

What happens when you get a kind of cancer so rare that your doctors have no clear path to treat it? Throw out the map and your fear, and try to embrace the strange freedom that comes from

becoming your own best

nope



In New York City, indoor cycling is a contact sport. A few minutes before Spinning class at a midtown gym, most women are already on bikes and pedaling hard to warm up; those who didn't sign up in advance jostle anxiously at the door, hoping for a no-show.

Amid this sea of black-clad intensity, Jennifer Goodmann Linn stands out like a burst of sunlight. She has wrapped her hair with an orange bandanna emblazoned with the words *Cycle for Survival* and sports a bright lemon-yellow jersey. She breezes past the jockeying around her, stopping to give the instructor a hug, then smiles quietly as she settles on a bike and sets the resistance. Arms poised, she's calm and happy as the first strains of Kanye West's "Heartless" pulse, a woman exactly where she wants to be.

That she is here at all is some kind of a miracle. Five years ago, at age 33, the marketing executive learned she had soft tissue sarcoma, a type of cancer that attacks body tissues such as nerves and muscles and strikes only 10,000 Americans each year (compared with 200,000 breast cancer diagnoses). She has slogged through three heartbreaking recurrences, three courses of chemotherapy to shrink her tumors and four grueling surgeries to remove them. Cycling has been the one constant: She begged her doctors to set up a stationary bike in her hospital room, and when she returned to class after her first remission, bald and weakened, her instructor and fellow riders welcomed her with applause. Moved by how her sport had helped her heal, in 2007 she launched *Cycle for Survival*, an event in which teams of riders hit the gym and pedal for hours to raise money for rare cancers. "I realized that I could either admit defeat or use the cancer to do a good thing," she says. "The choice seemed clear."

Linn's medical journey, on the other hand, has been anything but. Her first symptoms were odd but not particularly alarming: night sweats, a chronic cough and a sudden, sharp pang in her abdomen one afternoon while she was playing tennis with her husband, Dave. "I was losing weight," she recalls, "but my pants were tight." Was she pregnant? No, although the newlyweds were trying. And when Linn began taking her temperature to see if she was ovulating, she found she had a fever. With her worry building after several weeks of symptoms, Linn saw her doctor, who ordered blood tests, followed by a series of scans.

When the radiologist saw the results, he bluntly informed her, "You have a big tumor in your abdomen." Referred to a surgeon who would remove the mass—which was the size of a cantaloupe—Linn learned it could be sarcoma. Yet, like many people, she had never heard of the word *sarcoma* and didn't grasp what it meant. "I know it sounds strange, but because the surgeon never used the word *cancer*, and because I was so young, fit and healthy, I assumed it wasn't even a possibility. My main concern was that they take [the growth] out without doing a hysterectomy, so I could still have a baby someday," she says. "I was in deep denial."

Even as she was wheeled into surgery, she still hoped the mass would turn out to be a uterine fibroid. Only in recovery did Linn learn that it was indeed cancer; the medical team had removed it as best they could, along with part of her colon, appendix and abdominal tissue. When she and Dave arrived for her first oncologist appointment a few weeks later, reality finally hit full-force. It was, Linn says, "the first time I had an out-of-body-scared moment." That doctor told Linn and her husband that her odds of surviving five years were 50 percent—no better than a coin flip. Worse, there was no medical protocol for how to proceed.

"When Dave and I found out I had a rare cancer, we immediately wanted as much information as possible," Linn says. But facts were in short supply. As with all orphan cancers, the term used for any type that affects fewer than 200,000 Americans at one time, research was limited. The "big four" cancers—breast, lung, colon and prostate, which together account for about half of all new cancer cases in the United States—receive the lion's share of funding and attention. "With common cancers, there is more data, along with collective experience, to develop guidelines for treating these diseases," says David G. Pfister, M.D., chief of head and neck oncology at Memorial Sloan-Kettering Cancer Center in New York City. "The more you see something, the more experienced you get at dealing with it. We know if one drug works better than another and are able to understand the course of the disease." With orphan cancers, most physicians and patients have no blueprint. "In terms of treatment, there aren't many patients going through what I am," Linn says. "And with such a small pool, there isn't much incentive for drug companies to invest in research."

