DPYD Testing: Time to Put Patient Safety First

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In 2018, a patient received capecitabine without prior testing for dihydropyrimidine dehydrogenase (*DPYD*) and later presented with vomiting, rash, and diarrhea. The hospital failed to provide uridine triacetate in a timely fashion, and the patient died. The patient's widow filed a wrongful death lawsuit against Oregon Health Sciences University (OHSU) and assisted in the formation of a nonprofit organization to advocate for *DPYD* testing for fluoropyrimidines. A settlement for $1 million US dollars was reached requiring OHSU oncologists to undergo education about *DPYD* testing and inform their patients about its availability.[1] Clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) and ASCO still do not support testing for *DPYD* genetic variants before fluoropyrimidine chemotherapy. The US Food and Drug Administration (FDA) package inserts for capecitabine and fluorouracil (FU) acknowledge patients with dihydropyrimidine dehydrogenase protein (DPD) deficiency have increased risk of life-threatening toxicity; however, instead of recommending preemptive testing, they posit an unlikely scenario in which patients who have known DPD deficiency should discuss it with their physicians.[2,3] The European Medicines Agency, the French National Agency for the Safety of Medicines and Health Products, and the Medicines and Healthcare products Regulatory Agency have each approved guidelines for preemptive *DPYD* testing for patients treated with fluoropyrimidines.[4]

Like all genetic tests, levels of evidence vary for each allele, but sufficient data are now published in the literature to conclude that individuals harboring certain *DPYD* variants are at increased risk of toxicity or death when administered standard doses of fluoropyrimidines. The genetic basis for the association between slow FU metabolism, pharmacokinetics, and toxicity was established in 1988.[5,6] In 1990, DPD activity was associated with FU plasma concentrations.[7] *DPYD*2A*, exon skipping IVS14G>A variant (c.1905+1G>A, rs3918290), was identified in 1995 and associated with FU toxicity in 1996.[8,9] A large number of studies are now published establishing the relationship between *DPYD* variants and fluoropyrimidine pharmacokinetics.[10] This commentary will establish that pretreatment *DPYD* testing is well justified and recommend dose reduction in those patients with a decreased function variant. We recommend an immediate modification to the oncology treatment guidelines that include a fluoropyrimidine.

Severe Fluoropyrimidine-Associated Toxicity

A recent meta-analysis of 13,929 patients in 35 studies found that patients carrying *DPYD*2A* were much more likely to experience severe life-threatening toxicity from fluoropyrimidine therapy than those carrying only wild-type alleles.[11] The NCCN colon cancer guideline discusses some of these studies, and we agree with the view presented therein: "Pretreatment *DPYD* testing of all patients has the potential to identify the estimated 1%-2% of the population with truncating alleles that may herald an increased risk of severe toxicity." However, the NCCN statement is not broad enough: Other *DPYD* variants have sufficient levels of evidence to justify testing (eg, c.1679T>G, rs55886062, *DPYD*13*; c.1129-5923C>G, rs75017182, *DPYD HapB3*; and c.2846A>T, rs67376798, p.D949V), raising the number of at-risk patients to approximately 9% of the US population.[10] Table 1 shows the recommended initial dose based on *DPYD* genotype-predicted phenotype.[10]

Fluoropyrimidine Efficacy

A prospective *DPYD* genotype-guided dose reduction (53% dose intensity) study resulted in similar efficacy in 40 *DPYD*2A* carriers versus matched controls.[12] Retrospective studies involving standard dosing found no relationship between *DPYD* SNPs and progression-free survival or overall survival in spite of a 50% dose reduction in *DPYD*2A* carriers.[13] Seven more clinical studies examining *DPYD* polymorphisms with a dose reduction did not observe a difference in response, time to progression, progression-free survival, and/or overall survival.[14] We were unable to find a study demonstrating a decrease in efficacy in patients with *DPYD* variants who were treated with a reduced dose. Thus, there is no evidence that a priori dose

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TABLE 1. Initial Dose Recommendations

DPD Activity Score[a]	% of Standard Fluoropyrimidine Dose[a]
2.0	100
1.5	50
1.0	50
0.5	< 25% if avoiding therapy unsuitable[b]
0.0	Avoid

Abbreviation: AS, activity score.

[a]DPD phenotype is based on activity score, which is a score developed from variants in the *DPYD* gene. A score of 2 represents an individual carrying two normal function alleles. A score of 1 or 1.5 represents an intermediate metabolizer carrying one normal function allele and one allele with decreased function (AS = 1.5) or absent function (AS = 1.0). A score of 0-0.5 represents a poor metabolizer carrying one no function allele and one allele with decreased function (AS = 0.5) or absent function (AS = 0).

