A life-or-death pioneer in cancer treatment's new frontier

Experimental immunotherapy saved Stefanie Joho. Now the 'site-agnostic' advance is going to market.

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The oncologist was blunt: Stefanie Joho's colon cancer was raging out of control and there was nothing more she could do. Flanked by her parents and sister, the 23-year-old felt something wet on her shoulder. She looked up to see her father weeping.

"I felt dead inside, utterly demoralized, ready to be done," Joho remembers.

But her younger sister couldn't accept that. When the family got back to Joho's apartment in New York's Flatiron district, Jess opened her laptop and began searching frantically for clinical trials, using medical words she'd heard but not fully understood. An hour later, she came into her sister's room and showed her what she'd found. "I'm not letting you give up," she told Stefanie. "This is not the end."

That search led to a contact at Johns Hopkins University, and a few days later, Joho got a call from a cancer geneticist co-leading a study there. "Get down here as fast as you can!" Luis Diaz said. "We are having tremendous success with patients like you."

What followed is an illuminating tale of how one woman's intersection with experimental research helped open a new frontier in cancer treatment — with approval of a drug that, for the first time, targets a genetic feature in a tumor rather than the disease's location in the body.

The breakthrough, made official last week by the Food and Drug Administration, immediately could benefit some patients with certain kinds of advanced cancer that aren't responding to chemotherapy. Each should be tested for that genetic signature, scientists stress.

"These are people facing death sentences," said Hopkins geneticist Bert Vogelstein. "This treatment might keep some of them in remission for a long time."

In August 2014, Joho stumbled into Hopkins for her first infusion of the immunotherapy drug Keytruda. She was in agony from a malignant mass in her midsection, and even with the copious amounts of oxycodone she was swallowing, she needed a new fentanyl patch on her arm every 48 hours. Yet within just days, the excruciating back pain had eased. Then an unfamiliar

sensation — hunger — returned. She burst into tears when she realized what it was.

As months went by, her tumor shrank and ultimately disappeared. She stopped treatment this past August, free from all signs of disease.

The small trial in Baltimore was pivotal, and not only for the young marketing professional. It showed that immunotherapy could attack colon and other cancers thought to be unstoppable. The key was their tumors' genetic defect, known as mismatch repair (MMR) deficiency — akin to a missing spell-check on their DNA. As the DNA copies itself, the abnormality prevents any errors from being fixed. In the cancer cells, that means huge numbers of mutations that are good targets for immunotherapy.

The treatment approach isn't a panacea, however. The glitch under scrutiny — which can arise spontaneously or be inherited — is found in just 4 percent of cancers overall. But bore in on a few specific types, and the scenario changes dramatically. The problem occurs in up to 20 percent of colon cancers and about 40 percent of endometrial malignancies — cancer in the lining of the uterus.

In the United States, researchers estimate that initially about 15,000 people with this defect may be helped by this immunotherapy. That number is likely to rise sharply as doctors begin using it earlier on eligible patients.

Joho was among the first.

Even before Joho got sick, cancer had cast a long shadow on her family. Her mother has Lynch syndrome, a hereditary disorder that sharply raises the risk of certain cancers, and since 2003, Priscilla Joho has suffered colon cancer, uterine cancer and squamous cell carcinoma of the skin.

Stefanie's older sister, Vanessa, had already tested positive for Lynch syndrome, and Stefanie planned to get tested when she turned 25. But at 22, several months after she graduated from New York University, she began feeling unusually tired. She blamed the fatigue on her demanding job. Her primary-care physician, aware of her mother's medical history, ordered a colonoscopy.

When Joho woke up from the procedure, the gastroenterologist looked "like a ghost," she said. A subsequent CT scan revealed a very large tumor in her colon. She'd definitely inherited Lynch syndrome.

She underwent surgery in January 2013 at Philadelphia's Fox Chase Cancer Center, where her mother had been treated. The news was good: The cancer didn't appear to have spread, so she could skip chemotherapy and follow up with scans every three months.

By August of that year, though, Joho started having relentless back pain. Tests detected the invasive tumor in her abdomen. Another operation, and now she started chemo. Once again, in spring 2014, the cancer roared back. Her doctors in New York, where she now was living, switched to a more aggressive chemo regimen.

"This thing is going to kill me," Joho remembered thinking. "It was eating me alive."

She made it to Jess's college graduation in Vermont that May. Midsummer, her oncologist confessed he was out of options. As he left the examining room, he mentioned offhandedly that some interesting work was going on in immunotherapy. But when Joho met with a hospital immunologist, that doctor told her no suitable trials were available.

Joho began planning to move to her parents' home in suburban Philadelphia: "I thought, 'I'm dying, and I'd like to breathe fresh air and be around the green and the trees.' "

Her younger sister wasn't ready for her to give up. Jess searched for clinical trials, typing in "immunotherapy" and other terms she'd heard the doctors use. Up popped a trial at Hopkins, where doc-

tors were testing a drug called pembrolizumab.