Getting a cancer diagnosis is an isolating experience under the best of circumstances. But minimal medical options and few support groups mean people with orphan cancers are apt to feel especially singled out. "It's lonely and frustrating," admits Linn, who has gone through a series of different chemotherapies at Memorial Sloan-Kettering. Recently, her oncologist told her she is free of measurable disease. Remission is normally cause for celebration, but Linn has been given good news three times before, only to see the cancer return each time. When she asked what came next, the answer was less than reassuring. "I don't know," the doctor told her. "There's a 50-50 chance that it's coming back. We'll keep scanning you every 10 weeks, and if something turns up, we'll deal with it."

It's the uncertainty patients with orphan cancers find most agonizing—"Watching and waiting is the hardest part," Linn says—especially coming on the heels of baffling symptoms and catch-as-catch-can treatments. Yet despite the challenges, people

with orphan cancers are working urgently—swapping advice online, pushing for more clinical trials and raising awareness through efforts such as *Cycle for Survival*, which is now run by Memorial Sloan-Kettering. "I needed an outlet, but I also created the organization selfishly," Linn says. "If I leave it up to someone else to develop new therapies, it might never happen."

Awareness brings money, which in turn fuels research, and last year's federal stimulus package spurred new grants for the study of orphan cancers. "This is the era of orphan diseases, in large part because of the patients," says Alexandria T. Phan, M.D., associate professor in the department of gastrointestinal medical oncology at the University of Texas M.D. Anderson Cancer Center in Houston. "Their voices are even more important than doctors', because it's the patients who get the rest of the world excited." In the process, they are changing the destiny of almost anyone with cancer, uncommon or not, creating new treatments and forging a path to survival where none existed before.

An elusive diagnosis



One of the great challenges of treating an orphan cancer is detecting it in the first place. Some rare cancers grow silently, without symptoms; when there are signs, both patients and doctors might fail to recognize them. "Where I work, we specialize in rare cancers, so I see a lot of them," Dr. Phan says. "But most doctors don't, which means they're easy to miss." The resulting delay can be disastrous. "By the time I see patients, they've often spent years going from doctor to doctor, trying to figure out what's wrong, while the tumors continue to spread."

That was the case for Nancy Lindholm, (continued, page 136)



In the study at Memorial Sloan-Kettering and five other study sites, PLX 4032 shrank melanoma in 70 percent of participants.

Breakthroughs that benefit us all

Doctors predict these new treatments, which got their start in orphan cancer research, may also help common cancers. Good news ahead!

Breakthrough for	METASTATIC MELANOMA	SARCOMA	SARCOMA
Might also help with	<p>Breast, colon and lung cancer</p> <p>Advanced melanoma is rare enough to be an orphan, explains Gary Schwartz, M.D., who heads the drug-development lab at Memorial Sloan-Kettering in New York City. It's also vexing to treat, which is why Dr. Schwartz is excited about promising results from a Phase I trial of the drug PLX 4032. The drug inhibits a gene mutation known as BRAF, thought to fuel cancer cells. Present in at least half of people with metastatic melanoma, BRAF has also been found in 5 to 10 percent of colon and lung cancer patients, plus some thyroid and possibly breast cancer patients, too.</p>	<p>Breast and prostate cancer</p> <p>Researchers are diving deep within cells, focusing on cancer-stimulating proteins known as growth factor receptors. They've found that a receptor known as IGF-1R promotes some types of sarcoma, and they're exploring its action in other cancers, too. "IGF and other growth factors circulate in the blood, and when one of them finds a cancer cell with the right receptor, it locks in and ignites cell growth, like a key in the ignition," Dr. Schwartz explains. "New IGF-blocking drugs fit like a cap over the receptor and inactivate it, or freeze the ignition, so cancer can't spread."</p>	<p>Breast and ovarian cancer</p> <p>Another new medication, known as Brivanib, also works by interfering with the bond between a growth factor and its unique receptor. Brivanib is what's called a small molecule inhibitor; it works by binding to a fibroblast growth factor receptor, preventing the chain reaction that leads to out-of-control cancer growth. (Imagine filling in the keyhole rather than capping it.) "This truly represents a new direction in cancer therapy," Dr. Schwartz says. "Based on the biology, it's promising for sarcoma and possibly for cancers such as breast and ovarian."</p>

