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Mass General Brigham Becomes Latest US Health System to Adopt Pretreatment DPYD Testing

Jan 16, 2025 | Turna Ray

NEW YORK – Mass General Brigham (MGB) is instituting a new policy to screen all cancer patients for genetic abnormalities that place them at risk for severe, sometimes deadly, toxicities from a widely prescribed chemotherapy.

The Boston-based healthcare system will specifically test patients for variants in the DPYD gene that limit their body's ability to clear Xeloda (capecitabine), a backbone chemotherapy belonging to a class of drugs called fluoropyrimidines. "For our particular organization, we have moved to making DPYD testing available for all patients starting capecitabine as we feel the benefits of this approach outweigh any risks," an MGB spokesperson said.

The policy change follows the death of Larry Milesky on May 27, 2023, from a lethal overdose of Xeloda. The 73-year-old Massachusetts native was undergoing treatment at Mass General Hospital (MGH) for stage III colorectal cancer that had spread to several lymph nodes. After surgery, although PET scans were clear and a minimal residual disease test was negative for cell-free tumor DNA, his oncologist at MGH, Jeffrey Clark, prescribed Xeloda with oxaliplatin as an adjuvant treatment to stave off recurrence. Around a third of patients with stage III colorectal cancer have a recurrence within five years of surgery, and the risk increases with positive lymph nodes.

At the time of his diagnosis, Larry Milesky, a father of three, was still working as a radio marketing consultant and walking several miles each day with his wife of 33 years, Kerin Milesky. He loved Boston sports and gathering with family and friends at the beach in the summer. He didn't want chemotherapy and was very worried about how the toxicities would impact his active lifestyle, Kerin Milesky said. After weighing the risks of toxicities against the long-term survival benefits, her husband accepted his oncologist's treatment plan. "I was 59 at the time, and he said he didn't want me to be a widow at 63," she recalled.

By the time doctors at MGH performed DPYD testing and discovered Larry Milesky had a dihydropyrimidine dehydrogenase (DPD) deficiency, the chemotherapy had coursed through his body like wildfire.

Approximately 1 in 1,000 patients carry two copies of a variant in the DPYD gene that results in the absence of the DPD enzyme necessary to metabolize fluoropyrimidines, such as 5-FU (fluorouracil) and Xeloda. Between 3 percent and 8 percent of the general population has one copy of a variant

associated with lower levels of the DPD enzyme, showing up more frequently in African Americans. Fluoropyrimidines can quickly build up in patients with DPD deficiencies, increasing toxic exposure.

The Clinical Pharmacogenetics Implementation Consortium (CPIC), an internationally recognized guidelines body, focuses its recommendations on the four most-studied DPYD variants — DPYD*2A, DPYD*13, DPYD p.D949V, and DPYD HapB3 — and advises reducing starting doses of 5-FU or Xeloda by 50 percent in patients with a partial DPD deficiency. In patients with a complete DPD deficiency, those who have a DPYD activity score of zero, CPIC says to avoid 5-FU or Xeloda entirely.

Despite CPIC guidelines, the US-based National Comprehensive Cancer Network (NCCN), which is highly influential in shaping oncology treatment practices, doesn't recommend doctors test all cancer patients for actionable DPYD variants before prescribing fluoropyrimidines. And while the US Food and Drug Administration has updated the labels of these chemotherapies to warn of the risks in those with reduced or absent DPD activity, the agency only tells doctors to "consider testing for genetic variants of DPYD prior to initiating" Xeloda and 5-FU and discuss it with patients, but doesn't require testing.

As a result, most cancer centers in the US don't screen patients for such variants, citing concerns that genotype-guided dose adjustments will reduce the efficacy of these widely relied-on therapies; that evidence supporting genotype-informed dosing guidelines aren't precise enough; and that the specificity of DPYD testing may miss patients with rare variants and won't identify patients who experience chemo toxicities due to nongenetic factors.

The American Association for Cancer Research and the FDA are hosting a workshop Thursday to discuss the evidence on DPD testing and the regulatory considerations for requiring it in drug labeling.

