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## One girl's hope, a nation's dilemma

The Boston Globe

### A Cambridge firm's drug worked wonders, but was hugely costly - more than Costa Rica thought it could spend on one child among so many

By Stephen Heuser, Globe Staff | June 14, 2009

BARRANCA DE PUNTARENAS, Costa Rica - At the time, he had no way to know it would trigger a high-stakes controversy that reached all the way to Boston, but Jose Antonio Gonzalez remembers clearly the day he first heard that there might be a drug to help his little daughter.

To Jose, it sounded like a miracle. As a toddler, Tania had been a bright girl with a vivid smile and a penchant for dancing. But by age 8 she was in a strange and frightening decline. She struggled on frail limbs to carry her swollen abdomen. As other children rode their bikes on the tiny fishing village's dirt roads, Tania lay on the sofa in her orange cinderblock house, inert.

No one understood what was wrong. Specialists had run tests on Tania to rule out common diseases, then unusual ones. When Jose's phone finally rang with an answer, the doctor told him Tania had a genetic defect so rare that it strikes only a tiny scattering of people around the world.

"The first thing he said was, she could die," said Jose, a somber and powerfully built man. "The strength I was supposed to carry with me just vanished."

But the doctor had another piece of news. There was a drug that might halt Tania's suffering and perhaps even reverse the toll of her disease. The drug was called Cerezyme.

For Jose and his family, it was as though a hand had reached down to answer their prayers. But in that moment, something else had happened as well: The Cambridge drug company Genzyme had just found its first potential patient in Costa Rica. And now that it had found one, it would supply the drug to Tania, but at an astonishing cost - \$160,000 a year, possibly for the rest of her life.

This was far more money than the Costa Rican government had ever paid for a drug, and Genzyme would not bend on the price. The country's health officials were forced to weigh the prospect of a healing gift for one girl against the needs of a nation struggling to care for millions.

Should Tania get the drug?

What unfolded in that village was a dramatic example of the hard choices often forced by the inventions and ambitions of the biotechnology industry, an increasingly important part of global healthcare and a critical growth sector for Massachusetts. Its high-priced cures are creating both great wealth and great moral dilemmas, one new drug, one new patient at a time.

Jose Gonzalez felt indescribably lucky that his little girl, wasting away beneath hibiscus vines in Central America, had been found. But for Genzyme, it wasn't luck. It was another step in a remarkable business strategy: In countries from Colombia to Taiwan to Libya, the Cambridge firm has compiled an extraordinary track record of searching out patients like Tania, providing desperately needed treatment, and then successfully pressing their governments, even poor ones, to pay full price for the most expensive drugs in the world.

That strategy has helped Genzyme bring in more than \$1 billion a year on Cerezyme alone, and to develop an arsenal of similarly expensive drugs for other rare diseases. And Costa Rica would soon learn a lot about Genzyme's determination to be paid when it considered the cost of saving Tania Gonzalez, how it would drain resources from other patients, and decided that its answer was "no."

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The discouraging march of Tania's illness had been part of the Gonzalezes' lives since the night in 1996 that her bowels had emptied suddenly in her crib. Her parents suspected that this was not a typical childhood accident, and after they drove Tania 15 minutes to the doctor, they quickly learned they were right. The baffled doctors noted Tania's arms and legs were oddly thin, and her spleen enlarged - "very strange things in a 3-, 4-year-old girl," said Jose.

Only one institution in Costa Rica had the expertise to handle Tania's case, and so the Gonzalez family soon had a new ritual. Often setting out before dawn, Jose would climb into his car with his wife, Viviana, and his growing family, and the five would navigate the twisting three-hour drive that led from their house to the capital, San Jose. At the national children's hospital, Tania would see a specialist, or have another test, and they would all crowd in for the long drive back.

At her house, not far from the Pacific coast, Tania was declining with time. She remained spindly. Her organs swelled until they pressed her abdomen outward. When she walked, it tilted her to the side. Her back began to twist. "She looked like she was about six months pregnant," said Jose.

