Chemo toxicity: A common gene test could save hundreds of lives each year

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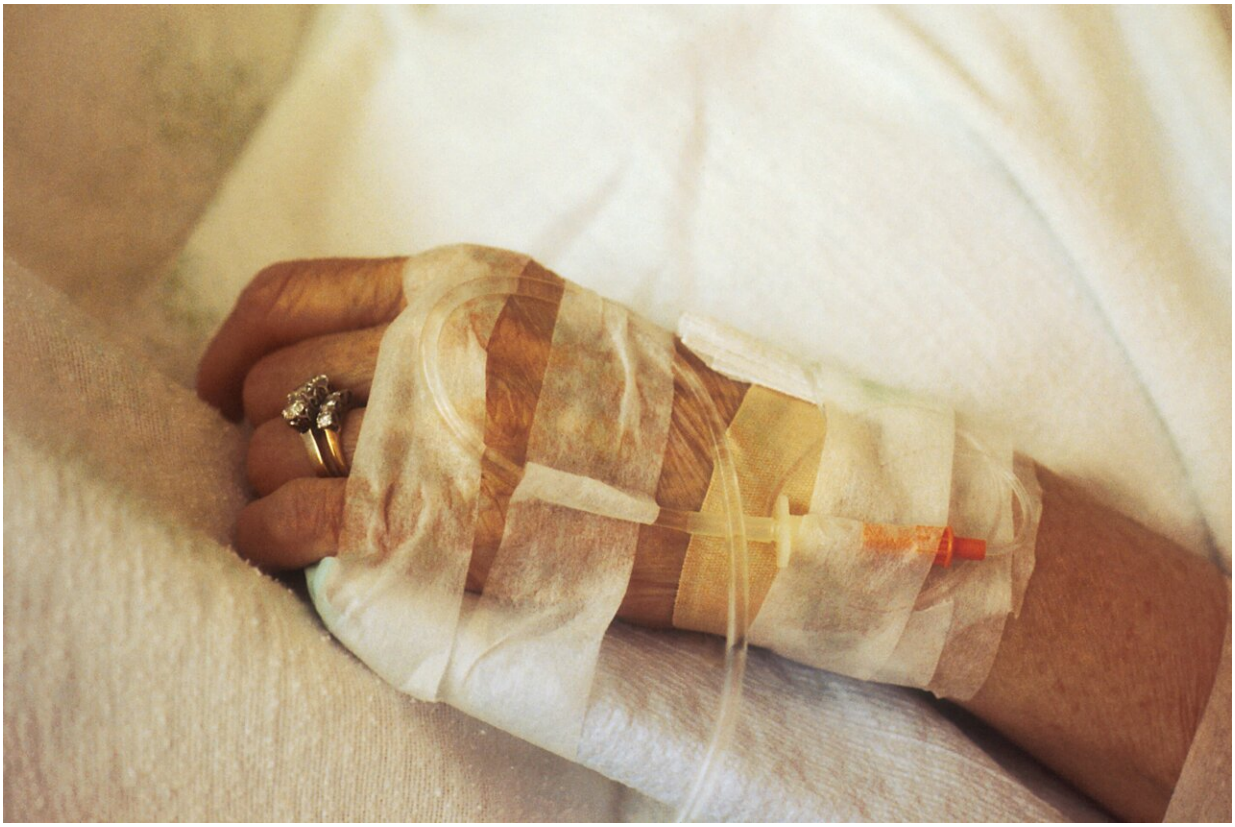

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One January morning in 2021, Carol Rosen took a standard treatment for metastatic breast cancer. Three gruesome weeks later, she died in excruciating pain from the very drug meant to prolong her life.

Rosen, a 70-year-old retired schoolteacher, passed her final days in anguish, enduring severe diarrhea and nausea and terrible sores in her mouth that kept her from eating, drinking, and, eventually, speaking. Skin peeled off her body. Her kidneys and liver failed. "Your body burns from the inside out," said Rosen's daughter, Lindsay Murray, of Andover, Massachusetts.

