PRECISION MEDICINE ONLINE

Cancer Centers Nudge Oncologists Toward DPYD Testing as PGx Supporters Push For Guidelines Change

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NEW YORK – Dana-Farber Cancer Institute this fall will launch a program to encourage oncologists to test for a genetic condition that significantly increases the risk of life-threatening and costly toxicities in some patients receiving the chemotherapies 5-FU (fluorouracil) and Xeloda (capecitabine).

The cancer institute is investing in clinical decision support so when oncologists indicate patients are slated to receive these therapies in the electronic medical record, they'll be alerted to test for DPYD genetic variants associated with the condition, called dihydropyrimidine dehydrogenase (DPD) deficiency. Approximately 1 in 1,000 patients carry two copies of a variant in the DPYD gene that renders completely inactive the DPD enzyme needed to metabolize fluoropyrimidines, such as 5-FU and Xeloda, while around 7 percent of Caucasian and 8 percent of African American patients have one copy of a variant associated with partial enzyme activity. In these patients, fluoropyrimidines can quickly build up, increasing toxic exposure and the risk for severe, sometimes fatal toxicities, particularly in those with a complete deficiency.

To avoid this, an internationally recognized guidelines body, called the Clinical Pharmacogenetics Implementation Consortium (CPIC), recommends testing for, at a minimum, four well-studied DPYD variants — DPYD*2A, DPYD*13, DPYD D949V, and DPYD HapB3 — and advises reducing starting doses of 5-FU or Xeloda by 50 percent in patients with a partial DPD deficiency. CPIC advises avoiding these drugs entirely in patients with a complete deficiency, but if fluoropyrimidines are necessary, starting at a 75 percent lower dose and monitoring them closely for toxicity.

After receiving a letter last fall from Lindsay Murray describing her mother's last days at Brigham and Women's Hospital after receiving Xeloda, Joseph Jacobson, a medical oncologist and Dana-Farber's senior consultant for quality and patient safety, decided to take a fresh look at DPYD testing at the institute. After meeting with stakeholders within and outside of Dana-Farber, he concluded that it was time to create a standardized process to encourage routine testing, even though practice-setting bodies like the National Comprehensive Cancer Network and the US Food and Drug Administration say there isn't adequate evidence to recommend pretreatment screening.

"We didn't want to wait for the NCCN to make changes or the FDA to add a black box warning [to drug labeling]" before implementing this program, said Jacobson, who was moved by Murray's letter to try to ensure what happened to her mother never happens to another Dana-Farber patient.

By January 2021, Carol Rosen had been a patient at Dana-Farber for three years and had gone through multiple rounds of chemotherapies and immunotherapies for metastatic breast cancer. But during her first round of Xeloda, Rosen lost 18 pounds in two weeks, developed worsening diarrhea, and pain in her mouth and esophagus.

Although doctors kept assuring these were common side effects of chemotherapy, in a matter of days, Rosen grew so weak she couldn't walk or talk. Murray drove her mother through a snowstorm to the emergency room at Brigham and Women's, where she went on supportive care. On the fourth day at the hospital, an outpatient oncologist mentioned DPD deficiency, but healthcare providers failed to procure an adequate sample for DPYD testing and waited too long to give an antidote for severe side effects, called Vistogard (uridine triacetate).

The oral medication, with an estimated list price of $75,000, has the best shot at reversing fluoropyrimidine-related toxicities if given within four days of receiving chemo. The medical team taking care of Rosen seemed "very unaware of what DPD deficiency was and how quickly you need to work to reverse this," Murray said.

By the end, Rosen's lips, mouth, and throat were covered in bloody lesions. Her skin was falling off her body. She was losing her hair. She couldn't control her bowels. Murray held a humidifier up to her mother's mouth for seven hours straight because she couldn't swallow her own saliva. She watched her mother pass away in agony on Feb. 22, 2021.

