

“MY DOCTORS WERE SO INVESTED IN MY GETTING BETTER — AND IN THEIR ABILITY TO GET ME BETTER — THAT IT JUST BECAME A VERY PERSONAL THING. IT WAS A JOURNEY WE ALL TOOK TOGETHER.”

—SAMANTHA EISENSTEIN

Real Life

For most young women, the middle of their senior year in college means worrying about getting final papers written, landing first jobs and apartments, and finding time to enjoy the months before “real life” begins. But for Brandeis University senior Samantha Eisenstein, “real life” began sooner — and much more cruelly — than she or anyone else expected.

Several years of bone pain and many fruitless visits to orthopedic surgeons finally led her primary care physician to recommend a bone scan. The scan showed a growth in the tibia (shin bone) of her right leg. Her mother, Cynthia, a former nurse practitioner in MSKCC’s adult Lymphoma Service (who now works in MSKCC’s Employee Health Service), drove her down from Massachusetts to Memorial Hospital, where John H. Healey, Chief of MSKCC’s Orthopedic Service, performed a biopsy in mid-December 1999.

“I handed in my last paper of the fall semester and my mom told me she was coming to get me because I needed to see a doctor in New York,” Ms. Eisenstein remembers. On Christmas Eve of 1999, Ms. Eisenstein and her family learned the results of the biopsy: She had Ewing’s sarcoma, a bone cancer usually found in children and young adults. She would have to begin a rigorous chemotherapy protocol

almost immediately to shrink the tumor, in preparation for the surgery that Dr. Healey would perform to remove it and save her leg. (Ewing's is named after James Ewing, first President of Memorial Hospital's Medical Board, who originally described the tumor in the 1920s. To read more about the genetics of the disease, see the sidebar "Genetics Reveals New Insights into the Diagnosis and Cause of Ewing's Sarcoma" on page 15.)

Ms. Eisenstein received chemotherapy from January through March 2000, and it stopped the growth of the tumor entirely. Indeed, after surgery, MSKCC pathologists pronounced it "completely necrotic" (meaning all the tumor cells were dead).

In April 2000, Dr. Healey performed an "intercalary allograft," which replaced the middle section of Ms. Eisenstein's tibia with bone from an unrelated donor. "The goal is to preserve as much normal, or uninvolved, tissue as possible — which in Samantha's case meant saving her knee joint," explains Dr. Healey. "Very careful imaging can determine if there's a piece of bone, including the joint surface, that can be preserved. If you're able to save the cartilage of the joint surface and all the ligaments, then you're able to preserve

the functionally important areas and replace the segment of bone that was removed with a donor bone. This is what we were able to do with Samantha." (Donor bone is available through several bone banks around the nation.)

"With surgery, we have been able to dramatically reduce the local recurrence rate in Ewing's," Dr. Healey says. "If there's good response to the preoperative chemotherapy, our local recurrence rate is four percent. There is great interaction here at Memorial Hospital between the effectiveness of the chemotherapy and what we can accomplish surgically. It's an excellent example of the multidisciplinary approach MSKCC physicians take to treatment."

After surgery, Ms. Eisenstein continued the chemotherapy regimen, an MSKCC clinical trial protocol called P6, which uses five drugs and, in particular, one drug in much higher doses than is standard elsewhere. "In the early 1990s, Memorial opened up a clinical trial for patients with Ewing's using P6," says MSKCC pediatric oncologist Leonard H. Wexler. "The early results were extremely promising."

These results led to a national randomized clinical trial in which the regimen used at MSKCC was compared to a longer course of chemotherapy with standard doses of the drug. "At the same time, we continued to conduct the P6 clinical trial at MSKCC, enrolling larger numbers of patients," says Dr. Wexler. "The major focus was whether we could escalate the dose of this one drug and whether this would help us improve outcome." The results of the trial, conducted by the MSKCC Departments of Pediatrics, Surgery, Pathology, Epidemiology and Biosta-

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—JOHN HEALEY, *Chief, Orthopedic Service*



Three MSKCC physicians worked together to treat Samantha Eisenstein's Ewing's sarcoma: pediatric oncologist **PAUL MEYERS** (LEFT); pediatric oncologist **LEONARD WEXLER** (CENTER); and orthopedic surgeon **JOHN HEALEY**.