Eventually Tania's doctors tried a new test, a genetic screening so complicated that it couldn't be processed in Costa Rica. They took blood samples not only from Tania, but also from her entire family. When the results came back, they came with an answer: Tania had Gaucher disease.

In one sense, the problem was tiny: her body's cells couldn't process a certain kind of metabolic waste. But over the years, those tiny bits of waste were building up and poisoning her. Gaucher disease is so rare that a country like Costa Rica might have only a handful of cases; fewer than 10,000 of the world's 6 billion people are known to have it.

But unlike many other crippling childhood diseases, Gaucher, named for the French doctor who first described it, had an effective treatment. If Tania responded to Cerezyme - an intravenous drug designed to clear out the accumulating waste - her body might be able to reverse the damage. She would probably need to receive Cerezyme for the rest of her life. Yet the drug offered the possibility that she would not just survive, but live normally.

There was just one catch: the six-figure price tag. Jose, a beer deliveryman, earned about \$800 per month; his house was worth perhaps \$16,000. For him, the price of Cerezyme might as well have been an imaginary number.

"The cost for us was unreachable," he said.

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If Cerezyme was not just another drug, the Cambridge firm that manufactured it did not consider itself just another drug company. When Genzyme Corp. first introduced a bioengineered drug for Gaucher (pronounced GO-shay) disease in the 1990s, the very idea seemed almost absurd to most people in the pharmaceutical industry. It was expensive to manufacture, there were vanishingly few known patients, and it wasn't clear how you could sell enough of it to recoup research costs, never mind make a profit.

Genzyme's solution, elegant in its way, was to set a price high enough to earn a substantial profit no matter how small its pool of patients. Then the company surprised the medical world - and its investors on Wall Street - by showing that American health insurers could be persuaded to pay the six-figure price tag. And with the only effective treatment for Gaucher disease, Genzyme never needed to lower the price, even as production efficiencies raised profit margins on the drug to as much as 90 percent.

The drug started to bring in tens of millions of dollars a year, then hundreds of millions. Today this one drug, prescribed for about 5,000 patients, has transformed Genzyme and its chief executive, Henri Termeer, into one of the great success stories of biotechnology, fueling its expansion into a \$16 billion company with offices and factories worldwide.

By the early 2000s, Genzyme had reached most of the known Gaucher patients in the United States, so it had begun pushing outward to new markets. Genzyme created divisions within the company to find overseas patients; it hired experts to cajole balky governments into paying for the patients' Cerezyme doses. Some of the company's successes were extraordinary: hundreds of patients in Brazil. Patients in Taiwan, Kuwait, and Bulgaria. The government of Libya's Colonel Moammar Khadafy pays for Cerezyme for a handful of patients.

As it notched these successes, the company stayed largely under the radar of public health activists who were pushing drugmakers to discount AIDS drugs and other lifesaving medications whose retail prices were financially out of reach to many governments.

Biotechnology drugs like Genzyme's, though crushingly expensive for each patient, were so rarely prescribed that they did not attract the same attention, and Genzyme followed an extremely disciplined "one price" strategy: find patients; donate the drug at first if necessary, but press constantly to be paid full retail price.

Costa Rica was part of this plan, a nearby country whose government, though poor, dedicates much of its budget to healthcare. Company executives began flying to the region and meeting with the person most likely to diagnose a Gaucher patient: Dr. Manuel Saborio Rocafort, who runs the only medical genetics department in Costa Rica. So when Saborio heard about Tania, not only did he know that he should test her for Gaucher disease, but he had the testing kit ready: Genzyme had provided it.

But confirming a Gaucher diagnosis and paying for the treatment were two different problems. The National Children's Hospital did have a special budget reserved for unusual cases requiring special drugs, but Tania's treatment alone would drain nearly half that money.

When Dr. Saborio wrote the prescription for Cerezyme, and hospital officials saw the price tag, they said the only thing that seemed reasonable to them: No. Saborio kept pressing, and the hospital kept refusing. Eventually the dispute made its way across the capital, to the tower that houses Costa Rica's national ministry of health.

