No dominant environmental trigger has emerged. They’ve found no smoking gun, said Haller, only “smoking BB guns.”

The study won’t officially be over until 2025, but researchers say big surprises are unlikely at this point. “We started TEDDY to find the smoking gun,” said Ziegler. “We thought it was realistic we would find it. But I think now after many years of TEDDY, we have to say, no, it is different.” Rather than one main cause, many smaller, interrelated factors appear to be associated with risk. These give credence to some original hypotheses, but even taken together, the links identified in TEDDY can’t explain most cases of Type 1 diabetes, or

explain the rise.

Without clear direction from TEDDY, primary prevention looks more challenging. “We’re still kind of just guessing at what we should do” to prevent at-risk children from developing Type 1 diabetes, said Haller, who is not involved in any of the primary prevention trials. “Until we have a hold on all those semi-black box things it’s tough to tell people [what] to do.”

Yet the stone turns. In SINT1A, as in other primary prevention trials, researchers are making the best of the limited evidence. The evidence that *B. infantis*-related dysbiosis is linked with Type 1 diabetes might not be bulletproof, said Bonifacio, but feeding babies a well-studied probiotic is not likely to harm anyone. Other than a few million bucks to run the trial, why not? There’s also value in taking a treatment off the table, he said, pointing to the situation with another suspected environmental factor: coxsackievirus B.

The same troubles with measuring other environmental exposures have stymied efforts to conclusively blame the otherwise harmless virus (“Tracking viruses is like tracking ghosts,” said Hagopian), but a number of studies, including TEDDY, found early-childhood infection with coxsackievirus B was a risk factor for Type 1 diabetes. Preventing infection with the virus could thus be another route to primary prevention. “We’ve been speaking about [coxsackievirus] for fifty years plus now,” said Bonifacio. “Whether you believe it or not, do a vaccination. Maybe you find that it works, and reduces the incidence. If it doesn’t, what harm have you done?”

Provention Bio, a New Jersey-based company focused on preventative treatments for autoimmune disease is developing a vaccine targeting the virus. Francisco Leon, the company’s chief scientific officer, said the company is planning a phase 2 trial for the vaccine; it’s nearly finished a phase 1 trial in Finland. From there, Leon estimates it could take ten or twelve years before the vaccine is on the market, assuming it is in fact protective against Type 1 diabetes, and the company finds financial support for future trials. This could be a tough prospect because there is a disincentive to do research on disease prevention, said

Leon. “The incentives are to *treat* chronic disease and that is not sustainable. The future is to prevent disease from happening. The science is there... We just need to demonstrate that this is favorable for the payers.”

Though funding emphasizes treatments, primary prevention has the best chance of significantly reducing the global burden of Type 1 diabetes, argues Bonifacio. Programmable insulin pumps and blood sugar sensors are now capable of working in tandem like an “artificial pancreas.” Even a cure could be on the horizon: a company called Vertex Therapeutics made news last year with promising early results for a stem cell therapy that would enable Type 1 diabetics to produce their own insulin. Provention Bio itself is testing a monoclonal antibody called teplizumab, which aims to stop people who develop autoantibodies to progress to full-on Type 1 diabetes.

But any of these approaches are likely to be expensive, and difficult to access, said Bonifacio. A probiotic, or dietary supplement, or even a vaccine, would be comparatively easy to make available to a large number of people. This would not prevent all cases, but “even if we were able to reduce [Type 1 diabetes] by 20 percent, that is a phenomenal amount compared to any of these other” treatments, Bonifacio said, saving billions of dollars in medical costs, and helping millions of people avoid a life-threatening chronic disease. If a prevention is shown to be effective in a trial like SINT1A, he thinks the next step would be to test it on a larger population not restricted to high-risk infants.

Ziegler too maintains her hopes for a “world without 1,” though she said it’s hard to know what exactly that would look like. The ambiguous results from TEDDY suggest it’s unlikely a single prevention could do all the work. More likely, she said, is a “combinatorial” approach where diabetes-specific treatments like feeding at-risk children insulin are paired with “more general approaches like having a healthy microbiome, or preventing early infections.” This would likely also involve widespread genetic risk screening for Type 1 diabetes. Currently, no standard newborn screening panels include risk screening for Type 1 diabetes, but increasingly cheap and fast genetic sequencing, including whole genome sequencing, could mean it’s only a matter of time.

It also remains possible that a single trigger strong enough to explain the rise does exist, but has so far been missed by TEDDY and other studies attempting to dissect the overwhelming complexity of all possible environmental exposures—the so-called “exposome.” New tools to more comprehensively measure the exposome and integrate it with genomic data could offer a way forward (this is also the promise of precision medicine, which aims to bring genomic and environmental data to bear to treat individuals). Indeed, there are mountains of data produced by TEDDY yet to be analyzed, said Haller, and millions of biological samples from TEDDY remain stored in freezers at the National Institutes of Health facility in Germantown, Pennsylvania, available for further scrutiny if anyone had the will or the reason.

If the search for environmental factors so far presents any lesson, though, it’s that more precise and voluminous data does not necessarily lead to answers. The world and how it interacts with the human body is more inscrutable than even the architects of TEDDY imagined. We’ve come to know there are dangers without knowing what to do about them.

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## List of Interviews

Sarah Howard - Founder and Manager, DiabetesandEnvironment.org – 11/10/21 (Phone call)

Mikael Knip – Research Director, University of Helsinki Children’s Hospital - 11/10/21  
(Phone call)

Michael Haller – Endocrinologist at the University of Florida – 1/26/22 (Phone call)

Anette Ziegler – Director of Institute for Diabetes Research, Munich – 2/3/22 (Zoom call)

William Hagopian – Endocrinologist at Pacific Northwest Diabetes Research Institute in  
Washington – 2/7/22 (Zoom call)

Tommi Vatanen – Microbiologist at the University of Auckland - 2/8/22 (Zoom call)

Steven Frese – Microbiology at the University of Nevada, Reno – 2/10/22 (Zoom call)

Francisco Leon – Chief Scientific Officer, Provention Bio – 2/14/22 (Zoom call)

Sonia Chritton – President, Children With Diabetes Foundation - 3/11/22 (Zoom call)

Franziska Lange – GPPAD Study Doctor at TU Dresden – 3/23/22 (In person)

Ezio Bonifacio – SINT1A Principal Investigator at TU Dresden – 3/23/22 (In person)

Angel Hommel – GPPAD Study Doctor at TU Dresden – 3/23/22 (In person)

Christiane Winkler – Principal Investigator on FREDER1K – 3/24/22 (In person)

Peter Achenbach - Deputy Director of the Institute of Diabetes Research, Munich – 3/24/22



(In person)

Anette Ziegler – Director of Institute for Diabetes Research, Munich – 3/24/22 (In person)

Franziska Reinmüller, Tiziana Welzhofer, and Anna Hofelich – Study Doctors in SINT1A –  
3/24/22 (In person)

Ada, Haydn, and Leo (Pseudonyms) – Family enrolled in SINT1A – 3/24/22 (In person)