Two Patients Faced Chemo. The One Who Survived Demanded a Test To See if It Was Safe.

About 1,300 Americans each year die from the toxic effects of capecitabine or 5-FU chemotherapy.

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JoEllen Zembruski-Ruple, while in the care of New York City's renowned Memorial Sloan Kettering Cancer Center, swallowed the first three chemotherapy pills to treat her squamous cell carcinoma on January 29, her family members said. They didn't realize the drug could kill her.

Six days later, Zembruski-Ruple went to Sloan Kettering's urgent care department to treat sores in her mouth and swelling around her eyes. The hospital diagnosed oral yeast infection and sent her home, her sister and partner said. Two days later, they said, she returned in agony — with severe diarrhea and vomiting — and was admitted. "Enzyme deficiency," Zembruski-Ruple texted a friend.

The 65-year-old, a patient advocate who had worked for the National Multiple Sclerosis Society and other groups, would never go home.

Covered in bruises and unable to swallow or talk, she eventually entered hospice care and died March 25 from the very drug that was supposed to extend her life, said her longtime partner, Richard Khavkine. Zembruski-Ruple was deficient in the enzyme that metabolizes capecitabine, the chemotherapy drug she took, said Khavkine and Susan Zembruski, one of her sisters. Zembruski-Ruple was among about 1,300 Americans each year who die from the toxic effects of that pill or its cousin, the IV drug fluorouracil known as 5-FU.

Doctors can test for the deficiency — and then either switch drugs or lower the dosage if patients have a genetic variant that carries risk. The FDA approved an antidote in 2015, but it's expensive and must be administered within four days of the first chemotherapy treatment.

Newer cancer drugs sometimes include a companion diagnostic to determine whether a drug works with an individual patient's genetics. But 5-FU went on the market in 1962 and sells for about $17 a dose; producers of its generic aren't seeking approval for toxicity tests, which typically cost hundreds of dollars. Doctors have only gradually understood which gene variants are

dangerous in which patients, and how to deal with them, said Alan Venook, a colorectal and liver cancer specialist at the University of California-San Francisco.

By the time Zembruski-Ruple's doctors told her she had the deficiency, she had been on the drug for eight days, said Khavkine, who watched over his partner with her sister throughout the seven-week ordeal.

Khavkine said he "would have asked for the test" if he had known about it, but added "nobody told us about the possibility of this deficiency."

Zembruski-Ruple's sister also said she wasn't warned about the fatal risks of the chemo, or told about the test.

"They never said why they didn't test her," Zembruski said. "If the test existed, they should have said there is a test. If they said, 'Insurance won't cover it,' I would have said, 'Here's my credit card.' We should have known about it."

Guidance Moves at a Glacial Pace

Despite growing awareness of the deficiency, and an advocacy group made up of grieving friends and relatives who push for routine testing of all patients before they take the drug, the medical establishment has moved slowly.

A panel of the National Comprehensive Cancer Network, or NCCN — specialists from Sloan Kettering and other top research centers — until recently did not recommend testing, and the FDA does not require it.

In response to a query from KFF Health News about its policy, Sloan Kettering spokesperson Courtney Nowak said the hospital treats patients "in accordance with NCCN guidelines." She said the hospital would not discuss a patient's care.

On January 24, the FDA issued a warning about the enzyme deficiency in which it urged health care providers to "inform patients prior to treatment" about the risks of taking 5-FU and capecitabine.

On March 31 — six days after Zembruski-Ruple's death — the network's expert panel for most gastrointestinal cancers took a first step toward recommending testing for the deficiency.

Worried that President Donald Trump's FDA might do nothing, Venook said, the panel — whose guidance shapes the practices of oncologists and health insurers — recommended that doctors consider testing before dosing patients with 5-FU or capecitabine.

However, its guidance stated that "no specific test is recommended at this time," citing a lack of data to "inform dose adjustments."

Sloan Kettering “will consider this guidance in developing personalized treatment plans for each patient,” Nowak told KFF Health News.

The new NCCN guidance was “not the blanket recommendation we were working toward, but it is a major step toward our ultimate goal,” said Kerin Milesky, a public health official in Brewster, Massachusetts, who’s part of an advocacy group for testing. Her husband, Larry, died two years ago at age 73 after a single treatment of capecitabine.