Those who don't think pretreatment DPYD testing is ready for broad implementation might point out after hearing Rosen's story that even if a test had been done, it may not have changed the outcome. The test could have been negative, because it didn't gauge the specific DPD-associated variant her mother had or she could have been DPD deficient due to nongenetic factors.

The FDA, for example, has expressed concern about the sensitivity of tests to detect specific DPYD variants associated with the condition. Experts in charge of NCCN guidelines, meanwhile, have argued that there are far too many other factors beyond genetics that impact Xeloda's toxicities — the patient's age, kidney function, microbiome, and diet — and they wouldn't know how to incorporate DPYD testing information to adjust dosing.

Test or no test, Rosen's symptoms were clearly indicative of DPD deficiency, Murray said, having spoken with DPD deficient patients who have survived these toxicities and family members who have watched their loved ones succumb to them. Murray and other DPD deficient patients and relatives founded Advocates for Universal DPD/DPYD Testing (AUDT) last year, a group that educates patients and oncologists and urges pretreatment testing.

In September, Murray wrote to Jacobson that she believed her mother's toxic reaction to Xeloda was likely due to a DPD deficiency and her death was preventable. She wanted to work with him to ensure this didn't happen to others.

"Dana-Farber has always been a leader in cancer treatment … [and] can be instrumental in helping change the standard of care by putting patient safety first," Murray wrote in her letter. "I am hoping that my mom's story can be a catalyst to institute change at Dana-Farber and beyond."

Convincing evidence

Fluoropyrimidines are commonly prescribed for gastrointestinal, breast, and head and neck cancers. Each year, around a third of the 250,000 people in the US receiving 5-FU experience grade 3 or higher treatment-related toxicities, and an estimated 1,300 people die from these adverse events. Studies have shown that patients with a partial deficiency, carrying one of the four best-studied DPYD variants, are 5 to 8 times more likely to have a grade 3 or higher adverse event from fluoropyrimidines, and patients with a partial and complete deficiency due to these variants are at more than 25 times greater risk of dying from toxicities than those who don't have these variants.

There's data showing that genotype-guided dosing reduces severe toxicities and deaths compared to the standard of care and that pretreatment testing is cost-effective. In one study where patients were prospectively screened for the DPYD*2A variant, and carriers received lower fluoropyrimidine doses, 28 percent experienced severe adverse events and none died, compared to 73 percent having severe toxicities and 10 percent dying in historical controls.

The NCCN panel in charge of colon cancer guidelines noted this data in its most recent recommendations, but has said it will not back pretreatment testing until there is evidence that giving lower, genotype-informed doses to cancer patients with a partial DPD deficiency won't also reduce fluoropyrimidine efficacy. These chemotherapies are often prescribed as part of adjuvant treatment to earlier-stage colorectal cancer patients, when there's a better chance for a cure.

"Our concern is the risk of jeopardizing a patient's potential for cure when adjusting doses based upon incomplete data in the adjuvant setting," Al Benson and Alan Venook, gastrointestinal oncologists who lead the NCCN's colon, rectal, and anal cancer guidelines panels, said in a joint statement. "There are currently no data to assure us that the dose reductions of fluoropyrimidines recommended by CPIC do not impact outcomes."

The FDA, in 2016, strengthened the toxicity warnings in labeling for Xeloda and 5-FU and told doctors to avoid these drugs in patients completely lacking DPD. But the agency also stated that "there is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test." Moreover, the agency placed the onus on patients to inform their doctors if they knew they had a DPD deficiency.

The labeling update was in response to a citizen petition from Ken Surprenant, whose first wife Kathryn had rectal cancer and passed away 10 years ago from the toxicities of FOLFOX (folinic acid, 5-FU, and oxaliplatin). Surprenant found out Kathryn was DPD deficient after her death, from testing their four children, who are all DPYD variant carriers; he is not. In responding to his petition, one of the main reasons the FDA gave for not recommending DPD screening was that available tests weren't reliably accurate.