Since 2014, doctors who support DPYD testing and family members who have lost loved ones to fluoropyrimidine toxicities because they learned they were DPD deficient too late have petitioned various NCCN guideline committees to recommend pretreatment testing at least half a dozen times without success. However, at cancer centers and hospitals in the US where DPD deficient patients have died, testing advocates have had more success shifting policies. The Advocates for Universal DPD/DPYD Testing (AUDT) in particular has been a force for change, penning citizen petitions that have spurred the FDA to update the labels of Xeloda and 5-FU with more information on DPD deficiency, though some believe the agency's language on testing could be stronger.

While the FDA doesn't require DPYD testing, Xeloda's label tells doctors that "no … dose has been proven safe in patients with complete absence of DPD activity." Larry Milesky had a DPYD*2A genotype, the most common and the best-studied variant, and his activity score was zero, putting him at risk of a fatal Xeloda overdose. Within about four days of taking Xeloda, he developed painful mouth sores. On a dinner date that Friday evening, he couldn't eat anything. The following Monday, after an excruciating weekend, his oncologist decided to stop chemotherapy over a virtual visit. At the ambulatory oncology clinic on Tuesday, he got fluids, steroids, and received a DPYD test. He ended up in the MGH emergency room soon after with difficulty breathing, an inability to swallow, bleeding sores, and his pain level at a 10.

There is an antidote for fluoropyrimidine-based chemo overdoses, SERB Pharmaceuticals' Vistogard (uridine triacetate), which has a wholesale-acquisition price of $75,000, but it must be given within four days of ending chemo for it to work. Larry Milesky was beyond this point by the time Vistogard was administered. Kerin Milesky describes the last 20 days of her husband's life as "a catastrophic decline," his body depleted of white cells, spiking different infections, going into septic shock, wasting away from malnutrition, and enduring multiple intubations and extubations. She said the chemotherapy burned his insides, which is how family members often describe the ravages of 5-FU and Xeloda on their loved ones with DPD deficiencies.

Precision medicine in a competitive market

The MGB spokesperson said that the hospital system decided to implement pretreatment DPYD testing after considering the latest evidence, best practices, and the perspective of advocacy groups. In the wake of her husband's death, Kerin Milesky began learning about DPD deficiency, joined AUDT's advocacy efforts, and began urging MGB to implement a screening program.

She believes her husband received "outstanding care" at MGH, including from Clark, his oncologist, who she said constantly checked in on her husband at the hospital. But she was also "devastated" to learn that while her husband was dying at MGH from the toxicities of his treatment due to a DPD deficiency, at the neighboring Dana-Farber Cancer Institute (DFCI), doctors were checking for DPYD abnormalities in cancer patients considering fluoropyrimidine-based chemo.

After Carol Rosen, a metastatic breast cancer patient at DFCI succumbed to the toxicities of Xeloda in 2021, Lindsay Murray, her daughter and a founding AUDT member, convinced administrators there to implement a pretreatment DPYD testing program. After 10 months of running the program, doctors at DFCI published data last year showing that more than 90 percent of patients are having DPYD testing before their first dose of 5-FU or Xeloda, compared to 26 percent when the program began.

In December 2024, Kerin Milesky, who is the director of the Office of Preparedness and Emergency Management at the Massachusetts Department of Public Health, wrote to Rachel Sisodia, chief quality officer at MGB, urging the hospital system that comprises MGH and Brigham and Women's Hospital, to similarly screen patients for DPD deficiencies. Although the Mileskys lived on Cape Cod, they decided to drive to MGH in Boston for its world-renowned oncology care, a trip that sometimes took up to two-and-a-half hours.

"It is not lost on me that if we had chosen DFCI rather than the Mass General Cancer Center, [my husband] would have been screened for his complete DPYD/DPD deficiency and his death would have been prevented," she wrote, pointing out that top cancer centers around the country, including the Cleveland Clinic, Johns Hopkins Medicine, the University of Pennsylvania Health System, Dartmouth Cancer Center, and Yale New Haven Medical Center, have DPYD testing programs.

"I hope you can imagine my shock," she added in her letter, "when I learned that following Larry's death no protocol changes were made at MGB to improve clinical outcomes for patients receiving 5-FU/capecitabine."

