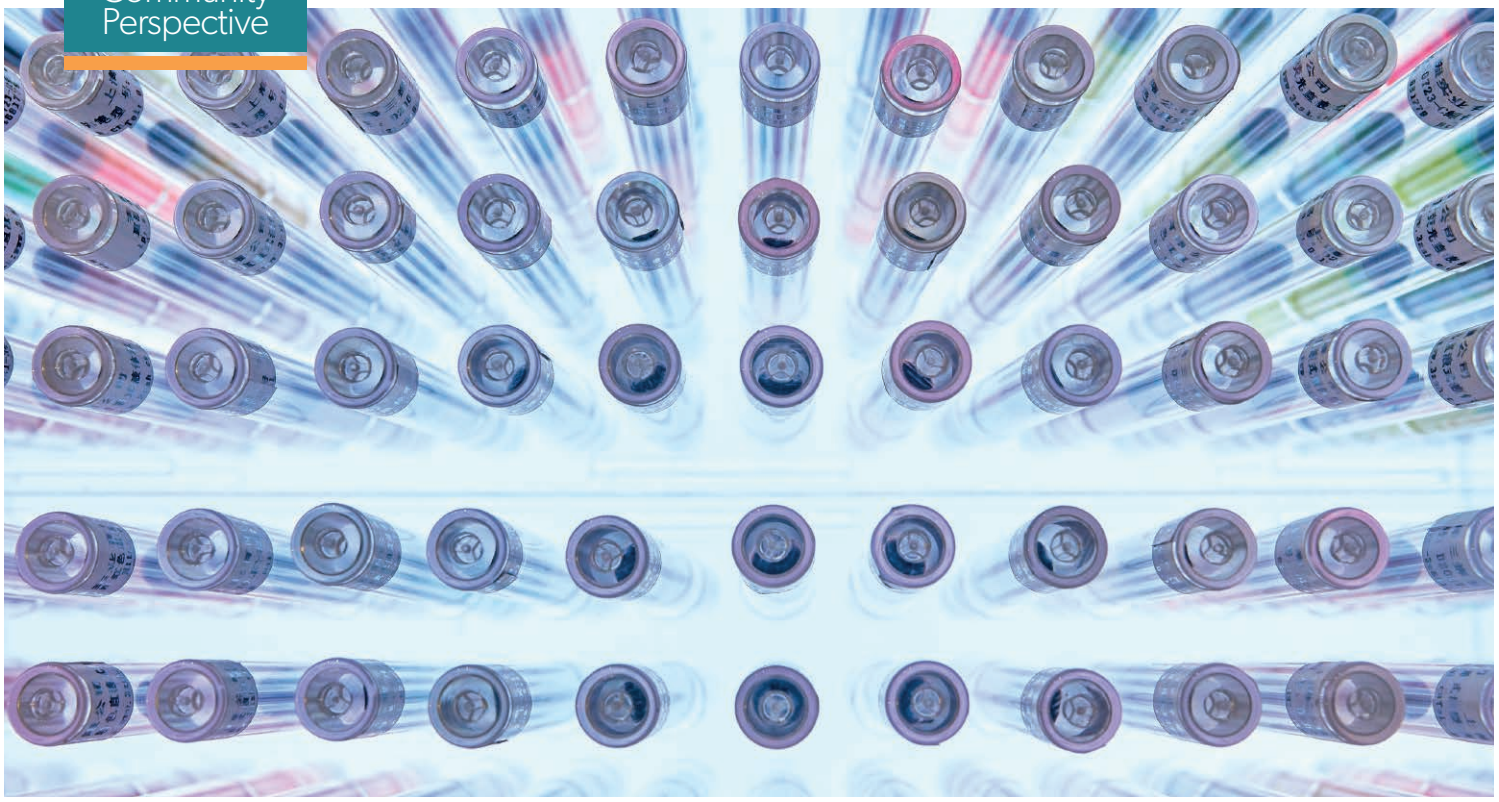


Advocating for Regulatory Approval to Improve Care for Patients With Dihydropyrimidine Dehydrogenase Deficiency

By Ken Surprenant, President, Advocates for Universal DPD/DPYD Testing

PRECISION MEDICINE plays two primary roles in healthcare: first, to point to safe and effective medicines for patients with a corresponding responder profile and, second, to identify medicines that cannot be metabolized or otherwise tolerated by patients. For instance, some individuals are unable to metabolize 5-fluorouracil (5-FU and its prodrug Xeloda), a drug that has a long history in cancer treatment.