Sitting under his corrugated roof in a town many hours away, it looked to Jose Gonzalez as though his daughter's future was being reduced to another piece of paper somewhere in San Jose, with one bureaucracy handing it off to another. He and his family felt helpless.

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The list of drugs approved by the Costa Rican government - fully paid for, and available to any citizen who needs them - fills a paperback book 190 pages long. The drug plan is just one part of a national healthcare system that Costa Ricans see as a source of national pride.

Dr. Albin Chaves is the official responsible for reviewing new drugs and helping decide whether the country should pay for them. His job, in short, is to stretch the country's drug budget so it helps as many people as

possible. And the choices he faces, between the needs of desperate individuals like Tania and the needs of the nation, can be unbearable.

"One is not God to decide," Chaves remembers thinking when he saw Tania's case.

Costa Rica's healthcare system was considered a success story, and it was succeeding not because it spent freely, but because it spent carefully. The challenge of paying for Cerezyme, a product at the extreme high end of the brand-name drug business, was something new.

Inside the health ministry, a committee of doctors met to decide Tania's case. They reviewed the medical literature on Cerezyme's effectiveness - whether all patients clearly benefited (they don't) and whether Tania would, which was uncertain. In the end, the committee voted, unanimously, to deny the payment.

"We have 600,000 hypertensive patients, 120,000 diabetics," said Chaves in an interview. "That's where they set the priorities."

Jose Gonzalez set his priorities differently; every morning, he left his eldest daughter lying on the sofa in a tiny house, getting worse. He wrote a letter to the country's top health official and decided that he should deliver it in person. He traveled to the capital and got through the first two security checks in the high-rise building that houses the ministry, took the elevator to the floor where the director worked, and physically confronted the national health minister.

"I told him that what he had done to my daughter, who was a child - he was going to pay for it," said Jose.

The confrontation was dramatic, but changed nothing. "I felt choked," he said. "Totally dead."

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In Genzyme's new glass Kendall Square headquarters, the president of the firm's international group, Sanford Smith, keeps a brass gong outside his office. Every time a foreign government agrees to pay for one of the company's drugs, he takes out a mallet and rings it.

In each country where it does business, Genzyme approaches the payment process differently. In Brazil, a single boy with Gaucher disease and his well-connected family helped get the costly drug approved; today Brazil is one of Genzyme's biggest customers. In China, the company is currently providing the drug for free to 130 patients, while building a research facility to strengthen its ties with the Chinese government. In some countries, too poor to ever afford the drug, Genzyme donates it indefinitely, taking a tax write-off in America.

What it won't do is offer a discount. Although discounts are becoming more common on pharmaceuticals sold in lower-income countries, Genzyme follows a "full price or free" model, and works hard to be sure it's the former.

"If you're going to give on the price someplace, everyone's going to ask for a deal, and then you've got a massive mess - so from day one, it was one price," said Alison Taunton-Rigby, a former Genzyme executive who was with the company when it began setting its price policy.

Geoff McDonough, current head of the division that sells Cerezyme, says the policy allows the company to maintain the profit margin needed to research future drugs, while also keeping a door open for the truly impoverished.

"We've chosen a way here that's been consistent across the company, and has met the specific needs and complexities of patients suffering from very rare diseases," he said.

It is a balancing act, he says, that amounts to an "extreme example" of a discounting policy: the company currently provides the drug free to more than 300 patients worldwide.

In Costa Rica, Genzyme offered to donate Tania's dose of Cerezyme for two months. But it had also hired a local healthcare consultant to figure out how the company could start getting paid. The consultant, an American-educated businessman named Roman Macaya, had an idea: use the Costa Rican courts to force the government's hand.

Genzyme, he suggested, could take advantage of a feature of his country's legal system: a national ombudsman who represents the rights of common people in cases where they feel wronged by the government. Tania was, by this time, 10 years old, a village girl, poor and photogenic. The health ministry had just denied her a potentially lifesaving drug. She was a perfect case.