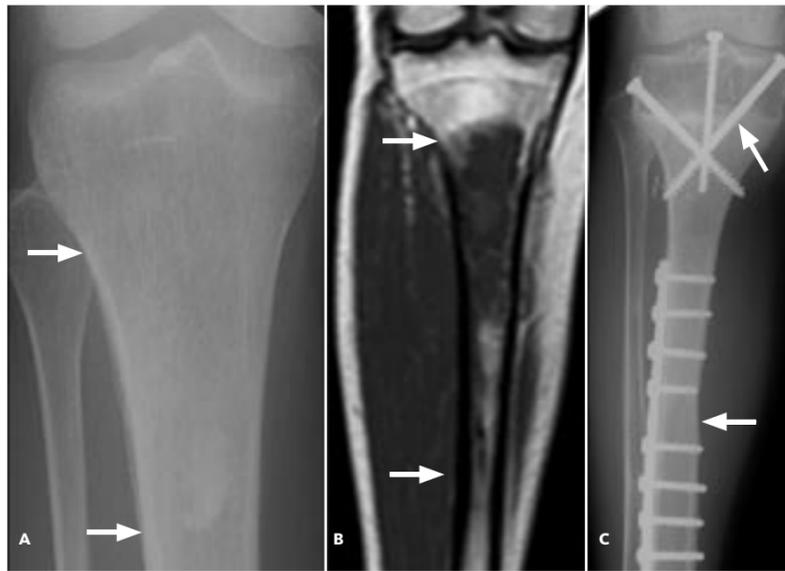


IMAGE A: Plain x-ray of Ms. Eisenstein's tibia. White arrows show elevation of the tissue covering the bone. This elevation is caused by cancer rupturing the confines of the bone.

IMAGE B: Magnetic resonance image. White arrows define the extent of Ms. Eisenstein's Ewing's tumor and show the mottled appearance of the tibia as the tumor replaced some of the bone mineral.

IMAGE C: Plain x-ray. White arrows highlight the junction of the transplanted cadaver bone with normal bone at the knee joint and in the lower tibia.

tistics, and Radiation Oncology and published in September 2003 in the *Journal of Clinical Oncology*, showed that short-term, high-dose chemotherapy (seven cycles delivered over a period of approximately six months) is effective in sustaining long-term event-free survival as well as overall survival in patients with local-regional Ewing's sarcoma (meaning, the disease has not spread to distant sites in the body).

The overall survival rate for Ewing's sarcoma for MSKCC patients is 70 percent, versus 58 percent worldwide. "I think the dose-intensive therapy we use has made a difference," says

MSKCC pediatric oncologist Paul A. Meyers, another one of the physicians who treated Ms. Eisenstein for her Ewing's sarcoma. "And there's no substitute for volume and experience. If you do a lot of something, you tend to do it better. It's a combination of our experience; very close collaborations among medical-pediatric oncologists, radiation oncologists, and surgeons; and the evolution of an intensive protocol that has given us a high rate of success."

Ms. Eisenstein finished her treatment in September 2000. "I was out of the hospital on Tuesday and went to my cousin's wedding that Saturday. Bald as a cue ball but thrilled to be there," says Ms. Eisenstein. She returned home to Vermont with her mother to recuperate and spend time with her beloved dog, Sophie — "really the best medicine," she says. She traveled to Florida to spend time with her father. Months of intense physical therapy also followed. In January 2001, she went back to Brandeis — to singing with her a cappella group, to her studies, and to her friends. But her odyssey wasn't over.

"I was tired all the time," Ms. Eisenstein says. "I caught every cold that went around, the flu, strep — everything. And the day before my 23rd birthday, Dr. Wexler told me he wanted me to have a bone marrow biopsy to see what was going on." She greeted the news with her usual aplomb. "I said, 'You guys had me on my 22nd birthday — you're not getting me on my 23rd. I'll see you the day after.'" Ms. Eisenstein and her family celebrated her birthday with an evening of Mexican food. The next day, MSKCC physicians performed the bone marrow biopsy. It turned out that Ms. Eisenstein had developed secondary myelodysplastic syndrome (MDS).