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Becoming your own best hope

(continued from page 135) 38, who remembers feeling exhausted when she was in law school in the mid-'90s. "I was studying all the time, burning the candle at both ends," she says. "I thought being tired was normal." After she graduated, she began experiencing other problems, including back and hip pain and deep blushing. "That was strange because I'm not shy at all," she says. She mentioned her maladies to doctors, but no one linked the random symptoms or found them alarming enough to trigger a closer look. "I think I was pegged as a yuppie hypochondriac," she says.

In 2000, Lindholm moved to Boston with her husband to begin a job as a tax lawyer. "I was working like crazy, not eating or sleeping well, so I was more tired than ever," she recalls. One physician who listened to her chest thought she heard a heart murmur; blood work also showed liver abnormalities. But the stressed and busy Lindholm put the results out of her mind. "I was troubled, sure, but I told myself I was basically healthy. Growing up, I was taught to push past any obstacle," she says.

Then, one day on her way to work, Lindholm was hit with searing abdominal pain and collapsed on the subway. She roused herself, got off the train and began walking until she felt better. She flagged down a cab to continue on to work, and then, suddenly, the pain returned. "I started screaming, 'Take me to the emergency room!' Then I'd feel better and say, 'No, turn around and take me to work!' Finally, the driver looked at me and said, 'Lady, I'm taking you to the ER.'"

Once she arrived and had a few tests, Lindholm recalls, "I got a sinking feeling that something was very, very wrong because everyone started being really, really nice to me." She learned that a scan of her abdomen had revealed that her liver was full of tumors. The doctors told Lindholm that their "best guess" was that she had advanced liver cancer and only three to four months to live. Lindholm's first thought wasn't about herself or even her husband—"I was most worried about giving my parents such terrible news," she says. When she phoned her father, a dermatologist, she put it to him directly, describing her symptoms and initial diagnosis without tears. His reaction was the last thing she expected. "Wait a minute," he said. "I remember hearing about this in medical school. I don't think you do

have liver cancer." He urged his daughter to look for other answers.

Lindholm's dad made a call that led to a specialist at Massachusetts General Hospital, who confirmed what he had suspected: She had a malignancy known as carcinoid, tumors that doctors diagnose only about 12,000 times in the United States each year. Lindholm's doctor told her that the tumors, which arise from hormone-making cells found mostly in the gastrointestinal tract, were triggering the release of hormones responsible for the mysterious flushing as well as her heart murmur.

In one sense, this was good news: Her particular carcinoid tumors were progressing slowly. But in Lindholm's case, the disease was also inoperable, in part because the cancer had metastasized to her bones. Still, Lindholm didn't despair. "I was glad that I had more time, glad that I had a diagnosis," she says. "I'd been having vague symptoms for years—the flushing, fatigue, achiness—and everything was getting worse. Now I felt as if I could move forward."

But she couldn't move forward, at least not very far. Carcinoid tumors are resistant to chemo, so Lindholm was limited to medicines to control her hormonal symptoms and bone loss. "When I started looking, I realized that there was little research on carcinoid treatments and no deep understanding even of the underlying biology," she says. "I was amazed at how disorganized it all was. From what I read, it seemed as if doctors looked at patients with the attitude, 'You're going to die anyway, so let's see how you do with this random treatment.' It was like throwing spaghetti against the wall."

