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## **A family's hopeful trip down an unproven road**

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The story so far: Ken and Julie Bihn of Olmsted Falls and Craig and Nichole Markowich of Amherst learned their young daughters have Tay-Sachs, a rare, fatal disease of the central nervous system. The couples decided to go to Duke University to pursue a risky, grueling procedure offered by a doctor who gave them hope but no guarantees. The procedure might stabilize the progressive disease and perhaps reverse some of its effects, the doctor said. Most other physicians disagreed.

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Durham, N.C. – Julie Bihn's stomach was in knots. She was nervous enough, and now she was about to get a preview of what might be in store for Dakota.

It was the first night in North Carolina for Julie, her husband, Ken, and their 6-year-old daughter, Dakota. Julie couldn't wait to check out the transplant floor at Duke University Medical Center, known simply as "5200" – fifth floor, main building. Most here knew 5200 was their last resort.

Alexis Markowich, 4, of Amherst, had been on 5200 for four weeks after undergoing a cord-blood transplant for Tay-Sachs disease. Julie wanted to see Alexis. Dakota would be here soon.

This is the terrain of Dr. Joanne Kurtzberg, who runs the pediatric stem-cell transplant program. For years, Kurtzberg treated blood diseases like leukemia with bone-marrow transplants. Now many of the children on 5200 came because their parents sought out Kurtzberg to perform umbilical cord-blood transplants for inherited metabolic storage diseases, a group of disorders that share one trait: A missing enzyme causes cell malfunctions that lead to severe disability and, in Tay-Sachs, certain death.

Like bone marrow, donated cord blood is a source for stem cells, undifferentiated cells that morph into certain specialized cells.

Kurtzberg has concluded that cord-blood cells can do more than that: She contends these cells can traverse the brain's protective lining to treat diseases like Tay-Sachs that affect the central nervous system. Kurtzberg believes that, once across the blood-brain barrier, they can become healthy cells with intact enzymes in the brains of kids with rare metabolic diseases.

But these are just beliefs. Most doctors say there is no medical evidence this will happen for Tay-Sachs children.

Transplants are drawn-out, grueling procedures with a high risk of death. First, high-dose chemotherapy wipes out the immune system, taking patients to the brink of death and making them vulnerable to infections for months. Then the cells are infused. Powerful drugs are administered to stave off rejection of the donor cells, another sometimes fatal complication.

Because the procedure can be so harmful and any benefit to patients is questionable, many of Kurtzberg's colleagues involved with stem-cell transplants vigorously oppose the procedure for

Tay-Sachs children. Some at Duke refuse to participate in the pre-procedure tests like the ones Dakota would undergo the next morning.

In the last decade, Kurtzberg had transplanted dozens of children with metabolic storage diseases. She said five were babies with Tay-Sachs. Two are dead; the others were alive but severely disabled as of July. Tay-Sachs progresses at varying rates, and no data demonstrates whether the treatment hastened their deaths or prolonged their lives. Studies are underway to chart the disease's natural progression.

Before last December, when Kurtzberg performed Alexis' transplant, the doctor had treated no children with juvenile Tay-Sachs, which differs from the more common infantile form. Children with juvenile Tay-Sachs have low levels of the enzyme that is absent in infantile cases, so symptoms appear later and the disease progresses more slowly, affecting development as it devastates the brain.

Kurtzberg performed her first three juvenile Tay-Sachs transplants in quick succession. First, Alexis. Two weeks later, Jashaia Small, a 2-year-old from Connecticut. Two weeks after that, on Jan. 27, she would transplant stem cells into Dakota.

Dr. Maria Escolar, a developmental pediatrician at a nearby university, collaborates with Kurtzberg and plays a key role in assessing Kurtzberg's patients.

Escolar said that research she and Kurtzberg published shows a transplant is unlikely to make a difference for children who had deteriorated too far neurologically. She said the disease had caused Dakota's and Alexis' neurological development to fall more than two years behind their chronological age. Because of this, Kurtzberg appeared to ignore her own criterion when she transplanted them.

The Bihns were relieved Kurtzberg took Dakota's case. As they arrived at Duke to begin treatment for a disease considered untreatable by most doctors, they were comfortable, even confident. Julie walked the busy halls of 5200 to visit Alexis' room, excited and ready to start the procedure.