Myelodysplastic syndromes, also called pre-leukemia or "smoldering" leukemia, are diseases in which the marrow does not function normally and not enough normal blood cells are made. Secondary MDS sometimes develops after treatment with chemotherapy or radiation therapy. The best known cure is a bone marrow

MSKCC'S Research Efforts in Pediatric Cancers: The Day One Program

"If we treat 100 children with Ewing's sarcoma, two or three of them will develop leukemia," pediatric oncologist Paul A. Meyers explains. "The risk is no higher with the protocol we use than with the protocol used by other centers. There is simply a risk of leukemia every time we treat a child with Ewing's."

"We don't know whether it's age-related. We don't know whether the drugs are metabolized differently by certain individuals," adds pediatric oncologist Leonard H. Wexler. "We do know that there are genetic factors that appear to underlie how a drug is metabolized, and that there are genetic factors that may underlie how an individual experiences the toxicities from a drug. This is an area of very fertile research opportunity."

As part of the research effort to study these and other late effects of pediatric cancer treatment, MSKCC's Department of Pediatrics has established the Day One Program. Headed by pediatric oncologist Richard G. Gorlick, the program was developed to look at every pediatric patient receiving chemotherapy from the moment he or she arrives at MSKCC. Patients will be enrolled for a period of four to five years. After obtaining parental consent, physicians will take a blood sample and a swab sample of the cells lining the inside of the cheek of each patient. The samples will be sent to Dr. Gorlick's laboratory for analysis. He and his colleagues will be looking for subtle differences in the genes of patients, called genetic polymorphisms. "We

want to figure out what's different between patients who have relatively few side effects and those who have more devastating side effects, including secondary cancers. The idea is to use this information before we treat patients in order to avoid these side effects." The program encompasses not only Dr. Gorlick's laboratory studies but MSKCC's Long-Term Follow-Up Program. This program has a patient base of approximately 1,000 survivors of pediatric cancers (most of whom received their treatment at MSKCC). "We hope that what we learn can help design treatment protocols and intervention strategies that will increase survival and minimize harmful health effects," says Charles A. Sklar, the program's director.



Pediatric endocrinologist **CHARLES SKLAR** (CENTER) directs the Long-Term Follow-Up Program and works closely with pediatric oncologist **RICHARD GORLICK** (RIGHT), who heads the Day One Program, and research fellow **ALEXANDER CHOU** (left).



Several of the physicians who treated Samantha Eisenstein (from left): **RICHARD O'REILLY**, Pediatrics Chairman and Chief of the Bone Marrow Transplant Service; **FARID BOULAD**, Medical Director of the Pediatric Day Hospital; and **NANCY KERNAN**, Assistant Chief of the Bone Marrow Transplant Service.

transplant. (To learn more about research into minimizing the late effects that sometimes follow treatment for pediatric cancers, see “MSKCC’s Research Efforts in Pediatric Cancers: The Day One Program,” on page 11.) “After they told me, everything was spinning,” Ms. Eisenstein recalls. “I was in the room with my whole family — my mom, my dad, my stepdad. And my uncle, who’s like my soul mate, came over and said, ‘Sometimes to win the game, you have to play a few extra innings.’” None of Ms. Eisenstein’s blood relatives was a suitable match, so as a search for a donor began, Ms. Eisenstein returned to Brandeis. “I said to my doctors, ‘If there’s anything I can be doing, let me know. If not, let me have my last month and graduate.’ And I had a great month.” Ms. Eisenstein graduated *cum laude* in Spanish from Brandeis in May 2001.

While the search was under way for an unrelated bone marrow donor, Ms. Eisenstein’s myelodysplastic syndrome progressed. (There are five types of MDS, ranging from refractory anemia to chronic myelomonocytic leukemia.) “She required chemotherapy to put her back into refractory anemia,” says MSKCC pediatric oncologist Trudy Nan Small, one of the bone marrow transplant physicians who treated Ms. Eisenstein for her secondary MDS. Through the National Marrow Donor Program®, a donor was found — a near-perfect match — and in August 2001 Ms. Eisenstein had her transplant. “They walked in carrying this tiny bag and I said, ‘How is that going to save my life? Are you kidding?’ I remember the infusion going through the IV. When it reached my vein, everyone who was in the room started applauding.”