[b]Clinical Pharmacogenetics Implementation Consortium guidelines also recommends use of phenotyping tests and therapeutic drug monitoring.

adjustments for *DPYD* carriers decreases fluoropyrimidine efficacy, and low-activity variant carriers treated with standard of care appear to have similar efficacy once an acceptable dose is found.

Pharmacokinetic Considerations

One study prospectively recruited heterozygous *DPYD*2A* carriers (n = 8) and wild-type carriers (n = 5) and demonstrated a significant difference in terminal half-life ($T_{1/2}$) between the two groups for single FU doses of 300 and 450 mg/m^2 (mean $T_{1/2}$ was 60% longer for those with a variant).[15] A larger study found a statistically significant 1.5-fold and 1.3-fold higher area under the concentration versus time curve (AUC) in patients with a *DPYD*2A* variant receiving a single FU dose of 300 mg/m^2 and 450 mg/m^2, respectively.[16] The mean FU clearance of *DPYD*2A* heterozygotes was 53% for controls.[17] Two case reports are published in which a heterozygous *DPYD*2A* carrier had a 2.5-fold higher $AUC_{0\text{-}3\ hours}$ and another had 66% lower FU clearance normalized for bioavailability than control patients.[18,19] Two genotype-guided dosing studies found no difference in the AUCs of *DPYD*2A* variant carriers receiving reduced doses compared with wild-type control patients receiving standard doses.[20,21] Thus, *DPYD*2A* carriers have greater exposure when provided standard dosing, and adjusting fluoropyrimidine dose on the basis of *DPYD*2A* genotype normalizes exposure across genotypic groups.

Practical Basis for a Study Involving Randomized Genotype-Guided Dosing

Although randomized clinical trial evidence is the gold standard for justifying clinical validity and clinical utility of genetic testing, obtaining such evidence is highly impractical, potentially delaying testing implementation for several years.

An ideal study design to prospectively validate *DPYD* genotyping before fluoropyrimidine administration would randomly assign a cohort to receive standard therapy despite a *DPYD*2A*, *DPYD*13*, *HapB3*, and *D949V* genotypes, which presents ethical and legal concerns because physicians may be obligated to act on this information to avoid severe toxicity in their patients. Another design could randomly assign patients to a nongenotyped cohort versus a genotyped cohort, with the genotyped cohort then receiving treatment with standard or reduced fluoropyrimidine dosing depending on genotype. Such a study likely would suffer from difficulty recruiting. Given these constraints, it is doubtful whether a randomized genotype-directed study will ever be conducted.

NCCN board members acknowledge the question of whether genotype testing should be implemented as standard of care is probably impossible to answer with traditional randomized studies, and they suggest a real-world study would be sufficient.[22] Yet, real-world studies published for the past 27 years in the scientific literature consistently demonstrate the relationship between *DPYD* variant carriers and toxicity. The NCCN and ASCO guidelines should act on these data to mitigate the incidence of ongoing life-threatening toxicity in the United States.[11]

Position of the Group

The NCCN guideline for the treatment of colon cancer (Table 2) states that *DPYD* variant carriers have significant risk of life-threatening toxicity and that *DPYD* testing is a cost-effective method to reduce such toxicity. NCCN's primary objection to testing DPD activity involves uncertainty that every patient with low DPD activity is at risk and the degree to which *DPYD* variants confer such risk. In public commentary, NCCN board members state further studies are required to mitigate the possibility that dose reduction would reduce fluoropyrimidine efficacy in some patients.[22] Current evidence suggests that dose adjustments do not alter efficacy; thus, a requirement for additional efficacy research should not supersede established concerns of unacceptable rates of life-threatening toxicity in *DPYD* low-activity variant carriers because the practice of medicine is guided by primum non nocere.

Risk/benefit analysis includes integrating evidence and uncertainties within the context of unmet needs.[23] Similar to most laboratory tests, *DPYD* testing has never been expected to provide certainty that a patient will develop drug toxicity; however, it does indicate a higher risk for severe or life-threatening toxicity that should be considered before treatment. The NCCN colorectal cancer guideline stipulates to the risk of life-threatening toxicity and then goes on to ignore it because "… it is not certain that every one of these patients is at risk." If one were to demand 100% predictive value for every test involving selection of an appropriate cancer treatment, almost no individual test would meet this standard for use in clinical care. Other tumor type NCCN

TABLE 2. NCCN Guideline for *DPYD* Testing (version 1.2022—February 25, 2022)