Her heart sank when she saw Alexis.

Alexis, who had had her transplant four weeks earlier, had lost her hair and could barely walk or talk. She had stopped eating, and doctors were discussing surgery to insert a feeding tube. Nichole, Alexis' mother, said Alexis hadn't smiled in weeks.

Julie looked at Alexis and wondered if this was what Dakota was going to be like.

Kurtzberg, 55, is petite, wears Mickey Mouse earrings and has a chatty, casual bedside manner that melts parents' anxiety. In her roomy clothes softened by repeated wash cycles, she looks more like a retired neighbor who putters in the garden than a doctor performing life-and-death procedures.

Get her talking about stem cells and the children she has transplanted, and Kurtzberg's soft-spoken constitution gives way to passion. She believes that 10 years from now, stem cells from cord blood will be used to rejuvenate diseased livers or stroke-scarred brains.

In the past 15 years, researchers learned that for patients with blood diseases who need stem-cell transplants, cells harvested from placentas and umbilical cords don't have to match as closely as bone marrow does to minimize the risk of rejection. The first studies found that when a

transplant succeeds – the cells take root and grow – it can effectively treat some cancers, such as leukemia, and other blood-borne disorders.

Kurtzberg has been at the forefront from the beginning, making cord-blood transplants her life's work for nearly two decades. She was among a handful of researchers who expanded the use of cord blood to include treating inherited metabolic storage diseases such as Hurler syndrome and Krabbe disease.

Kurtzberg's work with cord blood in these diseases has been characterized as pioneering in the Los Angeles Times, USA Today, Time and elsewhere in articles that lauded her for giving parents hope. She has appeared on "Today" and "Good Morning America" with families of sick children to prod insurance companies to pay for their transplants.

Kurtzberg has testified about the success of her cord-blood therapies for metabolic storage diseases as she campaigned for a national cord-blood registry, speaking before Congress half a dozen times in the past five years.

Kurtzberg's push to expand the use of umbilical cord blood has resonated, particularly with conservatives who oppose embryonic stem-cell research, which destroys human embryos. Many scientists say embryonic cells can grow into more kinds of cells than the "adult" cells in cord blood.

Congress recently passed legislation to provide \$79 million to collect 150,000 units of umbilical-cord blood for public cord banks over the next five years. The law also established a national registry, a single database of cord-blood and adult bone-marrow donors.

In January, in the early days of Alexis', Jashaia's and Dakota's transplants on 5200, Kurtzberg was with President Bush when he signed the registry into law.

Kurtzberg joined former Buffalo Bills football star Jim Kelly, whose son, Hunter, died of Krabbe disease, to push for mandated newborn screening in New York for Krabbe disease and other disorders, including Tay-Sachs. New York began screening newborns for these diseases in August.

Earlier this year, Cordus, a private cord-blood bank based in Florida, opened a branch at Duke that is run out of Kurtzberg's office. She receives a fee for every unit of blood collected and processed for Cordus.

Cord-blood transplants are generally accepted by some in the medical community as an effective treatment for appropriate cases of Hurler syndrome and Krabbe disease. But not for Tay-Sachs.

At the heart of physicians' questions about Kurtzberg's use of cord-blood transplants to treat Tay-Sachs patients is whether the technique has been sufficiently tested to be considered treatment or whether it should be classified as experimental.

In the small universe of physicians who study and treat metabolic storage diseases, Kurtzberg's transplants for children with Krabbe and Hurler are well known.

Kurtzberg was among the authors of a New England Journal of Medicine article on 20 children with Hurler syndrome, a progressive disease that damages the central nervous system and causes heart disease, bone abnormalities and eventual death.

In 15 of the 17 children who survived transplant, coordination and motor skills stabilized or improved, the May 2004 article reported. All continued to gain skills.

Another journal article in May 2005 outlined the results of transplants on 25 children with Krabbe, another debilitating disease. All 11 newborns with no neurological symptoms survived and improved. But six of the 14 infants who had symptoms died. The eight who survived showed little improvement. The authors concluded that the youngest children – those without symptoms – benefited from the transplant.