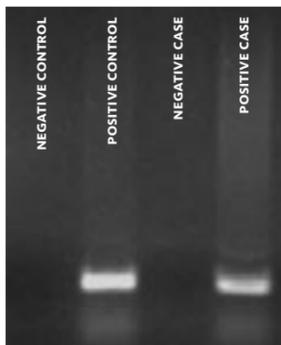
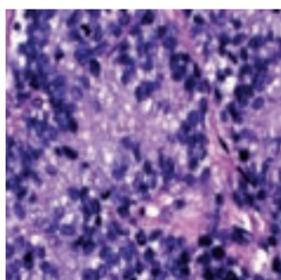
Ms. Eisenstein was treated on another clinical trial protocol.

“We have been trying for a long time to increase the cure rate of individuals who have developed therapy-related leukemia — which is notoriously difficult to treat — as well as those patients whose leukemia has recurred many times, or who never achieved remission,” Dr. Small says. Standard transplant regimens have usually proved ineffective or too toxic for patients with these conditions. “One of the things we do here at Memorial is try to develop therapies for certain conditions using novel regimens,” explains Dr. Small. Ms. Eisenstein was treated on a new protocol that included intravenous busulfan and melphalan. This combination is showing promise even in patients with advanced leukemia. “The ability to find a suitably matched unrelated donor, better supportive care, and a new regimen — all these things really worked for Samantha.”

“I saw Samantha every day on the transplant unit,” recalls Farid Boulad, a pediatric oncologist and Medical Director of MSKCC’s Pediatric Day Hospital. Dr. Boulad was one of the physicians who treated Ms. Eisenstein during her post-

“At Memorial, we try to develop therapies using novel regimens. . . . The ability to find a suitably matched unrelated donor, better supportive care, and a new regimen — all these things really worked for Samantha.”

—TRUDY NAN SMALL, *pediatric oncologist*



Most cases of Ewing's sarcoma contain a chromosomal rearrangement found in no other tumor type, involving an exchange of genetic material between chromosomes 11 and 22. **TOP:** An example of the tumor cells a pathologist might see under the microscope. **BOTTOM:** An example of the results of an assay based on the polymerase chain reaction. MSKCC's Laboratory of Diagnostic Molecular Pathology performs such testing to detect the presence of this specific chromosomal change in the patient's tumor cells. A positive result appears as a bright band. Samples with known negative or positive results (controls) are part of each clinical assay. MSKCC pathologists use this molecular testing to confirm the pathologic diagnosis of these uncommon cancers that otherwise have few distinguishing features under the microscope.

transplant period. "It's a tough time because patients go through hell for about two weeks, in terms of how they feel, how they look, how debilitated they are. But from the beginning I knew she was a very special person. I'd say to her, 'We're going to go up and down and up and down — and then we'll give you more treatment.' And she would say, 'Fine. Hit me. And I'll rebound — and keep on fighting.' She had that spirit. She smiles, and light comes in the room."

Following her transplant, Ms. Eisenstein remained hospitalized for about six weeks. Upon her release, she stayed with her mother in an apartment close to MSKCC so that she could be monitored for any complications, infections, or graft-versus-host disease (GvHD) — a complication in which donor T cells attack a patient's tissues. "Except for some mild GvHD, she didn't have any serious infections or complications," reports Dr. Small. By the summer of 2002, Ms. Eisenstein was feeling well enough to take a Spanish-language immersion course at Middlebury College.

Samantha Eisenstein now lives outside Boston and works for Education Development Center, a non-profit public health organization, in the Center for Research on High-Risk Behavior. Of her MSKCC medical teams, she cannot say enough. "They were all so invested in my getting better, they believed in me, and in my ability to get better — and in their ability to get me better — that it just became a very personal thing. It was a journey we all took together."