Patients who are deficient in dihydropyrimidine dehydrogenase (DPD) cannot metabolize 5-FU, which results in buildup of the drug and often leads to severe adverse reactions or even death. DPD deficiency is defined as having low or no levels of the DPD enzyme and is typically associated with deleterious polymorphisms in the gene encoding DPD (DPYD). Such polymorphisms may lead to partial or complete deficiency (see **Inset**). Detecting DPYD variants is critical to avoid administering 5-FU treatment in DPD-deficient individuals and to instead prescribe an alternative therapy.

Though the risk of using 5-FU to treat DPD deficient patients has been known for more than 30 years, the groups responsible for cancer treatment guidelines and drug labels in the US have not recommended pre-screening (see also **Inset**).

The Advocates for Universal DPD/DPYD Testing (AUDT) came together as a group in 2021 following

the death of yet another loved one whose suffering could have been prevented with genetic testing prior to the start of treatment with fluoropyrimidine-based chemotherapy.[1,2]

The human cost of failing to test for DPD deficiency prior to administering 5-FU is the common experience that created, and sustains, the bond among these advocates. In addition to that common experience, the advocates also share a passion to help prevent others from suffering similarly, especially when the ability to avoid adverse outcomes is so easy to achieve.

Since joining together, we have been afforded more opportunities to share our stories and raise awareness among healthcare organizations. As a result, we gained the support of the Institute of Safe Medication Practices[3] and the National Community Oncology Dispensing Association.[4]

The increase in dialogue has also served to reveal more of the concerns that prevent those responsible for treatment guidelines and drug labels from recommending pre-screening and dose adjustments for DPD-deficient patients.

Progress towards improving the standard of care is noticeable, though far from concluded.

Starting down the advocacy path: First steps on a journey of 1,000 miles

In every case that pushed an AUDT member into advocacy, a friend or loved one was diagnosed with a form of cancer involving a solid tumor, typically gastrointestinal, breast, or head and neck cancer. Following the diagnosis, chemotherapy relying on a fluoropyrimidine, 5-FU or Xeloda (capecitabine), became part of the treatment plan.

Our understanding was that there was little risk of toxicity (see **Inset**) associated with the use of the drugs; after all, 5-FU has been used for more than 50 years to treat gastrointestinal cancer while capecitabine has been used for certain forms of breast cancer. Yet our friends and loved ones suffered following treatment, and most died within weeks of a single treatment, though a few suffered longer, often compounded with treatment delays, before dying.

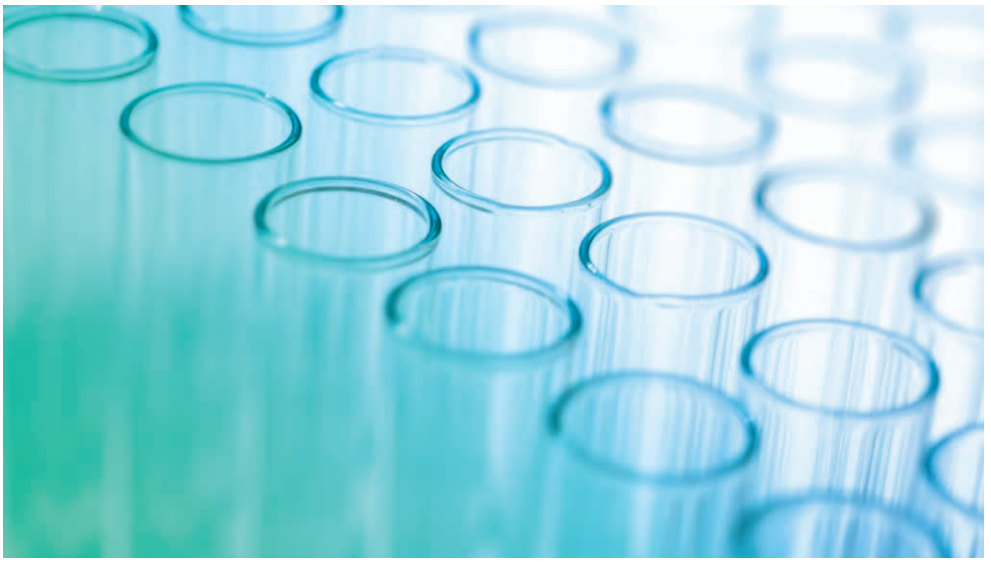
In our struggle to deal with our losses, we first sought to understand what happened and why. For 5-FU and Xeloda to work safely, a patient must have sufficient levels of DPD to reach and maintain a safe and effective therapeutic window following dosing. In brief, DPD serves to remove 5-FU from the body before it can damage healthy cells, but when DPD enzyme activity is compromised, the chemotherapy agents remain in the body longer, leading to severe toxicity and, in some cases, death.

