



Robyn Stoller's husband, Alan, died as drugs were being tested in mice carrying his sarcoma. None worked well, but she takes comfort in knowing that "we tried everything."

company called Champions Oncology, its main lab a 15-minute walk away. Champions aims to personalize cancer care with mice that, Sidransky argues, are unusually predictive of how individual patients will respond to particular drugs. That's because each mouse *is* an individual patient—or rather, carries tumor harvested from one.

Champions is far from alone in building these mice, called patient-derived xenograft (PDX) models. The drug company Novartis has more than 1000 PDX models from as many patients, which it's applying to drug testing. The National Cancer Institute in Bethesda, Maryland, is developing a bank of PDX mice for rare cancers and patients enrolled in trials. The Jackson Laboratory in Bar Harbor, Maine, a major mouse supplier for academic and corporate labs, has more than 350. "There's a big push" for these mice, says Carol Bult, scientific director of the PDX program there, and many scientists are using them to examine tumor biology and drug resistance.

What most people aren't doing is selling the models to patients. The Stollers paid many thousands of dollars to Champions, which markets the animals as a treatment guide. The mice are called avatars, analogous to a computer game in which an avatar is a graphical representation of the person playing it. "There may be hope for your specific cancer," Champions assures patients on its website.

Many find this pledge troubling. The company is "selling a promise to patients before that promise has been judged to be true by really rigorous data," asserts George Demetri, an oncologist who treats sarcomas at the Dana-Farber Cancer Institute in Boston. Even though he advises his own patients against paying for avatar mice, Demetri is part of Champions' scientific advisory board. There, he says, he acts as a "gadfly" pushing for more and better studies to prove how predictive avatars are and whether any benefits are enough to justify the cost.

Right now, Champions charges \$2000 to create an avatar mouse, and about \$2500 for each drug test it runs—normally a recommended minimum of about three or four, with no upper limit. The company says it loses money on the personalized service; from April 2013 to April 2014, it brought in \$2.3 million but spent \$2.7 million, not including marketing and other indirect costs. Champions makes money off a separate business: testing

# Hope in a mouse

## Selling personalized mouse models to cancer patients, a firm draws thanks and reproach

By Jennifer Couzin-Frankel

In the end, it became a race against time. "Maybe 5 days before he actually died, 4 days, I remember saying to him, 'Alan, you've got to hang on, you've got to hang on, the drugs are in the mice, they're looking at them,'" says his wife, Robyn Stoller. The couple had three children in elementary school and lived in a suburb of Washington, D.C. Alan, a 47-year-old who worked in real estate finance, had a virulent form of sarcoma that had spread to his brain.

Forty miles away, scientists at a company in Baltimore, Maryland, were pushing the limits of biology. They had implanted samples of Alan's tumor into mice without a

functioning immune system. Nine cohorts of animals received one of nine different drug combinations, a test of what might work best on Alan's tumor. But the process took months, time Alan didn't have. He died at home on 12 July 2010.

The journey to what Robyn calls "bleeding-edge technology" had begun almost 8 months earlier, on the couple's 13th wedding anniversary, when they drove to see oncologist David Sidransky at Johns Hopkins Hospital in Baltimore. Alan "was very sick," Sidransky remembers. "There was a lot of pressure not to treat him anymore."

The Stollers had sought out an alternative in Sidransky. He had recently formed a

therapies on PDX mice for drug companies.

Sidransky acknowledges that with avatars, patients are paying for a strategy that's still experimental. But he sees no other way to offer it.

**CHAMPIONS' STORY** began with a single patient. About 8 years ago, Sidransky and another Hopkins oncologist, Manuel Hidalgo, were studying PDX mice. The tissue for the models came from Hopkins patients, but the mice were intended solely for research. That is, until a man with metastatic pancreatic cancer asked Hidalgo, "Can't we use the results" for treatment? The oncologists sought permission from their institutional review board to transfer therapy from mouse to man. "It was all intuition," says Hidalgo, now an oncologist at the Spanish National Cancer Research Centre in Madrid. "Really, there were no data."

The patient lived almost 5 more years, unusually long for someone with his disease. "That wowed us," Sidransky says.

The pair began offering this boutique option to the small number of patients who had time to wait. Initially, it cost about \$50,000 per patient—funded by a clinical trial—and took about a year for mouse results to come in. "After 2 years of doing this, we decided to start a company," Sidransky says. In 2011, he and Hidalgo published outcomes on the 11 Hopkins patients they had treated. Fifteen of 17 treatments given (some people got more than one) "resulted in durable partial remissions," they wrote in the journal *Molecular Cancer Therapeutics*. "Overall, there was a remarkable correlation between drug activity in the model and clinical outcome."