Both articles came out of a larger study known as COBLT that the National Institutes of Health sponsored to test whether cord blood was a good alternative to bone marrow for a wide range of diseases. Among the participants were 69 children with inherited metabolic storage diseases, 67 of whom were treated in Kurtzberg's program at Duke. Three were babies with Tay-Sachs.

Kurtzberg described the results of these 69 children in a journal, reporting that 72 percent survived at least a year. The researchers concluded that cord-blood transplants extended the children's lives. No data were presented about their cognitive, language or motor skills after transplant, one of the points made by pre-publication reviewers, who criticized the paper for using words such as "clinical outcomes" and "efficacy" when only survival data for the transplants was reported.

"It's a 'you're alive or you're dead' paper," said Dr. Paul Martin, lead author of the study and a hematologist who works with Kurtzberg. "It doesn't address neurological outcomes."

Kurtzberg cites these studies to explain why she considers transplants for Tay-Sachs to be therapy rather than experiments, even while many unknowns remain.

"To deny a child an option for therapy at the time we can offer it while we continue to learn is sort of state-of-the-art for transplant medicine and oncology, for that matter," Kurtzberg said in a February interview.

Kurtzberg later said in an e-mail that Dakota, Alexis and Jashaia were on treatment plans, because following the COBLT study, "we now consider this standard of care."

But Dr. Liana Harvath, who oversees research funded by the Blood Disease and Resources division at the NIH's National Heart, Lung and Blood Institute, said treating Tay-Sachs with a transplant is considered investigational.

Dr. Charlie Peters, director of stem-cell transplantation at Children's Mercy Hospital in Kansas City, said Kurtzberg is stretching the notion of accepted medical practice by basing Tay-Sachs transplants on results from other diseases.

"The only place transplanting (for) Tay-Sachs is considered standard of care is in Dr. Kurtzberg's head," Peters said.

Ken and Julie were eager to get Dakota's transplant started when a nurse asked them to sign the consent form.

Informed consent is an important part of any medical procedure. There's no reality check like seeing the hard road ahead spelled out in black and white.

Dakota's consent form was nine pages. The cord-blood transplant is a treatment plan for an inherited metabolic disorder, the form said. Tay-Sachs wasn't specifically mentioned. He said he skimmed the rest, signed it and handed it to Julie.

She said she signed without reading any of it.

Kurtzberg said she decided to transplant juvenile Tay-Sachs cases like Dakota's and Alexis' because the good cognitive results of older children in the Hurler study suggested that older Tay-Sachs children would benefit, too.

Juvenile Tay-Sachs is rarer than the infantile form, and different. In infants, neurological problems usually appear by 6 months of age, with rapid loss of abilities and death by age 5. In juveniles, the disease makes itself known later, between 2 and 5, because the brain produced the needed enzyme at some point. The decline begins when the brain stops producing the enzyme, often meaning a slower deterioration than in the infantile form. Death occurs between the ages of 5 and 15.

"They lose these things at a slower pace, and when you come in with a transplant you have more time to rescue and repair than you would with a child with a faster-developing disease," Kurtzberg maintains. "We have to find out, but I do expect that the principles follow each other and that there is no reason why the juvenile Tay-Sachs kid should not get more benefit than the infantile Tay-Sachs kids."

Kurtzberg's critics say her theory is flawed. Just because a transplant may help Disease A doesn't mean it will help Disease B, they said. For one, they say the missing enzyme that characterizes Hurler and Krabbe doesn't cause brain cells to die like Tay-Sachs does.

Unlike in Krabbe and Hurler, the missing enzyme in Tay-Sachs makes brain cells balloon up to three times their normal size, profoundly affecting the central nervous system, Peters said.

"And there is no evidence that bone marrow or cord-blood transplants can correct enzyme deficiencies affecting the central nervous system in Tay-Sachs disease," he said.

Doctors at the University of Minnesota in 1990 were the first to treat a juvenile Tay-Sachs patient with a bone marrow transplant. The cells took, so the transplant worked, but the girl died more than three years later. Dr. Chet Whitley, who treated the girl, said the procedure was deemed to have no benefit because no evidence showed the cells halted the onward march of the neurological damage.

Peters said stem cells from bone marrow and cord blood work the same way when it comes to brain tissue. Cord blood would bring no better results than the bone marrow tried 16 years ago, he said.