However, patient advocates like Surprenant and an increasingly vocal group of PGx proponents have continued to petition the NCCN and FDA asking them to reconsider their position, especially as regulators in Europe and elsewhere now back DPYD screening, and test quality, cost, and reimbursement are improving in the US.

The European Medicines Agency, as of 2020, recommends testing patients for DPD deficiency before prescribing fluoropyrimidines. The National Health Service in the UK and the provincial government in Quebec also back pretreatment genotyping.

In the US, even though DPYD testing isn't included in guidelines, dozens of labs offer tests, and some like Invitae, have a patient self-pay price of around $250 if insurance won't pay. Meanwhile, MolDX, a program that establishes local Medicare coverage policy for molecular diagnostics, has agreed to cover PGx tests that are deemed actionable by CPIC. This means that tests assessing the DPYD variants in CPIC guidelines should have Medicare coverage in 28 US states that follow MolDX policies. At least one commercial insurer, Cigna, covers DPYD testing, as well.

Surprenant made these points in his second petition to the FDA in 2020, asking the agency to add a boxed warning to 5-FU and Xeloda's labels highlighting the risk of severe toxicity in patients with DPD deficiency; to recommend doctors screen patients for DPYD variants and adjust dosing in carriers; and to place the responsibility on doctors to discuss DPD deficiency-related toxicity risks with patients. In this petition, which is still pending with the FDA, Surprenant also addressed the FDA's concern about the accuracy of available tests.

Detractors have argued that a negative DPYD test result doesn't necessarily mean that a patient is not DPD deficient or won't experience severe toxicities due to nongenetic factors and to variants not tested for. CPIC maintains lists of DPYD variants and their functionality, and as of February 2020, has flagged 27 no function or reduced function variants backed by varying levels of evidence.

PGx tests on the market don't test for a standard set of DPYD variants, however, and patients may get a negative result but still be at risk for toxicities. The risk of a false-negative result is particularly high in African Americans, for example, who can have deleterious DPYD variants (i.e., DPYD-Y186C) that haven't been seen in Caucasians and may not be included in commercial test panels.

Surprenant in his latest petition acknowledges that currently available tests can yield false-negative results. However, the positive predictive value of available tests, studies show, range from 82 percent to 88 percent. "If you get a false-negative test, then we're treating the patient the same as we would today without testing," said Surprenant, who is also president of the AUDT patient advocacy group. "Doctors take an oath to do no harm. The tests aren't perfect, but the patients the tests do identify as at risk, you can adjust the dose and that's better than the standard of care today."

The opposite concern, which is the NCCN's main worry, is that not all patients with a partial DPD deficiency are at risk for severe toxicities and therefore may lose the chance to fully benefit from treatment because they received lower fluoropyrimidine doses. Studies suggest up to 40 percent of partially deficient variant carriers may not have severe reactions from chemo.

Testing supporters counter there's no evidence that DPYD-guided dosing reduces treatment efficacy, and that the NCCN panel is ignoring key evidence that should alleviate their concerns. Douglas Rubinson, a GI oncologist at Dana-Farber, who began screening patients years before the cancer institute decided to launch a formal DPYD testing program, said that he starts variant carriers at reduced doses following CPIC guidelines and then increases the dose in the second cycle. "If they do well then, they're receiving a full dose by the third cycle," Rubinson said. "But if they have a hard time at a 50 percent dose, then you saved them from having a potentially severe or lethal adverse event."

Daniel Hertz, assistant professor of pharmacy at the University of Michigan College of Pharmacy, has cited pharmacokinetic analyses showing that genotype-guided dosing normalizes fluoropyrimidine exposure in variant carriers to that of wild-type patients receiving standard doses. Given the challenges of addressing NCCN's efficacy concerns via a sufficiently powered clinical trial, Hertz has argued that drug exposure data should provide assurance that CPIC-recommended dosing is appropriately calibrated and does not lower fluoropyrimidine efficacy.