"Dihydropyrimidine dehydrogenase is the enzyme that catabolizes fluoropyrimidines. Individuals with certain variants of the dihydropyrimidine dehydrogenase gene, *DPYD*, have a significantly elevated risk for severe, life-threatening toxicity after a standard dose of fluoropyrimidine because these variants result in a truncated protein and prolonged systemic exposure to fluoropyrimidine. Pretreatment *DPYD* testing of all patients has the potential to identify the estimated 1%-2% of the population with truncating alleles that may herald an increased risk of severe toxicity. These patients could receive dose reductions or could be offered nonfluoropyrimidine regimens, although it is not certain that every one of these patients is at risk. Two prospective studies have shown *DPYD* genotyping and fluoropyrimidine dose individualization to be feasible in clinical practice, improve patient safety, and be cost effective. In a prospective study, 22 patients with the *DPYD*2A* variant allele (of 2,038 patients screened; 1.1%) were given a fluoropyrimidine dose reduction of 17%-91% (median, 48%). Results showed a significant reduction in the risk of grade ≥ 3 toxicity compared with historic controls (28% *v* 73%; $P < .001$). None of the patients died from drug toxicity, compared with a 10% death rate in the historical control group. Another prospective study identified 85 patients with any of the four *DPYD* variant alleles (8% of 1,103 patients screened) who received an initial fluoropyrimidine dose reduction of either 25% or 50% depending on the specific allele. This study reported that the RR of severe fluoropyrimidine-related toxicity was reduced for genotype-guided dosing for all studied alleles compared with the historical cohorts. However, because fluoropyrimidines are a pillar of therapy in CRC and it is not known with certainty that given *DYPD* variants are necessarily associated with this risk, universal pretreatment *DPYD* genotyping remains controversial, and the NCCN Panel does not support it at this time."[38]

Abbreviations: CRC, colorectal cancer; NCCN, National Comprehensive Cancer Network; RR, relative risk.

guidelines that use fluoropyrimidines as a treatment option fail to mention *DPYD*.

Evidence demonstrates that standard doses of FU and capecitabine are intolerable for most *DPYD*2A* carriers anyway.[13,17,24-26] Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for dosing fluoropyrimidines in DPD intermediate or poor metabolizers explicitly recommend dose escalation as tolerated.[10] We, therefore, believe *DPYD* genotyping should be recommended in the NCCN and ASCO guidelines for any patient diagnosed with cancer in which fluoropyrimidines are administered, provided testing does not interfere with clinical scenarios in which it does not add value (eg, the patient already tolerated a specific dose) or testing delays urgently needed therapy (eg, test results are available in 3-10 days).

Modification of these guidelines must be addressed immediately. OHSU originally denied fault in the wrongful death suit, justifying this claim by referring to national expert consensus.[1] OHSU is clearly relying on guidelines set forth by NCCN and ASCO. Although the NCCN stance against routine *DPYD* genotyping may have been acceptable in the past, accumulating data regarding the strong association of *DPYD* gene variants with severe toxicity make that stance increasingly untenable and possibly leaves cancer centers vulnerable to claims of malpractice in cases of fatal toxicity. On the basis of a survey of 18.2% of US medical oncologists, *DPYD* testing is limited by a lack of guidelines or recommendations for dosing decisions,[27] although some institutions are launching *DPYD* testing programs to avoid fluoropyrimidine toxicity.[22] Updating the guidelines to promote testing would mitigate a significant amount of toxicity and would increase the likelihood that such toxicity would be readily identifiable.

Limitations

Several limitations are apparent.[28] *DPYD* genotyping has a small up-front cost that will be applied to all patients while only benefiting the relatively small number of *DPYD* carriers. However, avoiding severe toxicity in the small population of *DPYD* variant carriers has been found to be ultimately cost-effective and possibly cost saving.[20,29,30] Pharmacogenetic panel testing could spread the cost over multiple medications. Moreover, as genomic sequencing is performed more commonly in patients with cancer at diagnosis, incidental data on *DPYD* variants will be generated, and clinicians will be obligated to act on such data anyway. Treatment delays may occur because of the time taken to generate genotyping results.[31] However, treatment delays and dose adjustments are already common in patients carrying *DPYD* variants who experience toxicity with standard dosing,[13] and turnaround times for genetic sequencing are becoming increasingly more rapid. Preemptive pharmacogenetic testing also obviates this concern. Although dose reductions of anticancer agents are sometimes associated with reductions in efficacy, dose optimization strategies are commonly used in oncology to normalize systemic drug concentrations relative to a traditional patient while maintaining efficacy.[32] In fact, a recent FDA initiative, Project Optimus, is designed to emphasize the selection of doses that maximize both efficacy and safety/tolerability of oncologics. To this end, the FDA should consider that evidence already shows accounting for *DPYD* genotype normalizes pharmacokinetics, toxicity, and outcome of fluoropyrimidines.[33] The FDA has previously proposed a PGx Pyramid Framework and used this mechanism to assess the evidence for HLA/allopurinol, which eventually led to a package insert change to recommend HLA testing.[34,35] Citizen petitions have also led to acknowledgment of the risk to *DPYD* variant carriers in the capecitabine and FU package insert, and other petitions are submitted to the FDA to include pretreatment testing.[36,37] Thus, the FDA has several mechanisms in place to overcome barriers to recommending *DPYD* testing. It would also be reasonable to expect that avoiding fluoropyrimidine overdoses in variant carriers would reduce the use of highly expensive uridine triacetate and costly hospitalizations. Thus, we consider genotype-guided dosing to be dose optimization, not simple dose reduction. Finally, DPD activity is a function of several allelic variants in the gene, and the levels of evidence for these polymorphisms