Putting lives on the line



With limited treatment options, the best hope many patients have is joining a clinical trial. Except, surprise, those aren't easy to find either. "It's tough to get an adequate sample size. You have to coordinate with centers across the country, and there are fewer physicians and centers with special expertise in these uncommon diseases," Dr. Pfister says. Other options? "Talking with colleagues who may have handled a few cases. Or you can look in the literature for a case where a patient

responded well to a particular therapy."

Lindholm, for her part, has managed to get into two trials, although with limited success. Linn has never been in a trial but is benefiting from one: "Three years ago, a trial found that combining certain drugs used to treat pancreatic and breast cancers could help shrink tumors more effectively in patients with sarcoma," she says. Cycle for Survival has already funded a trial at Memorial Sloan-Kettering that has helped other patients, too.

Searching for a trial was the best hope for Susan Ahr, a 54-year-old teacher in Levittown, New York, after her sarcoma spread to her liver in 2008. "If the growth is on the end, they can cut it out and the liver will regenerate, but my tumor was in the very center, so they couldn't operate," she says. As it happened, doctors told Ahr about a therapy they'd been developing with the National Cancer Institute, a combination of an experimental medication, flavopiridol, with a traditional chemotherapy drug.

Ahr was happy to have any option but wasn't thrilled to hear that her proposed treatment had no track record. "If you must get cancer, you want to get the kind that has a 95 percent cure rate," she says. Despite her misgivings, she entered the trial in March of 2008. "If I'd been diagnosed a year earlier, the trial wouldn't have existed," she says.

Ahr's doctors were initially amazed by her results. After several months, scans showed this very aggressive tumor shrinking and stabilizing. "I felt we'd licked it," Ahr says. Last fall, however, the cancer began growing again. "That was really, really difficult," Ahr says, her voice breaking. "I thought we were done."

Gary K. Schwartz, M.D., Ahr's oncologist and chief of the melanoma and sarcoma service at Memorial Sloan-Kettering, suggested she try yet another experimental treatment: a pill known as Brivanib. Within a few weeks, her cancer stopped progressing yet again. The drug inhibits a type of protein (known as a fibroblast growth factor receptor) that seems to fuel certain cancer cells. "Researchers first studied it in several orphan cancers, including sarcoma, where the molecular mechanisms are being worked out," Dr. Schwartz explains. "Now this drug that targets this receptor is being explored in lung and breast cancer, too." In other words, there may

finally be an incentive for drug companies to attend to these long-neglected orphan cancers: therapies for the many, and not just the few. (See "Breakthroughs That Benefit Us All," page 135.)

Thank the rapidly evolving fields of molecular biology and genetics for these thrilling discoveries—advances in cellular science that doctors hope will someday help eradicate all cancers. "We really are on the cusp of a major breakthrough when it comes to cancer treatment," Dr. Schwartz says. "Now that we have the technology to dissect the cancer cell and see whether a certain growth factor or a genetic mutation turns it on, we've opened up whole new possibilities for therapeutic approaches."

Patients as researchers

These breakthroughs haven't yet helped Lindholm, who has survived nine years despite a scary lack of options. And her family has suffered a double blow: Sadly, nearly a year after Lindholm's diagnosis, her mother committed suicide. "She'd never been depressed before, but I think she was shocked by how widespread my cancer was and the discouraging prognosis I got," Lindholm says softly. "This wasn't her vision for my future."

But Lindholm had her own vision. "I've always been a determined person, and I know firsthand the sorrow that these diagnoses bring," she says. And so, no longer strong enough to work full-time as a lawyer, she started the Caring for Carcinoid Foundation (CFCF), which has awarded more than \$4.5 million for research since 2005. And Lindholm herself, with no medical background, is moving the field forward. "I realized that there were so many carcinoid subtypes that standard terms didn't exist; some doctors were calling the tumors one thing, some another," she says. "That was making it twice as hard to get an accurate diagnosis."