The NCCN panel, meanwhile, has remained steadfast that fluoropyrimidine exposure data is not a reliable surrogate for efficacy, particularly when patients get these therapies as part of combination regimens and there can be cumulative toxicity. Further, many of the key studies on genotype-guided dosing considered patients who received 5-FU or Xeloda, and the panel wants to see more data on 5-FU specifically given its importance as a mainstay of colon cancer treatment. "We need data with fluorouracil alone, not coupled with capecitabine because … capecitabine dosing is just too complex to study in this manner" since its metabolism can be affected by so many other nongenetic factors, said Benson and Venook.

Hertz and other testing supporters have been puzzled as to how to conduct the studies and procure the data NCCN wants. Since reduced or no-function DPYD variants are uncommon in the population, it would take too long and cost too much to conduct a randomized trial comparing the outcomes in genotyped and non-genotyped patients receiving reduced and standard doses. It could also be considered unethical to give standard fluoropyrimidine doses to patients known to have DPD deficiency-associated high-risk variants.

"It's ludicrous to want evidence that will never exist," said Mark Ratain, director of University of Chicago Medicine's Center for Personalized Therapeutics. Ratain is a proponent of testing cancer patients at diagnosis for not just DPYD variants but also a panel of clinically actionable PGx variants that can be used to inform current and future therapies.

Benson and Venook acknowledged that the question of whether PGx-informed fluoropyrimidine dosing reduces efficacy is "probably impossible to answer" with a randomized-controlled trial and suggested that convincing data may come from a prospective, real-world study. "But right now, dose reduction levels based upon DPYD variants are not based on high-quality evidence or clinical outcomes," they maintained, adding that they don't know what the next version of the NCCN's colon cancer guidelines will say on DPYD testing but that the panel will continue to discuss the issue and consider petitions with new data.

Hertz was encouraged that Benson and Venook seemed at least open to considering real-world outcomes data, which he said can be gathered from institutions in Europe and the US that have implemented DPYD testing. But he was disappointed they didn't find systemic drug exposure data to be a reliable proxy for therapeutic efficacy, pointing out that the FDA has considered exposure

data when recommending drug doses in special populations and when approving generic equivalents, even for systemic fluoropyrimidines. (The FDA did not answer questions for this article, since it deals with a pending citizen petition.)

As the chief hospital pharmacologist at UChicago Medicine, Ratain said any physician who understands pharmacology would not need any more evidence on the impact of DPYD-informed chemo dosing. "There are many oncology drugs where the dose can be reduced by 50 percent or more without reducing efficacy and this would also reduce the cost of drugs, adverse drug reactions, and patient suffering," he said. "But we've paid so little attention to accuracy in dosing."

He's encouraged that the FDA seems to be finally paying attention to optimizing dosing for newer molecularly targeted cancer therapies through Project Optimus. The agency approved AstraZeneca/Daiichi Sankyo's Enhertu (trastuzumab deruxtecan) at a lower dose for HER2-mutated lung cancer last week using guidance from this program.

Not waiting

Even though the appeals and petitions from testing advocates have not swayed the FDA and NCCN, they have succeeded in convincing several cancer centers around the country to educate oncologists about DPD deficiency and nudge them to order testing for patients considering fluoropyrimidine treatment. At these institutions, these efforts usually start at the urging of an oncologist who has seen firsthand the devastating consequences of not doing pretreatment testing.

In 2013, early in Gabriel Brooks' medical oncology career at Dana-Farber, he had a patient who was having up to 10 bowel movements a day soon after receiving FOLFIRINOX (folinic acid, 5-FU, irinotecan, and oxaliplatin). Brooks, a GI oncologist, kept adjusting the irinotecan dose thinking that was the cause, but it didn't help, and she was considering stopping her cancer treatment. When he finally performed DPYD testing, it revealed a deleterious variant. "She didn't have a fatal toxicity, but she had a severe toxicity, and I was adjusting the wrong drug," he said. "Had I known [her DPYD status] from the start, I could have saved her two months of misery."