Whitley, who was a member of the Minnesota team and is now with the Gene Therapy Center and Institute of Human Genetics in Minneapolis, said in an e-mail that neither type of cell seems to prevent neurological deterioration in Tay-Sachs.

Kurtzberg disagrees. She said she has demonstrated that missing enzymes can penetrate the brain and repair damaged brain cells in Krabbe. Two brain autopsies of Krabbe patients found the missing enzyme characterizing that disease in the dead men's brain tissue, she said.

Evan Snyder, director of the Burnham Institute of Stem Cells and Regeneration in San Diego, who interpreted the autopsy reports with Kurtzberg, said cord-blood cells "do go throughout the brain, and they appear to make missing enzyme material which is crucial in these types of diseases."

But the autopsies were done on patients with Krabbe disease, not Tay-Sachs.

"What we know is that not every enzyme can be taken up by the cells," said Dr. John Wagner, director of stem cell transplantation at the University of Minnesota. "Some enzymes can be; others won't be. So the fact that the enzyme is there doesn't necessarily mean anything, unfortunately. I wish that it did."

Wagner said he's not aware of any data in the last 20 years that demonstrate a transplant will help Tay-Sachs.

"It can't just be, 'Well, I'm crossing my fingers.' It's got to have something more objective than that, that says this could work," Wagner said.

Kurtzberg's supporters stand by her efforts to go down unproven roads because of her expertise, and because so little is known about Tay-Sachs.

"Physicians are human and physicians want to help kids," said John Falletta, chairman of Duke's Institutional Review Board, which oversees human research. "Physicians want to help parents of kids, and Joanne is very much a human and very interested in trying to help people."

It is not unreasonable to try something that has the potential to reverse a devastating disease, said Dr. Mary Laughlin, a transplant doctor at University Hospitals Case Medical Center who trained under Kurtzberg at Duke.

"Physicians who are innovators will raise controversy," Laughlin said. "And in this circumstance, if you have the potential high risk, potential high impact using new medical technology, you're going to raise someone's hackles."

Even at Duke. Martin, the Duke hematologist in Kurtzberg's unit, now refuses to do pre-transplant work-ups on her patients with metabolic storage diseases, although he has come to see the value in trying in certain cases of Krabbe and Hurler.

"I have a hard time informing a family of what their child is going to be like in the future when I've seen other kids with the same metabolic disease go through [this] for nothing," said Martin, who helped care for nearly 70 children in the large study Kurtzberg cited. "I've been burned out."

Transplant Day. Friday, Jan. 27, would be known from here on as Day 1 on the calendar Ken and Julie posted on the Web page that allowed family and friends to follow Dakota's progress.

"This is the day Dakota's getting 'The Gift of Life,' " Julie sing songed.

Julie counted her days away from home in Olmsted Falls, her daughter, her friends. In that calendar in her head, it was Day 24. They had such a long way to go, and already some days she felt paralyzed by homesickness.

Dakota had spent the last two weeks receiving chemotherapy. She still had her hair and plenty of energy and coordination to pull stickers from a page and plunk them onto paper, color within the lines and interact with her older sister, Bailey. Ken and Julie had trouble keeping Dakota in bed.

A few minutes after 2 p.m., the nurse arrived with the donor's cells. The plastic bag looked like a sandwich-size Ziploc of thickened cherry Kool-Aid. The nurse hung the bag on a pole and attached another IV line to the central line in Dakota's chest.

"Blue's Clues" played on the TV, and Dakota didn't take her eyes off the screen. As the nurse started the drip, she warned that Dakota probably would start to smell like creamed corn because of the preservatives.

Fifteen minutes later, the transplant was done.

"Is that it?" Julie asked. The nurse nodded, yes.

The moment seemed woefully anticlimactic. Julie suggested the hospital compose a song and clapping routine, like restaurants do for birthdays.

"This is your Transplant Day, this is your Transplant Day," Julie sang and clapped before erupting into giggles. She was giddy with expectation and hope.

The room began to smell like creamed corn. Ken put a mask on because the smell nauseated him.

"The smell of life," Julie teased.

Two days later, Dakota was vomiting blood nonstop and couldn't get out of bed.

Tuesday: The rigors of the treatment take their toll on the families, and predictions about the consequences of treatment begin to ring true.

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