As a Massachusetts resident, it's also not lost on Kerin Milesky that DFCI and MGB were partners for nearly 30 years, but are now vying for patients in the highly competitive Boston hospital market. DFCI announced in the fall of 2023 that it would split with MGB and partner instead with Beth Israel Deaconess Medical Center. MGB, in turn, is expanding its own cancer institute.

In pointing out that DFCI has enhanced its precision medicine program with DPYD testing in her letter, Kerin Milesky was hoping MGB would review its policies from a competitive lens. "In an environment where MGB now finds itself with a rival for cancer care in Boston and is aggressively promoting the Mass General Brigham Cancer Institute, having protocols that do not include pre-screening will not be overlooked," she wrote.

She met with leaders at MGB this week to further the discussion with "very low expectations," knowing that change comes slowly at a health system as large as MGB. She said she was speechless upon learning the health system had already committed to implementing DPYD testing before prescribing Xeloda across all their hospitals. "They shared that, while plans to implement [testing] had been discussed, my letter and approach to advocacy resulted in the fast-tracking of implementation," Kerin Milesky said.

She also credited her husband's oncologist, MGH's Clark, for "moving mountains" to accelerate DPYD testing implementation. She believes Clark deeply felt her husband's loss and recounted how he said he would start screening patients for DPD deficiencies even if it wasn't standard practice at MGB. Clark didn't answer questions ahead of press time.

Changing practice one oncologist at a time

The new MGB testing program is a win for patient advocates trying to change attitudes on DPYD testing one oncologist, one cancer center at a time. By AUDT's estimate, around 23 US institutions make DPYD testing available, and only at a few of them is pretreatment testing standard practice.

Oncologists have been reluctant to reduce fluoropyrimidine starting doses or give an alternative therapy based on DPYD genotyping because Xeloda and 5-FU are so widely used, and in the adjuvant colorectal cancer setting, have shown the ability to cure patients. Some doctors want more evidence proving that genotype-guided dose reductions won't rob patients of deriving the most benefit from treatment.

Alan Venook, head of the gastrointestinal oncology program at the University of California, San Francisco, and vice chair of NCCN committees responsible for anal and colon cancer treatment guidelines, is an influential voice against implementing universal DPYD testing until dosing guidelines are more evidence-based. In an interview last year, he characterized CPIC's guidelines on DPYD genotype-informed dosing as "educated guesswork at best."

Critics also point out that DPYD is a highly variable gene and that only a handful of variants on chemo response have been well studied; that the CPIC guidelines only address the four variants that occur largely in patients of European ancestry; and that test panels aren't standardized in the variants they detect and may miss identifying DPD-deficient patients with rare variants. The FDA, which is moving to regulate lab tests, has raised concerns about the reliability of DPYD tests that labs have commercially launched in its response to citizen petitions from AUDT members.

"Changing the standard of care in a conservative world full of disbelievers is not easy," said Jan Schellens at the Netherlands Cancer Institute. Research by Schellens and others swayed the European Medicines Agency to recommend that patients have DPYD testing before getting fluoropyrimidines. "There is a wagon load of evidence that adaptive dosing of fluoropyrimidines [and] employing genotyping of DPYD in poor metabolizers is saving lives, reduces toxicity, leads to equal exposure to active drug as in normal metabolizers who get full dose, is preserving efficacy, and is cost-effective," he said.

In one recently published study conducted in Italy, for example, patients with gastrointestinal cancer and actionable genotypes in DPYD and UGT1A1, variants in which are associated with toxicity to the anticancer drug irinotecan, had a 90 percent lower risk of adverse events, were hospitalized less, and had lower costs associated toxicity management than those in the control arm. Three-year overall survival also didn't differ between the arms.

One complaint among naysayers has been that PGx studies are often retrospective and low quality, but this was a prospective, randomized trial. "These findings further reduce the excuses for the slow adoption of [pharmacogenomics]-guided cancer therapy," Howard McLeod, director of the Center for Precision Medicine and Functional Genomics at Utah Tech University, and Grace Nguyen, a clinical pharmacogenomics specialist at Atrium Health, wrote in an accompanying editorial.