European drug regulators began urging oncologists to test patients for deficiency in May 2020. Patients with potentially risky genetics are started on a half-dose of the cancer drug. If they suffer no major toxicity, the dose is increased.

A Lifesaving Ultimatum?

Emily Alimonti, a 42-year-old biotech salesperson in upstate New York, chose that path before starting capecitabine treatment in December. She said her doctors — including an oncologist at Sloan Kettering — told her they didn’t do deficiency testing, but Alimonti insisted. “Nope,” she said. “I’m not starting it until I get the test back.”

The test showed that Alimonti had a copy of a risky gene variant, so doctors gave her a lower dose of the drug. Even that has been hard to tolerate; she’s had to skip doses because of low white blood cell counts, Alimonti said. She still doesn’t know whether her insurer will cover the test.

Around 300,000 people are treated with 5-FU or capecitabine in the United States each year, but its toxicity could well have prevented FDA approval were it up for approval today. Short of withdrawing a drug, however, U.S. regulators have little power to manage its use. And 5-FU and capecitabine are still powerful tools against many cancers.

At a January workshop that included FDA officials and cancer specialists, Venook, the NCCN panel’s co-chair, asked whether it was reasonable to recommend that doctors obtain a genetic test “without saying what to do with the result.”

But Richard Pazdur, the FDA’s top cancer expert, said it was time to end the debate and commence testing, even if the results could be ambiguous. “If you don’t have the information, how do you have counseling?” he asked.

Two months later, Venook’s panel changed course. The price of tests has fallen below $300 and results can be returned as soon as three days, Venook said. Doubts about the FDA’s ability to further confront the issue spurred the panel’s change of heart, he said.

“I don’t know if FDA is going to exist tomorrow,” Venook told KFF Health News. “They’re taking a wrecking ball to common sense, and that’s one of the reasons we felt we had to go forward.”

On May 20, the FDA posted a Federal Register notice seeking public input on the issue, a move that suggested it was considering further action.

Venook said he often tests his own patients, but the results can be fuzzy. If the test finds two copies of certain dangerous gene variants in a patient, he avoids using the drug. But such cases are rare — and Zembruski-Ruple was one of them, according to her sister and Khavkine.

Many more patients have a single copy of a suspect gene, an ambiguous result that requires clinical judgment to assess, Venook said.

A full-gene scan would provide more information but adds expense and time, and even then the answer may be murky, Venook said. He worries that starting patients on lower doses could mean fewer cures, especially for newly diagnosed colon cancer patients.

Power Should Rest With Patients

Scott Kapoor, a Toronto-area emergency room physician whose brother Anil, a much-loved urologist and surgeon, died of 5-FU toxicity at age 58 in 2023, views Venook's arguments as medical paternalism. Patients should decide whether to test and what to do with the results, he said.

"What's better — don't tell the patient about the test, don't test them, potentially kill them in 20 days?" he said. "Or tell them about the testing while warning that potentially the cancer will kill them in a year?"

"People say oncologists don't know what to do with the information," said Karen Merritt, whose mother died after an infusion of 5-FU in 2014. "Well, I'm not a doctor, but I can understand the Mayo Clinic report on it."

The Mayo Clinic recommends starting patients on half a dose if they have one suspect gene variant. And "the vast majority of patients will be able to start treatment without delays," Daniel Hertz, a clinical pharmacologist from the University of Michigan, said at the January meeting.

Some hospitals began testing after patients died because of the deficiency, said Lindsay Murray, of Andover, Massachusetts, who has advocated for widespread testing since her mother was treated with capecitabine and died in 2021.

In some cases, Venook said, relatives of dead patients have sued hospitals, leading to settlements.

Kapoor said his brother — like many patients of non-European origin — had a gene variant that hasn't been widely studied and isn't included in most tests. But a full-gene scan would have detected it, Kapoor said, and such scans can also be done for a few hundred dollars.

The cancer network panel's changed language is disappointing, he said, though "better than nothing."

In video tributes to Zembruski-Ruple, her friends, colleagues, and clients remembered her as kind, helpful, and engaging. "JoEllen was beautiful both inside and out," said Barbara McKeon, a former

colleague at the MS Society. “She was funny, creative, had a great sense of style.”

“JoEllen had this balance of classy and playful misbehavior,” psychotherapist Anastatia Fabris said. “My beautiful, vibrant, funny, and loving friend JoEllen.”

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