Brooks wasn't routinely doing pretreatment DPYD testing back then because he didn't want to be an outlier among his colleagues, but after this experience he didn't care. "I thought I was right about this, and I would just do it," he said. He continued testing patients when he joined Dartmouth Cancer Center a few years later and urged his colleagues to do the same. "I've become a little obsessed with this," Brooks admitted.

In 2019, after a patient at the cancer center had a severe reaction to 5-FU and reactive testing revealed a DPD deficiency, it wasn't difficult to convince the other GI oncologists to start testing. Brooks declined to go into the specifics of that case because he didn't have permission to speak on the record about it, but simply stated: "It was a toxicity that we never wanted to see again."

Now, the institution's lab performs DPYD testing three times a week and reached 90 percent testing compliance in GI cancer patients considering 5-FU or Xeloda last year.

At Dana-Farber, after Jacobson got Murray's letter, he reached out to Rubinson, a self-described DPYD testing proselytizer, and convened a workgroup that included doctors, pharmacists, nurses, financial experts, and patient advocates including Murray. Together, they designed a program to try to make DPYD pretreatment testing readily available for the around 1,000 patients each year who receive 5-FU or Xeloda at the cancer center. When it launches this fall, the program will focus initially on breast and GI cancer patients, who often receive fluoropyrimidines.

The program will educate patients and train hospitalists and physician assistants on DPD deficiency; develop electronic decision support alerts on DPYD testing; and create a process through which PGx-trained pharmacists can help doctors adjust dosing for patients with DPD deficiency. Dana-Farber has ambitions to set up its own in-house PGx panel, but for now is outsourcing DPYD testing to Mayo Clinic Labs. The institution will track the program's progress in terms of how many patients are tested, whether the results come back in time to aid medical decision making, and how doctors change treatment decisions.

While payor coverage is improving, it's still variable, and this is a major reason why at institutions like UChicago Medicine, even with PGx champions like Ratain, preemptive testing for DPYD and other actionable genes is largely provided within studies. "It's kind of hard to say you'll do genotyping for one patient but for another patient, whose payor doesn't cover it, there should be a different standard of care," said Ratain. To get around this access disparity, cancer centers that are actively encouraging DPYD test adoption, like Dana-Farber and Dartmouth, have committed not to balance bill patients.

Cleveland Clinic has also determined that "it is worth it in terms of the harm prevented to patients to take a loss [on DPYD testing] if we need to," said Alok Khorana, director of the GI malignancies program. Although the high cost of genotyping and lengthy turnaround times had previously been reasons against routine testing, when Cleveland Clinic revisited the issue in 2020, these were no longer concerns.

The institution is now providing pretreatment DPYD testing to all GI cancer patients considering fluoropyrimidines at its main campus through a pilot and plans to extend it to patients with other tumor types and roll out the program at regional centers and its Florida campus. DPYD testing is performed at Cleveland Clinic's in-house lab twice a week and results are returned in two to three days, well within the time for most patients' first dose of Xeloda or 5-FU.

Khorana has been waiting for such a program for a long time. Two decades ago, a patient of his had a severe toxicity from fluoropyrimidines, and even though the patient didn't die, Khorana never forgot it. "I know it happens rarely. I know that's the argument against screening," he said. "But those arguments don't take into account the devastating consequences that can happen to patients and families, as well as the provider that's taking care of them. We're in this business to help people, not hurt them."

Ask the patient

At its annual meeting in June, the American Society of Clinical Oncology, which also doesn't recommend DPYD testing, hosted a debate on the topic, where Venook took the position against pretreatment testing. Venook, who is a medical oncology and translational research professor at the University of California, San Francisco, in addition to being the vice chair of the NCCN colon cancer panel, acknowledged that one would expect "obviously horrendous, if not lethal, toxicity almost for sure" in patients with a total absence of DPD activity, but he still didn't back testing.