Rosen was one of more than 275,000 cancer patients in the United States who are infused each year with fluorouracil, known as 5-FU, or, as in Rosen's case, take a nearly identical drug in pill form called capecitabine. These common types of chemotherapy are no picnic for anyone, but for patients who are deficient in an enzyme that metabolizes the drugs, they can be torturous or deadly.

Those patients essentially overdose because the drugs stay in the body for hours rather than being quickly metabolized and excreted. The drugs kill an estimated 1 in 1,000 patients who take them—hundreds each year—and severely sicken or hospitalize 1 in 50. Doctors can test for the deficiency and get results within a week—and then either switch drugs or lower the dosage if patients have a genetic variant that carries risk.

Yet a recent survey found that only 3% of U.S. oncologists routinely order the tests before dosing patients with 5-FU or capecitabine. That's because the most widely followed U.S. cancer treatment guidelines—issued by the National Comprehensive Cancer Network—don't recommend preemptive testing.

The FDA added new warnings about the lethal risks of 5-FU to the drug's label on March 21 following queries from KFF Health News about its policy. However, it did not require doctors to administer the test before prescribing the chemotherapy.

The agency, whose plan to expand its oversight of laboratory testing was

the subject of a House hearing, also March 21, has said it could not endorse the 5-FU toxicity tests because it's never reviewed them.

But the FDA at present does not review most diagnostic tests, said Daniel Hertz, an associate professor at the University of Michigan College of Pharmacy. For years, with other doctors and pharmacists, he has petitioned the FDA to put a black box warning on the drug's label urging prescribers to test for the deficiency.

"FDA has responsibility to assure that drugs are used safely and effectively," he said. The failure to warn, he said, "is an abdication of their responsibility."

The update is "a small step in the right direction, but not the sea change we need," he said.

Europe ahead on safety

British and European Union drug authorities have recommended the testing since 2020. A small but growing number of U.S. hospital systems, professional groups, and health advocates, including the American Cancer Society, also endorse routine testing. Most U.S. insurers, private and public, will cover the tests, which Medicare reimburses for $175, although tests may cost more depending on how many variants they screen for.

In its latest guidelines on colon cancer, the Cancer Network panel noted that not everyone with a risky gene variant gets sick from the drug, and that lower dosing for patients carrying such a variant could rob them of a cure or remission. Many doctors on the panel, including the University of Colorado oncologist Wells Messersmith, have said they have never witnessed a 5-FU death.

In European hospitals, the practice is to start patients with a half- or quarter-dose of 5-FU if tests show a patient is a poor metabolizer, then raise the dose if the patient responds well to the drug. Advocates for the approach say American oncology leaders are dragging their feet unnecessarily, and harming people in the process.

"I think it's the intransigence of people sitting on these panels, the mindset of 'We are oncologists, drugs are our tools, we don't want to go looking for reasons not to use our tools,'" said Gabriel Brooks, an oncologist and researcher at the Dartmouth Cancer Center.

Oncologists are accustomed to chemotherapy's toxicity and tend to have a "no pain, no gain" attitude, he said. 5-FU has been in use since the 1950s.

Yet "anybody who's had a patient die like this will want to test everyone," said Robert Diasio of the Mayo Clinic, who helped carry out major studies of the genetic deficiency in 1988.

Oncologists often deploy genetic tests to match tumors in cancer patients with the expensive drugs used to shrink them. But the same can't always be said for gene tests aimed at improving safety, said Mark Fleury, policy director at the American Cancer Society's Cancer Action Network.

When a test can show whether a new drug is appropriate, "there are a lot more forces aligned to ensure that testing is done," he said. "The same stakeholders and forces are not involved" with a generic like 5-FU, first approved in 1962, and costing roughly $17 for a month's treatment.

Oncology is not the only area in medicine in which scientific advances, many of them taxpayer-funded, lag in implementation. For instance, few cardiologists test patients before they go on Plavix, a brand name for the

anti-blood-clotting agent clopidogrel, although it doesn't prevent blood clots as it's supposed to in a quarter of the 4 million Americans prescribed it each year.