Most patients are unaware if they are DPD deficient; they are asymptomatic and unless tested before the start of treatment, they will not know they are at a high risk of severe toxicity.

What has been done to raise awareness, change policy

Nearly 10 years ago, one of our advocates sought to raise awareness of the risk of DPD deficiency by creating a website.[5] Unfortunately, most people visited this site after experiencing a tragic outcome, not before. Nonetheless, the site has served to bring advocates together over time and to provide a means to share the stories of their loved ones' experiences.

As individual advocates, we tried in different ways to bring about an improved standard of care. For example, to support a young family whose mother tragically struggled with long-term suffering and care expenses, a community of friends created the StrongMom[6] website to support the family and to raise awareness of this health issue.



A few of us were afforded opportunities to share our stories. For example, the wife of one of our members shared her experience of how her toxic reaction resulted in halting her treatment. When she and her husband found a pharmacologist in France to phenotype her blood, she discovered she had partial DPD deficiency. While she found an oncologist willing to treat her at a reduced dose level and though she tolerated the adjusted dose of 5-FU chemotherapy, the treatment resumed too late to curb her cancer. Although her death was not reported as a toxic reaction, the delay cost her precious treatment time.

Meanwhile, in New York and New Jersey, individual advocates proposed legislation to require screening for DPD deficiency prior to the use of 5-FU. These bills stalled.

Our individual attempts to revise treatment guidelines have also included submitting multiple petitions to the National Comprehensive Cancer Network's (NCCN) Colorectal/Anal panel to update its guidelines to recommend pre-screening. To date, the NCCN has unanimously voted down each petition and treatment guidelines remain unchanged.

We have also attempted to revise drug labels to include a warning to 5-FU and Xeloda users of the issues with DPD deficiency. In 2014, one of our advocates submitted a petition through the US Food and Drug Administration's (FDA) citizen petition process, seeking changes to the drug labels to heighten awareness of the risk of DPD deficiency and to recommend pre-screening and dose adjustments for patients found to have partial deficiency.[7]

After two years of deliberation, the FDA responded in 2016.[7] The agency agreed to revise the drug labels' warnings and precautions to describe more clearly the risk of severe toxicity to DPD-deficient patients. In doing so, the labels no longer describe the risk of severe toxicity as "rare" or "unexpected." The FDA also agreed to add fatalities to the list of possible outcomes.

But the agency denied the recommendations to pre-screen patients and did not endorse dose reduction guidelines for patients with partial DPD deficiency, stating that these practices are not recommended by NCCN guidelines. The agency also questioned the predictive accuracy and reliability of genetic testing.

The FDA's response fell short of what we as advocates sought, but it served as a big first step for our efforts.

Impact in Canada, US court cases

While unsuccessful in the US, one of our members succeeded in bringing about

pre-screening in Quebec. After several years of tireless work, this widow saw the fruits of her labor when the province mandated pre-screening along with dose adjustment guidelines in 2019.[8]

Another widow brought a lawsuit against the US hospital where her husband died following adjuvant treatment with Xeloda. The parties settled out of court in 2022 with a payment to the grieving party and with a pledge to introduce staff training to address the risk of DPD deficiency.[9] Still, the hospital has not adopted pre-screening procedures, citing the absence of national treatment guidelines for testing. This settlement, however, has sent a signal to cancer centers of the potential liability of ignoring this important safety issue.

Encouraging road signs: Europe and elsewhere

Meanwhile, there has been heightened interest in DPD deficiency in peer-reviewed medical journals. A number of European teams published reports citing the cost effectiveness and the benefits to patients of using test results to guide treatment.[10,11,12] Indeed, some teams urged that the time had come to require pre-screening and dose guided treatment plans.[2,13]

France set the bar for improved outcomes in 2019 when it mandated testing for DPD phenotypes before the use of 5-FU or Xeloda. Within a year, the European Medicines Agency issued its recommendation to pre-screen patients using either DPYD genotyping or DPD phenotyping; it also recommended adjusting 5-FU or capecitabine dosage based on the level of DPD deficiency.[14]

Encouraged by these changes in Europe, we expected to see change in the US but that has not been the case so far. Despite the failure of US regulators to adopt these guidelines to date, we have seen an increased willingness among oncologists and pharmacologists to recognize the risk to DPD deficient patients.