"Pembro" is part of a class of new medications called checkpoint inhibitors that disable the brakes that keep the immune system from attacking tumors. In September 2014, the treatment was approved by the FDA for advanced melanoma and marketed as Keytruda. The medication made headlines in 2015 when it helped treat former president Jimmy Carter for melanoma that had spread to his brain and liver. It later was cleared for several other malignancies.

Yet researchers still don't know why immunotherapy, once hailed as a game changer, works in only a minority of patients. Figuring that out is important for clinical as well as financial reasons. Keytruda, for example, costs about $150,000 a year.

By the time Joho arrived at Hopkins, the trial had been underway for a year. While an earlier study had shown a similar immunotherapy drug to be effective for a significant proportion of patients with advanced melanoma or lung or kidney cancer, checkpoint inhibitors weren't making headway with colon cancer. A single patient out of 20 had responded in a couple of trials.

Why did some tumors shrink and others didn't? What was different about the single colon cancer patient who benefited?

Drew Pardoll, director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy at Hopkins, and top researcher Suzanne L. Topalian took the unusual step of consulting with the cancer geneticists who worked one floor up.

"This was the first date in what became the marriage of cancer genetics and cancer immunology," Pardoll said.

In a brainstorming session, the geneticists were quick to offer their theories. They suggested that the melanoma and lung cancer patients had done best because those cancers have lots of mutations, a consequence of exposure to sunlight and cigarette smoke. The mutations produce proteins recognized by the immune system as foreign and ripe for attack, and the drug boosts the system's response.

And that one colon-cancer patient? As Vogelstein recalls, "We all said in unison, 'He must have MMR deficiency!' " — because such a genetic glitch would spawn even more mutations. The abnormality was a familiar subject to Vogelstein, who in the 1990s had co-discovered its role in the development of colon cancer. But the immunologists hadn't thought of it.

When the patient's tumor tissue was tested, it was indeed positive for the defect.

The researchers decided to run a small trial, led by Hopkins immunologist Dung Le and geneticist Diaz, to determine whether the defect could predict a patient's response to immunotherapy. The pharmaceutical company Merck provided its still-experimental drug pembrolizumab. Three groups of volunteers were recruited: 10 colon cancer patients whose tumors had the genetic problem; 18 colon cancer patients without it; and 7 patients with other malignancies with the defect.

The first results, published in 2015 in the New England Journal of Medicine, were striking. Four out of the 10 colon cancer patients with the defect and 5 out of the other 7 cancer patients with the abnormality responded to the drug. In the remaining group, nothing. Since then, updated numbers have reinforced that a high proportion of patients with the genetic feature benefit from the drug, often for a lengthy period. Other trials by pharmaceutical companies have shown similar results.

The Hopkins investigators found that tumors with the defect had, on average, 1,700 mutations, compared with only 70 for tumors without the problem. That confirmed the theory that high numbers of mutations make it more likely the immune system will recognize and attack cancer — if it gets assistance from immunotherapy.

The studies were the foundation of the FDA's decision on Tuesday to green-light Keytruda to treat cancers such as Joho's, meaning malignancies with certain molecular characteristics. This first-ever "siteagnostic" approval by the agency signals an emerging field of "precision immunotherapy," Pardoll said, one in which genetic details are used to anticipate who will respond to treatments.

For Joho, now 27 and living in suburban Philadelphia, the hard lesson from the past few years is clear: The cancer field is changing so rapidly that patients can't rely on their doctors to find them the best treatments. "Oncologists can barely keep up," she said. "My sister found a trial I was a perfect candidate for, and my doctors didn't even know it existed."

Her first several weeks on the trial were rough, with an early hospitalization after she cut back too quickly on her fentanyl and went into withdrawal. She still has some lasting side effects today — joint pain in her knees, minor nausea and fatigue — but they are manageable.

"I have had to adapt to some new limits," she acknowledged. "But I still feel better than I have in five years."

The FDA's decision last week was an emotional moment. Diaz, now at Memorial Sloan Kettering Cancer Center in New York, immediately texted her. "We did it!" he exulted.

"I got chills all over my body," Joho said. "To think that I was at the end of the road, with no options, and then to be part of such a change."

Her experience has prompted her to drop plans to go back into marketing. Now she wants to help patients navigate the new cancer landscape. "Become an expert on your cancer" is her message. "Don't be passive." She encourages patients to try clinical trials.

As a cancer survivor with Lynch syndrome, Joho will be closely watched; if she relapses, she is likely to be treated again with immunotherapy. And if her mother relapses, Keytruda might now be her best chance.

"Coming out the other side, I feel really lucky," Joho said. She's also grateful for something else: A few years ago, her sister Jess was tested for the disorder that has so affected their family. She was negative.

"This treatment might keep some of them in remission for a long time," says Johns Hopkins geneticist Bert Vogelstein.