Lindholm put together a board of scientific advisors and a research road map: "Our first goal is to develop the fundamental research tools, such as cell lines, so scientists can experiment," she says. Among other initiatives, in 2008, CFCF organized a bio consortium, bringing together leaders in the field to pool data and biological samples from patients. "Working together, we'll collect enough samples to yield robust, reliable studies," Lindholm enthuses. Five or 10 years ago, Dr. Phan says, no one was interested in

doing work in this area. "Now, partly because of patient advocacy like this, researchers are waiting in line to get in."

Pushing ahead

For more than five years, Jennifer Goodman Linn has kept pedaling, sometimes faster, sometimes more slowly, always in a state of uncertainty. Again and again, she has suffered hair loss from chemo and exhaustion from surgery. Through it all, she says, "exercising has been my therapy. Sometimes I could do only a little bit, but I've never stopped."

Although in remission, she has not gone more than 13 months free of disease since her diagnosis. "I talk a good talk, but whenever the cancer comes back, it's devastating," she says. "Last time I got the news, I needed a week to just be depressed, scream and cry. Even though I'm doing everything I'm supposed to do and trying to be as healthy as I can, it came back. It makes you realize you're not in control of anything."

So Linn has had to let go of her need for control: "I'm better now at figuring out how to spend my time and who I want to spend it with. I'm making the most of my relationships," she explains. She and Dave froze a set of embryos before she began her first course of chemo, and knowing they have the option to try for a baby at some point has been a comfort. If her cancer comes back—again—Linn says she's ready for it. "I know I can handle it because I've handled it before."

In three years, Cycle for Survival has raised \$4 million for Memorial Sloan-Kettering's research into rare cancers. And Linn is constantly strategizing how to raise more and attract attention for its cycling events. Beneath her sunny exterior is a woman of uncommon grit. "I understand my purpose now," she says. "I know what I have to do. My efforts have created more options—I feel good about that. Meanwhile, I'm seeing what I can learn along the way and enjoying the ride."

Want to help? Click here

- To contribute or jump on a bike for the cause, go to CycleForSurvival.org.
- Donate to Nancy Lindholm's research efforts at CaringForCarcinoid.org.
- Find the latest studies and therapies at Cancer.gov or ClinicalTrials.gov.

Meet the swingers!

(continued from page 125) even though this couple likens swinging to experimenting with, say, a sex toy, there's a key difference: "Sex toys are inanimate objects that aren't likely to threaten your adequacy," Greer says.

Even swingers who maintain they are happy with the lifestyle admit to jealousy and resentment at times. Stephen, 32, and Melissa, 30, both medical professionals who have been married for five years and live near New York City, first experimented with swinging two years after getting married, attending parties at which Melissa would hook up with another woman while Stephen watched. "It felt like a safe way to live out my fantasy," she explains. They slowly built up to their first full swap—an experience that left them, in Melissa's words, "feeling pretty gross afterward." They found the couple online, met them for drinks and went back to their apartment. "We had way too much to drink," Melissa recalls. "I lost all clarity and ended up having sex with the guy, which was a big mistake, because I wasn't really into him. I was upset the next day, and Stephen was upset because I was upset. He kept telling me we didn't have to do it anymore if I didn't want to."

A few months later, however, they both decided to book a vacation at a swingers resort. "The places are very low-pressure—you don't have to get into anyone's pants if you don't want to," Melissa says. "We knew we'd have a good time, even if we ended up being only with each other." Their second night there, they hit it off with a European couple and swung with them throughout the vacation. "It was completely different from our other encounter," Melissa says. "We enjoyed their company." But the friendship soured a few months later, after Melissa and Stephen invited the couple to visit them at their home. "The woman contacted Stephen constantly when they returned to Europe," Melissa says. "Once Stephen understood that it was upsetting me, he stopped responding to her."

The couple continued to swing up until Melissa's first pregnancy, going to resorts a few times a year. The routine was the same: days spent by the pool, nights spent at the disco, where they could drink, dance and head to the playroom in the back for a swap. But there were a few instances when Melissa acknowledges she was a reluctant participant. "I'm choosier than he is, so there were times I wouldn't see anyone I was (continued on page 138)