The rallying point

Up until 2021, our individual advocacy activities took place in isolation. Then, Lindsay Murray, who had recently lost her mother due to DPD deficiency, reached out and compelled us to

DPD deficiency and avoiding drug toxicity

1. Fluorouracil (5-FU) and Xeloda are used to treat solid tumors typically found in gastrointestinal, breast, and head and neck cancer patients.
2. The DPD enzyme plays an essential role in removing the chemotherapy drug from the body before it can damage healthy cells. When DPD enzyme activity is diminished, severe toxicity is a highly likely outcome.
3. An estimated 10 percent to 40 percent of all patients suffer severe toxic reactions (grade >3) when treated with standard dosing[1,2,3] One notable US study, Alliance N0147, found 33 percent of patients receiving standard doses suffered severe toxicity.[4] The same study found DPD-deficient patients were at a significantly higher risk of adverse reactions: patients with partial DPD deficiency had a 50 percent to 88 percent risk of severe toxicity.
4. The death rate due to DPD deficiency in the US is controversial and not well documented but is estimated at 700 to 1,400 annually.[5]
5. Warning signs of early onset toxicity include severe forms of diarrhea, mucositis that inhibits drinking or eating, vomiting, peeling or blistering skin, and neutropenia.[6]
6. Genetic variants of the DPYD gene have been shown to lead to compromised DPD enzyme activity as first reported in 1988 by Robert Diasio, then at the University of Alabama and now of the Mayo Clinic.[7]
   - Four DPYD variants (c.1905+1G>A, c. 1679T>G, c.2846A>T, and c.1236G>A/HapB3) are associated with increased risk of severe toxicity for an estimated 5 percent to 7 percent of European descendants.[8,9]
   - Another deleterious variant, p.Y186C (rs115232898), has been discovered among an estimated 5 percent of African Americans.[10]
7. Tests are available to detect DPD deficiency and have been demonstrated to be life-saving and cost effective.[11,12,13] In most cases patients with DPD deficiency are asymptomatic prior to receiving 5-FU or Xeloda.[14]
8. Treatment guidelines, published by the National Comprehensive Cancer Network and the US Food and Drug Administration's drug labels have not required pre-screening.[15]

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Figure 1: Highlighting the human cost of ignoring DPD deficiency

join our efforts under an umbrella advocacy group. Her passion to bring about an improved standard of care, to honor the loss of her mother, and to help others avoid that suffering was the rallying cry for us.

We organized as a group loosely that year and worked to bring our voices together in two ways: first, we established a new website;[15] and then collaborated with the American Society of Pharmacovigilance (ASP) to share a booth at the American Society of Clinical Oncology's Quality Care Symposium in Boston in September of that year. There we attempted to highlight the human cost of ignoring DPD deficiency (see **Figure 1**) with our stories available online.[16]

Then with encouragement from medical professionals who shared our interest in changing the standard of care, we formed officially as a 501(c)3 non-profit organization in 2022.

Picking up the pace

When we formed AUDT, we hoped that by joining our voices together we would have a larger impact. Since its founding, we have certainly been given more opportunities to present our case. Thanks to our medical advisors and to other supporters, including ASP and the GI Cancer Alliance, we have had opportunities to share our stories in different virtual forums and garner increased support.

As a result, the Institute for Safe Medication Practices came out to support pre-screening and dose adjustment in its July 2021 newsletter[17] and the National Community Oncology Dispensing Association published in December 2021 a recommendation for DPYD testing prior to fluoropyrimidine treatment.[18] We contributed to a workshop on the need and benefit of pre-screening for DPD deficiency for the Hematology Oncology Pharmacy Association's continuing education program and we had news coverage of our efforts.

We learn more as we go along. One of the lessons we learned came as a result of the ISMP newsletter. The co-chairs of the NCCN Colorectal/Anal Cancer panel responded by expressing their concern that reducing doses in response to DPD deficiency may reduce the chance to treat patients effectively.[18] Subsequently, one of our medical advisors, Daniel Hertz from the University of Michigan College of Pharmacy, reported in the *Journal of Clinical Oncology* that there is "no direct evidence of efficacy reduction."[20]

While the NCCN has not budged, the FDA edged forward in 2022 in response to another citizen petition. This petition, submitted in 2020 with the support of four experts – oncologists and pharmacologists – cited the new practices in Europe, among other compelling reasons, for the agency to reconsider its stance. The petition made the case that testing is a much safer route than not. The petition also noted that once the FDA approves testing, the market will respond with even better testing capabilities. The petition also recommended, as the previous one did, to use test results to guide chemotherapy dosing levels for DPD-deficient patients as well as to encourage physicians to discuss the risk of DPD deficiency with patients and to offer them testing.[21]

The FDA responded only to the recommendations pertaining to Xeloda while the 5-FU drug label remains under review as part of the FDA's Project Renewal.[21] The FDA agreed to revise the warnings and precautions section of the Xeloda drug label to make discussion of DPD deficiency more prominent and have it ask physicians to "consider testing for genetic variants of DPYD prior to initiating Xeloda to reduce the risk of serious adverse reactions if the patient's clinical status permits." The FDA label goes on to warn that serious adverse reactions may still occur and that current tests may vary in accuracy.