In 2021, the state of Hawaii won an $834 million judgment from drugmakers it accused of falsely advertising the drug as safe and effective for Native Hawaiians, more than half of whom lack the main enzyme to process clopidogrel.

The fluoropyrimidine enzyme deficiency numbers are smaller—and people with the deficiency aren't at severe risk if they use topical cream forms of the drug for skin cancers. Yet even a single miserable, medically caused death was meaningful to the Dana-Farber Cancer Institute, where Carol Rosen was among more than 1,000 patients treated with fluoropyrimidine in 2021.

Her daughter was grief-stricken and furious after Rosen's death. "I wanted to sue the hospital. I wanted to sue the oncologist," Murray said. "But I realized that wasn't what my mom would want."

Instead, she wrote Dana-Farber's chief quality officer, Joe Jacobson, urging routine testing. He responded the same day, and the hospital quickly adopted a testing system that now covers more than 90% of prospective fluoropyrimidine patients. About 50 patients with risky variants were detected in the first 10 months, Jacobson said.

Dana-Farber uses a Mayo Clinic test that searches for eight potentially dangerous variants of the relevant gene. Veterans Affairs hospitals use a 11-variant test, while most others check for only four variants.

Different tests may be needed for different ancestries

The more variants a test screens for, the better the chance of finding

rarer gene forms in ethnically diverse populations. For example, different variants are responsible for the worst deficiencies in people of African and European ancestry, respectively. There are tests that scan for hundreds of variants that might slow metabolism of the drug, but they take longer and cost more.

These are bitter facts for Scott Kapoor, a Toronto-area emergency room physician whose brother, Anil Kapoor, died in February 2023 of 5-FU poisoning.

Anil Kapoor was a well-known urologist and surgeon, an outgoing speaker, researcher, clinician, and irreverent friend whose funeral drew hundreds. His death at age 58, only weeks after he was diagnosed with stage 4 colon cancer, stunned and infuriated his family.

In Ontario, where Kapoor was treated, the health system had just begun testing for four gene variants discovered in studies of mostly European populations. Anil Kapoor and his siblings, the Canadian-born children of Indian immigrants, carry a gene form that's apparently associated with South Asian ancestry.

Scott Kapoor supports broader testing for the defect—only about half of Toronto's inhabitants are of European descent—and argues that an antidote to fluoropyrimidine poisoning, approved by the FDA in 2015, should be on hand. However, it works only for a few days after ingestion of the drug and definitive symptoms often take longer to emerge.

Most importantly, he said, patients must be aware of the risk. "You tell them, 'I am going to give you a drug with a 1 in 1,000 chance of killing you. You can take this test. Most patients would be, 'I want to get that test and I'll pay for it,' or they'd just say, 'Cut the dose in half.'"

Alan Venook, the University of California-San Francisco oncologist who

co-chairs the National Comprehensive Cancer Network, has led resistance to mandatory testing because the answers provided by the test, in his view, are often murky and could lead to undertreatment.

"If one patient is not cured, then you giveth and you taketh away," he said. "Maybe you took it away by not giving adequate treatment."

Instead of testing and potentially cutting a first dose of curative therapy, "I err on the latter, acknowledging they will get sick," he said. About 25 years ago, one of his patients died of 5-FU toxicity and "I regret that dearly," he said. "But unhelpful information may lead us in the wrong direction."

In September, seven months after his brother's death, Kapoor was boarding a cruise ship on the Tyrrhenian Sea near Rome when he happened to meet a woman whose husband, Atlanta municipal judge Gary Markwell, had died the year before after taking a single 5-FU dose at age 77.

"I was like … that's exactly what happened to my brother."

Murray senses momentum toward mandatory testing. In 2022, the Oregon Health & Science University paid $1 million to settle a suit after an overdose death.

"What's going to break that barrier is the lawsuits, and the big institutions like Dana-Farber who are implementing programs and seeing them succeed," she said. "I think providers are going to feel kind of bullied into a corner. They're going to continue to hear from families and they are going to have to do something about it."