Ms. Eisenstein and her friends have created a foundation to provide financial assistance for young adult survivors of cancer, between the ages of 17 and 30, who are recently out of treatment and "trying to get back on their feet," explains Ms. Eisenstein. It is called the SAM Fund for Young Adult Survivors of Cancer. "I didn't want it to be all about me," Ms. Eisenstein says, of the choice of the name. "So we negotiated and I was outvoted." She smiles ruefully. "Well at least it's an acronym. It stands for Surviving And Moving Forward. In its simplest terms, the idea is to allow someone to put a deposit on an apartment, to help them out with a few months of student loan payments, to write a check to help with a few medical bills or to help someone go back to school. It's hard, obviously, for anyone just starting out. But for these young people, there's a question of 'How do I rejoin the world?' The transition after treatment for cancer is difficult enough; we don't want it to also be financially difficult."

Ms. Eisenstein concludes: "I think I started to realize in the past six months or so that cancer is always going to be there. It's always going to be part of my life, whether I get sick again or not. But it's only one of the chapters — it's not the whole book."

Summing up, Ms. Eisenstein's surgeon, Dr. Healey, observes, "I like this story. It's not pabulum — it's real life. You don't get something for nothing. But with perseverance, and the highest quality of care, we can often solve the problems, overcome the complications, and get patients like Samantha back to an open-ended life."



Genetics Reveals New Insights into the Diagnosis and Cause of Ewing's Sarcoma

Modern molecular genetics is playing an increasingly important role in the diagnosis of cancer in children and adults. Accurate diagnosis is essential in order for patients to receive the most appropriate treatment for their particular disease. Several pediatric tumors, including Ewing's sarcoma, have characteristic genetic alterations. "The vast majority of Ewing's sarcomas contain an exchange of genetic material between a gene on chromosome 11 and one on 22," says Marc Ladanyi, Director of MSKCC's Laboratory of Diagnostic Molecular Pathology. "We can detect these rearrangements on a molecular level, and they're very specific for Ewing's sarcoma. They are found only in the tumor cells. The patient's normal cells don't have these chromosomal translocations."

Under the microscope, cells of Ewing's tumors have few distinctive features; i.e., the cells are undifferentiated and primitive-looking (immature). Molecular testing is used because it can be difficult to distinguish Ewing's sarcoma

from other primitive sarcomas.

"Few centers in the country do this test routinely," says Dr. Ladanyi.

In Samantha Eisenstein's case (see her story, beginning on page 6), the tumor sample pathologists received after her surgery was completely necrotic, meaning all the tumor cells were dead, because her chemotherapy had been so effective. (Members of MSKCC's bone sarcoma team have also shown that a Ewing's sarcoma of the bone that has had a grade III or IV response to chemotherapy — complete or near-complete necrosis — such as Ms. Eisenstein's had, is an important predictor of survival.)

"There was nothing left for us to do the molecular assay on," says Dr. Ladanyi. However, in a case such as Ms. Eisenstein's, in addition to a careful analysis of the microscopic appearance of the cells, an immunohistochemistry assay can help to confirm the diagnosis. Such assays employ antibodies to detect specific antigens (proteins) that are present on the surface of specific cancer cells.

MARC LADANYI, Director of MSKCC's Laboratory of Diagnostic Molecular Pathology, shown with pathology fellow **VIOLETTA BARBASHINA**.

Ewing's sarcoma cells express an antigen called CD99 at very high levels and fail to express antigens that are associated with other tumors that look similarly primitive and undifferentiated under the microscope, such as some lymphomas and rhabdomyosarcomas.

MSKCC also has experts in the microscopic diagnosis of sarcomas in the Department of Pathology, Andrew G. Huvos and Cristina R. Antonescu, "who can very reliably make the diagnosis, even if molecular test data are not available," says Dr. Ladanyi. "So we have the best of both worlds — excellent conventional histopathology and, on top of that, state-of-the-art molecular assays."

The gene translocations of Ewing's sarcoma are not inherited. "They are accidents of nature," says Dr. Ladanyi. "You get this genetic rearrangement in the wrong cell at the wrong time, and it triggers the development of a sarcoma."