The agency also approved revisions to the patient counseling section of the label, including moving it higher in the order of topics discussed and adding that physicians should "inform patients of the potential for serious and life-threatening adverse reactions due to DPD deficiency and discuss with your patient whether

they should be tested for genetic variants of DPYD." It further addressed the risk of DPD deficiency in the patient information section and the drug label's new pharmacogenomics section.

The FDA, however, did not recommend universal testing prior to prescribing these drug treatments. The agency raised questions and concerns about test reliability and accuracy, the inapplicability of testing to the general US population, and stated that "most known DPYD variants associated with decreased DPD activity are reported to be of low frequency." It further added that there was "insufficient evidence … regarding the relative benefits and risks of existing testing approaches" as well as the possible detriment to a patient's cure if treatment is withheld or insufficiently adjusted.

We applaud this progress, but it again comes short of our goal of universally requiring pre-treatment screening for DPD deficiency. Though the FDA now encourages physicians to discuss and consider testing, this leaves patients to deal with many oncologists who may point to the absence of NCCN guidelines as reasons to dismiss the need for testing. To help patients navigate along their journey of seeking treatment, we have published what we have found as Clinical Laboratory Improvement Amendments-certified laboratories that offer DPYD tests.[22]

There is also little guidance for physicians who receive test results. The FDA has not come out in support of dose adjustment for patients with partial deficiency despite the presence of guidelines published and maintained by the Clinical Pharmacogenomics Implementation Consortium.[23]

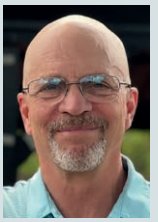
While the FDA and NCCN do not recommend pre-screening and dose management, we have found a number of US institutes and practitioners who are implementing some form of DPD deficiency pre-screening as part of their practice.[24] An early leader in testing, Dartmouth Cancer Center's Gabriel Brooks saw the tragic effects of 5-FU toxicity during his fellowship and has implemented pre-screening in his practice for treating GI cancer patients; he serves as another of our group's medical advisors. Brooks and other clinical leaders offer hope that the NCCN and FDA will soon update their positions.

Perhaps the single largest breakthrough in creating test leaders is a direct result of the efforts of our team's vice president. Murray, whose passion for change led us to form AUDT, succeeded in bringing about change at the cancer institute that treated her mother. Starting in 2021, she worked with a team at the Dana Farber Cancer Institute (DFCI) in Boston to initiate and implement DPD deficiency pre-screening.[25] Effective since December 2022, DFCI pre-screens patients unless they "opt out." Processes were put in place to ensure patients with DPD deficiency are identified and then treated accordingly, such as with dose adjustment. This response at DFCI demonstrates that once there is agreement upon addressing the problem of patient safety, procedural change is not insurmountable. DFCI's leadership, along with the other test leaders, gives us hope that other leading cancer centers will follow and ultimately prompt the NCCN and FDA to embrace the need for pre-screening and dose management.

The journey continues

We have seen progress towards improving the standard of care in the US, however, we have not concluded our journey. Since the time of our first advocacy steps, too many patients have died from standard dose chemotherapy treatment of DPD deficient patients. Estimates place the US death toll from DPD deficiency at more than 700 deaths per year.[26]

If you too see the current standard of care as inadequate to ensure safe treatment with 5-FU, please consider joining in our advocacy efforts. Only when prescreening and dose management is adopted across the US will we be able to rest our advocacy efforts. PMQ



Ken Surprenant

President, Advocates for Universal DPD/DPYD Testing

Ken has advocated for improved treatment guidelines for DPD deficient patients following the loss of his first wife, Kathryn, due to a toxic reaction to 5-FU chemotherapy in 2012. He is a founding member of Advocates for Universal DPD/DPYD Testing (AUDT), a group of patient advocates and medical advisors who seek to improve the standard of care for DPD deficient patients with pre-treatment screening and dose adjustment. With the help of many contributors, Ken's citizen petitions led the US Food and Drug Administration to update drug product labels (2016 and 2022) to more clearly identify the risk of severe toxicity for DPD deficient patients. Ken served over 40 years in federal service, managing multiple program managers and staff responsible for the development and operations of logistics information systems. He enjoys traveling, projects, and activities with his new wife, Elizabeth, and his children and grandchildren.

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