Citing a study he led several years ago where more than 1,000 metastatic colorectal cancer patients received a first-line regimen containing 5-FU and none died from treatment-related toxicities, he asserted that a complete DPD deficiency is "vanishingly uncommon and [it's] very unlikely that doing a test to look for the total lack of DPYD activity would be very likely to bear fruit."

Venook's rationale, even if made for argument's sake as part of a debate, struck Brooks as paternalistic. "Why not ask the patient if they'd like to take a 1-in-a-1,000 crapshoot?" he said.

Even if patients don't die, there's still a significant risk of severe nonfatal toxicities in carriers of DPYD deleterious variants. As part of an analysis modeling the cost-effectiveness of pretreatment DPYD testing in colon cancer patients, Brooks and colleagues calculated that 1 in 48 patients will avoid a grade 3/4 toxicity with screening. While the oncologists in charge of NCCN guidelines seem willing to not recommend PGx testing and roll the dice that patients won't experience severe toxicities or die, it's not they, but the patients who bear all the risk of that gamble, Brooks said.

Given those odds, Rubinson said he has an ethical obligation to offer DPYD testing to his patients, because he himself would want it if he were a cancer patient about to receive 5-FU or Xeloda. "If I knew there was an inexpensive test with rapid turnaround that would eliminate a 1-in-a-1,000 chance that these drugs would kill me, I would want that test," said Rubinson.

It's not lost on Brooks that his risk/benefit calculation for implementing PGx testing is very different than those heading up the NCCN panel and suggested it may be due to generational differences about acceptable levels of toxicity in cancer care. Brooks recalled he had a mentor who used to say, "You have to fear the cancer more than the chemotherapy." He doesn't agree with his mentor, he said, and is open to tools that can identify the best drug and dose for his patients.

Others blame the reluctance around DPYD testing in the US to the lack of PGx know-how among oncologists. "Most oncologists have never even heard of CPIC. They don't recognize it as a guidelines body," said Kristine Ashcraft, medical affairs director of pharmacogenomics at Invitae, a provider of DPYD testing. Ashcraft spearheaded a petition to the NCCN earlier this month, supported by other PGx experts, asking it to recommend DPYD testing.

PGx supporters are hopeful that some of the hurdles DPYD testing has experienced may be addressed by the Right Drug Dose Now Act. The bill, introduced in the US House of Representatives this year, would advance PGx-related awareness campaigns for the general public and education programs for doctors and provide funding for PGx implementation research, among other things.

The fact that the US, often hailed as a leader in precision medicine, is behind Europe when it comes to adoption of DPYD testing has struck some as odd. Murray chalks it up to the profit-driven healthcare system in the US. The pharmaceutical industry has historically not advocated for PGx because tests can direct patients to get lower doses of their drugs or an entirely different therapy. Xeloda was a blockbuster for Roche, but since generics hit the market in 2013, some industry observers said perhaps there is little reason for the company to take a position on DPYD testing either way.

"Genentech should be advocating for this, and they don't," Murray insisted. Roche subsidiary Genentech declined to comment on whether it has discussed updating Xeloda's labeling with DPYD testing information with the FDA, but noted that the agency's Oncology Center of Excellence has selected Xeloda for Project Renewal, an initiative to update drug labels based on post-marketing data.

Threat of liability

If nothing else, some PGx experts said the pall of liability might move some cancer centers to seriously consider implementing DPYD testing. Since regulators in the EU have recommended testing, CPIC has issued dosing guidelines, and there is better testing and reimbursement, "this creates some interesting issues with regard to liability if testing is not performed," said Ratain.