While Venook acknowledged that recent studies have suggested that efficacy may not be compromised in advanced cancer patients who have their doses adjusted based on DPYD genotyping,

he said there's no evidence showing that dose reductions won't negatively impact treatment efficacy in patients with early-stage disease, in the adjuvant setting for example, where the goal is a cure.

This worry doesn't make much sense to Schellens. "The exposure to a drug drives the efficacy and toxicity. [Studies have shown that] the exposure to active drug is the same in poor metabolizers who received a dose reduction compared with normal metabolizers who got a full dose," he said. "One cannot ignore the vast amount of published evidence obtained by different and independent investigators. There is no reasonable argument to suggest that the exposure-efficacy relationship is different in the adjuvant and metastatic setting."

Had Larry Milesky known he had the DYPD*2A genotype, given how worried he already was about chemo side effects, his wife is certain this information would have altered his risk-benefit calculation. "This was an adjuvant therapy to try and prevent a recurrence," Kerin Milesky said. "That conversation would have been very different if we had known ahead of time that he was DPD deficient."

Testing proponents further point out that CPIC guidelines recommend reducing the first dose in DPD deficient patients and then increasing dosing in subsequent cycles if the patient doesn't experience toxicities. Testing can cost around a few hundred dollars and although reimbursement can be inconsistent, it's improving. Testing for the well-studied variants minimizes the risk of harm, said Douglas Rubinson, a gastrointestinal oncologist involved in implementing DPYD testing at DFCI. The argument that "the CPIC guidelines are imperfect is not a reasonable justification to expose patients to harm by treating blind [when there can be] an easily, rapidly, and inexpensively determined DPYD genotype," he added.

Among supporters, DFCI's program is often upheld as a model of how to implement DPYD testing, including a multidisciplinary advisory group, physician education, and clinical decision support that is set up to ensure doctors receive test results before initiating chemotherapy. To date, DPYD testing for eight common variants has found 156 of 3,018 patients, or around 5 percent, to be abnormal fluoropyrimidine metabolizers.

Although Rubin isn't aware of any groups of physicians at DFCI who aren't ordering DPYD testing, 100 percent adoption isn't really the goal, he noted, as there must be room for physicians to exercise their judgment. "There are some patients who are known to be tolerant of fluoropyrimidines due to prior treatment outside of DFCI," he noted. "There are also situations where there is clinical urgency to start chemotherapy where delaying treatment by a few days to get DPD results would be inappropriate."

As it stands in the US, however, the arguments that Venook has made are recapitulated by the NCCN colon cancer guidelines committee that he helms for why it "does not recommend universal pretreatment DPYD genotyping at this time." And Venook and Bani Tamraz, associate professor of clinical pharmacy at UCSF, made their reservations about DPYD testing known in an editorial responding to the data published on DFCI's program, and concluded that "until we can convince clinicians that the dosing recommendations … are on solid footing, at DFCI and UCSF, experienced clinicians need the choice to opt-in or to opt-out."

That editorial hit a nerve with patient advocates. In a letter to the editor, members of AUDT pointed out that while testing methods could be improved, that's no reason to hold up testing for validated variants. They further noted that in the labels of Xeloda and 5-FU, the FDA tells doctors to warn patients about the risk of severe toxicities from DPD deficiencies and discuss testing. "This should bring to a close any discussion of who should opt in/opt out of testing: it is the patient's choice," AUDT members wrote. "Any patient who finds a clinician unwilling to discuss or offer this life-saving test should exercise their right to opt out of that care and find another provider."

For now, details on MGB's plans are sparse. The MGB spokesperson didn't answer questions on how many DPYD variants will be tested, which lab will do the testing, and how results will be implemented into the clinical decision support system. It's not immediately clear how the decision was made to focus only on testing patients considering Xeloda, but not 5-FU.

Upon learning about the change in policy at MGB, Kerin Milesky said she feels "joy that there is at least one positive outcome from my husband's devastating death and relief that MGB patients across all of their hospitals will be prescreened for DPD deficiency and protected from needless illness and death."

This experience has made her optimistic that other cancer centers will follow MGB's example. "The MGB implementation and the general trajectory of our advocacy efforts will have a huge impact on adoption of pretreatment testing," she said.

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