affecting fluoropyrimidine therapy vary. Although this limitation exists, there are those who are curating the strength of evidence for these alleles for public consumption.[10] Opportunities to understand less common polymorphisms will be increasingly possible if pretreatment *DPYD* testing becomes standard practice.

Recommendations

We recommend that pretreatment *DPYD* variant testing should be incorporated immediately into the standard of care for fluoropyrimidine regimens. Since fluoropyrimidine pharmacokinetic exposure is higher in reduced-function *DPYD* variant carriers, starting at a reduced dose and titrating upward to avoid undue toxicity should be adequate to maximize benefit while reducing risk in patients carrying heterozygous genotypes. Homozygous patients are at unacceptably high risk of fatal toxicity, and fluoropyrimidine therapy should be avoided unless it is absolutely necessary, in which case $< 25\%$ of the dose should be administered with DPD phenotyping tests and therapeutic drug monitoring. These methods are already recommended in the CPIC guidelines, and high evidence variants are included therein.[10] Thus, we recommend oncologists order testing before initiating fluoropyrimidine chemotherapy and follow the CPIC dosing guidelines, and the FDA should require updates to the package insert. We recommend that NCCN and ASCO treatment guidelines be modified to reflect the relationship between fluoropyrimidine and toxicity and that a priori testing should be adopted as the standard of care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Honoraria: Merck, Astellas Pharma, Pfizer, CLD Inc, Axiom Healthcare Strategies, EMD Serono, IntrinsiQ, ISMIE, NAMCP, Seattle Genetics, Curio Science, FirstWord, MedLearning Group, Research to Practice, Great Debates and Updates, MJH Life Sciences, Peerview, Vaniam Group, Institute for Enquiring Minds
Research Funding: Boehringer Ingelheim (Inst), Merck (Inst), Genentech/Roche (Inst), AstraZeneca/MedImmune (Inst), Acerta Pharma (Inst), Janssen (Inst), Seattle Genetics (Inst), Bristol Myers Squibb (Inst), Astellas Pharma (Inst)
Expert Testimony: Oregon Health & Science University (OHSU)
Travel, Accommodations, Expenses: Curio Science
Other Relationship: Janssen, Nektar, NIH, Dragonfly Therapeutics, G1 Therapeutics

Mary V. Relling
Stock and Other Ownership Interests: Bioskryb
Research Funding: Servier

Michelle A. Rudek
Employment: GlaxoSmithKline (I)
Leadership: American Society for Clinical Pharmacology & Therapeutics, Geminus Therapetuics
Stock and Other Ownership Interests: Geminus Therapetuics
Consulting or Advisory Role: Leidos, EMMES Corporation
Research Funding: RenovoRx (Inst)
Other Relationship: British Pharmacological Society, UpToDate, CMTx Biotech Inc

D. Max Smith
Research Funding: Kailos Genetics Inc (Inst)

Sandra M. Swain
Leadership: Seattle Genetics
Stock and Other Ownership Interests: Seattle Genetics
Consulting or Advisory Role: Genentech/Roche, Daiichi Sankyo, Molecular Templates, Athenex, AstraZeneca, Exact Sciences, Natera, Lilly, Merck, bioTheranostics, Aventis Pharma
Research Funding: Genentech (Inst), Kailos Genetics (Inst)
Travel, Accommodations, Expenses: Daichi Sankyo, Aventis Pharma
Other Relationship: AstraZeneca, Roche, AstraZeneca
Uncompensated Relationships: Genentech/Roche
Open Payments Link: https://openpaymentsdata.cms.gov/physician/801195

Christine M. Walko
Employment: Mission Healthcare
Consulting or Advisory Role: Jackson Laboratory for Genomic Medicine, Intermountain Precision Genomics, Clarified Precision Medicine

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