Joanne McIntyre's 2019 negligence lawsuit against Oregon Health & Science University, recently settled for $1 million, came up during the ASCO annual meeting debate on DPYD testing and created some buzz among oncologists in the audience. McIntyre's late husband, David, had undergone successful whipple surgery at OHSU in 2018 and been prescribed adjuvant Xeloda.

Shortly after his first round of chemo, the vomiting and diarrhea started, then he developed mouth sores and a body rash, and within days had to be hospitalized for rapidly worsening symptoms that could not be managed with medication. By the time he was in the hospital, he couldn't eat, he had intractable diarrhea, and his white blood cell count was extremely low. The medical staff were constantly suctioning out phlegm clogging up in his mouth and throat. The admitting doctor suspected DPD deficiency and ordered a genetic test as well as the Vistogard antidote, but it was all too late. David died Dec. 12, 2018.

"The capecitabine eats your body alive," said McIntyre, who is a member of AUDT. "David had a partial DPD deficiency. Those who have a full deficiency turn black. Their bodies just burn up inside."

In her lawsuit, McIntyre accused OHSU of failing to secure informed consent. Had the institution informed her husband before starting Xeloda about the risks associated with DPD deficiency and the availability of a test, he would have wanted to be tested and not gotten Xeloda once he knew he was at risk for severe toxicities.

As part of the settlement, OHSU denied wrongdoing, but agreed to inform patients who are candidates for Xeloda or 5-FU about DPD deficiency and educate fellows about this condition. OHSU will also host an educational seminar for medical staff on how to test for DPD deficiency, recognize early-onset toxicities from chemotherapy, and quickly administer Vistogard.

When asked if OHSU is considering implementing pretreatment DPYD testing following McIntyre's lawsuit, the institution said that it follows national cancer guidelines and practices evidence-based medicine set forth by national expert consensus in the field. "National treatment guidelines established by the major cancer societies in the US do not recommend DPD … testing prior to starting chemotherapy," OHSU said in a statement.

In her advocacy work educating patients and doctors about DPD deficiency, McIntyre underscores that the hospital billed the insurance company $500,000 for the nearly two weeks her husband was admitted. "He could have had a test for $250," McIntyre said, and added, "I wish my attorney had asked for testing as one of our demands" in the settlement.

Still, she commended OHSU for committing to DPD deficiency education. "Training the fellows is huge," she said. "After they finish their fellowship, they will go to other hospitals and take that training with them. And that's one way to spread the word."

While McIntyre's lawsuit has garnered the attention of some oncologists, as long as the NCCN and FDA aren't on board with DPYD testing, cancer centers can always say it's not the standard of care. For example, several testing supporters pointed out that the Mayo Clinic, a leader in PGx and in DPYD research in particular, doesn't have a framework for routine DPYD testing among its oncologists. Meanwhile, Mayo Clinic Labs does offer DPYD testing as a commercial service, and other institutions like Dana-Farber are outsourcing their testing to the lab.

Thor Halfdanarson, a GI oncologist at Mayo Clinic Comprehensive Cancer Center, said that DPYD testing is ordered selectively at present, though medical oncology, pharmacology, and PGx groups are discussing more routine application among patients receiving fluoropyrimidines. For now, the test is "readily available and easy to order" at the institution, and trainees and clinical staff are educated on its use, Halfdanarson said. "As the data regarding the utility of testing get better, we will be discussing if this test should be more routinely used."

The fact that most cancer centers are still not encouraging greater DPYD testing, despite potential liability and the human cost of not testing, illustrates the power the NCCN and FDA have in shaping the standard of care. A recent survey led by Hertz of around 60 US oncologists found that only two had ordered DPYD testing for at least 10 percent of patients. When asked why they're not testing, more than half said it was because DPD deficiency is rare, and nearly half pointed to the lack of guidelines.

"We keep getting more cancer centers doing [DPYD testing]. There seems to be a lot of momentum building," Hertz said. "But the guidelines or the regulatory agency are the key to unlocking this."

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