Champions says it has replicated that study many times over. About 175 people have gone through the full process—avatars created, drugs tested on the mice, and information on those drugs offered to the oncologist. At the European Society for Medical Oncology meeting in Madrid this week, the company presented data on 102 drug regimens in 70 patients; 89% benefited from a given therapy if a mouse did, too, says Ronnie Morris, the company's president. The few correlations recorded by other researchers are roughly comparable to those claimed by Champions.

There are lingering questions, though, about what exactly "benefit" means—for instance, is it assessed by objective rules? "It is all about how one phrases the questions," Demetri notes, and the definition of "benefit" is "not a trivial concern." He is in discussions with Champions about designing clinical trials to address these issues. The first

of several Champions trials, focused on sarcoma, will launch this fall. All the studies will offer avatar mice at no cost and will track more systematically whether a mouse response matches a patient's. The company has no plans to perform a randomized trial, in which some patients receive the therapy their doctors recommend and others follow the mice.

"We can't be responsible for good and bad drugs," Morris explains. "We want to be an empiric test" of which drug a patient should take.

Avatar studies outside Champions are also picking up. Hidalgo is beginning a randomized trial comparing therapy directed by avatars against standard therapy in pancreatic cancer. At the Mayo Clinic in Rochester, Minnesota, oncologist Paul Haluska has created mice from about 400 ovarian cancer patients, with an eye toward successfully treating the relapses so many

cancer, you are misleading them because often, there is no time to play the game," says Pier Paolo Pandolfi, who is studying genetically engineered mouse models at Harvard University.

Although Champions has sped up the avatar-making process, it still takes about 4 months. Sidransky doubts it can get much faster. Many people die in that interim or become too sick to consider additional toxic therapy. This drop-off helps explain why more than 500 people have signed on with Champions, but only about 175 have been offered the option of mouse-inspired therapy.

Alan was in the two-thirds who don't reach the finish line. When he signed on with Champions, he was in such bad shape that he couldn't undergo surgery to gather fresh tumor tissue. Instead, the company convened an "expert panel" of sarcoma physicians and researchers who studied his initial biopsy, its sequence and molecular profile, and

recommended a course of action as a stopgap until, they hoped, mice could be created. (The company no longer offers expert panels.) Alan began that chemotherapy, which appeared somewhat successful. Doctors were then able to remove some of his tumor and implant it in avatar mice.

Ultimately, Robyn says, two regimens had a very modest effect in the mice, but none was aggressively killing off the cancer. One of those two was what the expert panel had already recommended. By the time the mouse results began streaming in, he was hours from death. Even a perfect avatar is only as good as the drugs available, and in Alan's case, none was good enough, at least not for the mice. "You want an answer," Sidransky says. "If the answer is no"—nothing works—"it's sobering, but it's still an answer."

Robyn feels the same way. She believes the initial analysis and treatment recommendations coordinated by the company helped extend her husband's life by perhaps 6 months. The mice ravaged by his cancer despite a barrage of drugs confirmed, for her, that there was nothing else they could have done. "We left no stones unturned," she says. "My kids and I can sleep at night. I don't ever wonder, 'If only.'" She has spoken out in support of Champions and now runs a website called CancerHAWK to connect families fighting cancer with resources that can help them.

To those who question whether Champions should be selling its promise, Robyn has a ready response. "It would really frustrate me as a patient advocate if there was a technology that might help" and yet was inaccessible, she says. "No matter what it costs—let me get my hands on it." ■

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**George Demetri**, Dana-Farber Cancer Institute

women suffer. All four approved therapies for ovarian cancer are tested on the avatars, and Haluska offers the most successful to a patient if her cancer resurges. "I need to prove that this is the way to go," he says, "that doing the avatars is better than standard" therapy.

One scientific shortcoming of PDX mice is that the animals lack a functioning immune system. This precludes trying immunologic therapies; it may also give misleading information about how drugs will behave in a person. Today's PDX mice, Hidalgo says, are "version 1.0." Several labs are developing and testing mice with a "humanized" immune system, but widespread use may be a year or more off.

Champions has run into other problems, too. Like anyone working with PDX mice, the company is unable to build avatars for everyone, and fails 30% of the time. For example, some tumor types, such as certain breast cancers and prostate cancer, don't readily engraft.

Of the patients who get a mouse, "about half choose to go further" into the drug testing phase, Morris says. Most who don't are bedeviled by time. In fact relatively few patients with advanced cancer survive long enough to use avatars as a road map, as critics of Champions are quick to point out.

"If you are selling ... to patients the idea of an avatar that could benefit their