"There was no way, knowing Tania, knowing her family, walking them through the process, that anyone could let her not get therapy," said Macaya.

Soon, Jose Gonzalez began to find out what it felt like for Genzyme's attention to be trained on his family. "We found out that we had great friends," said Jose. "New friends."

Macaya helped Tania's family prepare the complicated paperwork necessary to sue the federal government. He was joined by a Genzyme employee from Cambridge, Jhon Cuervo. The national ombudsman agreed to meet with the Gonzalez family. As Macaya predicted, he promptly took the case.

To Jose, to his neighbors, it did not look like an American drug company putting pressure on their nation's healthcare system. It looked like the little guy against the government, with Genzyme quietly helping out the little guy. "People who didn't even know us would call us," says Jose, "said they would pray for us, ask how they could help get the medication."

The case reached Costa Rica's constitutional court in July 2003, and the results were swift. At the hearing, Dr. Saborio testified about Tania's diagnosis; he said she definitely had Gaucher disease.

"They asked me what her future would be if she didn't receive the medication. And I told them exactly what would happen: eventually she would die," said Saborio. "And that was it . . . I think there was little doubt about what the right decision was."

It took an hour. The court told Costa Rica that Tania would get her treatment, and Genzyme would get paid.

Within a month, Tania was in a room at the children's hospital, getting the first infusion of Cerezyme ever delivered in her country. Her family stood around her, relieved and joyous. Dr. Saborio was there. Roman Macaya was there, as was Jhon Cuervo and another executive from Genzyme. Jose Gonzalez, the stoic family man, began to cry.

Today, Tania is 17 years old; her posture has unfurled, her spleen reduced to near normal size. Every two weeks, her mother wakes up before dawn for the long bus trip to San Jose. By now Tania's infusions have become routine; she asks for the newspaper, watches soaps on TV or just lies quiet while hooked to the infusion machine.

The worries about effectiveness proved unfounded; the drug, clearly, has changed her life. She has ambitions to study medicine, and someday to see Boston, where the drug in her veins is made. "It has done a lot for me, that medicine," she said in a phone interview last week.

Her father sees Genzyme, and Macaya, and Cuervo, as the heroes in his family story. Asked about the price of

the drug, he is almost indifferent - in Costa Rica, every drug is free.

"They say you shouldn't dwell on material things, but Genzyme is the greatest thing that ever happened to us," he said.

To Saborio and Macaya, it is not clear at all. They are delighted that they found a way to pay for Tania's drug. Both, however, say they have grave misgivings about a system in which an American company can set its prices in America and then charge them in relatively poor countries like Costa Rica.

The Costa Rican healthcare system has survived paying for Tania's medicine. What worries its leaders is the precedent. Energized by Genzyme's success, more companies have developed high-tech drugs for other rare diseases. Genzyme's pricing approach has become the standard for similar drugs. Overall, biotechnology drugs like Genzyme's account for a growing share of pharmaceutical spending every year - more than \$75 billion worldwide.

And as cures become ever more expensive, even first-world governments and insurers find themselves wrestling with decisions much like the one Costa Rica faced.

Albin Chaves, in the ministry of health, has begun pressing for an international agreement that would force drug companies to scale their prices to a country's GDP. Under such a scheme, Costa Rica would pay more than impoverished Nicaragua, but far less than wealthy countries like the United States and those in Europe.

Specialists who follow global drug pricing say those agreements will be reached in the future, if ever, and it's not clear who would even administer them. With global health activists still focusing chiefly on vaccines and tropical diseases, the cost of biotechnology drugs remains far from center stage.

For Costa Rica, this is not the end of the story: It is the beginning, and there is no way to know how it will end. Other biotech drugs loom on the horizon. Recently another Gaucher patient was diagnosed, and the cost of Cerezyme has increased. By this summer, the country expects to be paying Genzyme \$350,000 per year, indefinitely, to treat just two of its 4 million people.

*Maria Cramer of the Globe staff contributed to this report. ■*